Interdisciplinary S3 Guidelines for the Diagnosis, Treatment and Follow-up Care of Breast Cancer

1\textsuperscript{st} updated version 2008
Interdisciplinary S3 Guidelines for the Diagnosis, Treatment and Follow-up Care of Breast Cancer

1st updated version 2008

Coordination:
Information Center for Standards in Oncology (ISTO)
Deutsche Krebsgesellschaft e.V.
Tiergarten Tower
Straße des 17. Juni 106–108
10623 Berlin
Germany
Tel.: +49 (0) 30 3229 32900
E-Mail: isto@krebsgesellschaft.de

Authors:
R. Kreienberg, I. Kopp, U. Albert, H. H. Bartsch,
M.W. Beckmann, D. Berg, U. Bick, A. du Bois,
W. Budach, J. Dunst, J. Engel, B. Ernst, M. Geraedts,
U. Henscher, D. Hölzel, C. Jackisch, K. König,
H. Kreipe, T. Kühn, A. Lebeau, S. Leimung,
H. Link, H.-J. Lück, H. Madjar, A. Maiwald,
G. Maiwald, N. Marschner, M. Marx, G. von Minckwitz,
I. Naß-Griegoleit, K. Possinger, A. Reiter, W. Sauerbrei,
W. Schlake, R. Schmutzler, I. Schreer, H. Schulte,
K.-D. Schulz †, R. Souchon, C. Thomssen, M. Untch,
U. Wagner, J. Weis, T. Zemmler
Product liability
Despite meticulous information-gathering and processing, neither the publishers nor the authors can assume any
liability for the information presented in these Guidelines on doses or forms of administration. It is up to the indi-
vidual user to verify the correctness of this information in each individual case by consulting the literature or the
information for medical professionals provided by the manufacturers.

Title photo: © istockphoto.com

Distributed by W. Zuckschwerdt Verlag GmbH

Bibliographic information for the German National Library
The German National Library has entered this publication in the German National Bibliography. Detailed bibli-
ographic data can be called up on the Internet at http://dnb.ddb.de.

Registered brand names (trademarks) are not always identified as such. The absence of such a brand name or trade-
mark does not justify the conclusion that the brand name or trademark is not registered.

All rights – in particular, the rights to duplicate, distribute or translate this work – are reserved. No part of this
work may be reproduced in any form (e.g. by photocopy, microfilm, etc.) without the written consent of the pub-
lisher.

© 2008 by W. Zuckschwerdt Verlag GmbH, Industriestraße 1, D-82110 Germering/Munich.
ISBN 978-3-88603-948-7
## Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Subsection</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreword</td>
<td>Foreword of the German Cancer Society</td>
<td>IX</td>
</tr>
<tr>
<td>Section A</td>
<td>General</td>
<td>1</td>
</tr>
<tr>
<td>A 1</td>
<td>Introduction</td>
<td>2</td>
</tr>
<tr>
<td>A 1.1</td>
<td>Objectives and tasks of the \textit{S3 Guidelines}</td>
<td>2</td>
</tr>
<tr>
<td>A 1.2</td>
<td>Preliminary remarks</td>
<td>4</td>
</tr>
<tr>
<td>A 2</td>
<td>Patient Information</td>
<td>5</td>
</tr>
<tr>
<td>A 2.1</td>
<td>Informing the patient of the diagnosis</td>
<td>6</td>
</tr>
<tr>
<td>A 2.2</td>
<td>Informing the patient about the treatment</td>
<td>6</td>
</tr>
<tr>
<td>A 3</td>
<td>Early Detection, Mammographic Screening</td>
<td>10</td>
</tr>
<tr>
<td>A 4</td>
<td>Women at Increased Risk of Developing Breast Cancer</td>
<td>13</td>
</tr>
<tr>
<td>A 4.1</td>
<td>Familial breast cancer</td>
<td>13</td>
</tr>
<tr>
<td>A 4.1.1</td>
<td>Counseling and genetic testing</td>
<td>13</td>
</tr>
<tr>
<td>A 4.1.2</td>
<td>Treatment of BRCA-associated carcinoma of the breast</td>
<td>14</td>
</tr>
<tr>
<td>A 4.1.3</td>
<td>Pathology of hereditary carcinoma of the breast</td>
<td>15</td>
</tr>
<tr>
<td>Section B</td>
<td>\textit{Locoregional Primary Disease}</td>
<td>17</td>
</tr>
<tr>
<td>B 1</td>
<td>General Diagnostic and Therapeutic Concepts</td>
<td>18</td>
</tr>
<tr>
<td>B 2</td>
<td>Pretherapeutic Diagnostic Measures to Assess the Spread of Cancer in Symptomatic Patients</td>
<td>21</td>
</tr>
<tr>
<td>B 2.1</td>
<td>Basic diagnostic measures</td>
<td>21</td>
</tr>
<tr>
<td>B 2.2</td>
<td>Imaging methods</td>
<td>22</td>
</tr>
<tr>
<td>B 2.3</td>
<td>Diagnostic confirmation</td>
<td>23</td>
</tr>
<tr>
<td>B 2.4</td>
<td>Staging</td>
<td>24</td>
</tr>
<tr>
<td>B 3</td>
<td>Preinvasive Lesions</td>
<td>27</td>
</tr>
<tr>
<td>B 3.1</td>
<td>Preliminary remark</td>
<td>27</td>
</tr>
<tr>
<td>B 3.2</td>
<td>Risk of developing breast cancer</td>
<td>27</td>
</tr>
<tr>
<td>B 3.3</td>
<td>Pathomorphological examination</td>
<td>28</td>
</tr>
<tr>
<td>B 3.4</td>
<td>Prevention</td>
<td>29</td>
</tr>
<tr>
<td>B 3.5</td>
<td>Therapeutic decisions and options</td>
<td>30</td>
</tr>
<tr>
<td>B 3.6</td>
<td>Therapeutic methods</td>
<td>32</td>
</tr>
<tr>
<td>B 3.6.1</td>
<td>Surgery</td>
<td>32</td>
</tr>
<tr>
<td>B 3.6.2</td>
<td>Radiotherapy</td>
<td>33</td>
</tr>
<tr>
<td>B 3.6.3</td>
<td>Drug therapy</td>
<td>33</td>
</tr>
<tr>
<td>B 3.7</td>
<td>Treatment, support and continuing care</td>
<td>34</td>
</tr>
<tr>
<td>B 3.8</td>
<td>Preinvasive recurrence or invasive breast carcinoma</td>
<td>34</td>
</tr>
<tr>
<td>B 4</td>
<td>Surgical Treatment of Invasive Breast Cancer</td>
<td>38</td>
</tr>
<tr>
<td>B 4.1</td>
<td>General recommendation</td>
<td>38</td>
</tr>
<tr>
<td>B 4.2</td>
<td>Breast-conserving treatment</td>
<td>39</td>
</tr>
<tr>
<td>B 4.3</td>
<td>Mastectomy</td>
<td>40</td>
</tr>
<tr>
<td>B 4.4</td>
<td>Plastic reconstructive procedures</td>
<td>41</td>
</tr>
<tr>
<td>B 4.5</td>
<td>Surgical treatment of the axilla</td>
<td>42</td>
</tr>
<tr>
<td>B 5</td>
<td>Pathomorphological Examination</td>
<td>47</td>
</tr>
</tbody>
</table>
B 5.1 Foreword ............................................................................................... 47
B 5.2 General principles ................................................................................. 47
B 5.2.1 General patient data, previous findings, information from the history . 48
B 5.2.2 Documentation of the macroscopic processing................................. 48
B 5.2.3 Documentation of the microscopic processing and reporting .......... 48
B 5.2.4 Investigation of mammographically detected microcalcifications...... 55
B 5.2.5 Frozen section examination ............................................................... 55
B 5.3 Percutaneous biopsies performed within the framework of interventional diagnostics ................................................................. 56
B 5.3.1 Percutaneous biopsy (high-speed core biopsy, vacuum-assisted biopsy) 56
B 5.3.1.1 Specimen processing for macroscopic examination ......................... 56
B 5.3.1.2 Specimen processing for microscopic examination and reporting ...... 56
B 5.3.2 Fine-needle biopsy/aspiration cytology .............................................. 57
B 5.4 Excisional biopsies ............................................................................... 58
B 5.4.1 Macroscopic specimen processing ..................................................... 58
B 5.4.2 Microscopic specimen processing and reporting ................................ 59
B 5.5 Mastectomy specimens ......................................................................... 61
B 5.5.1 Macroscopic specimen processing ..................................................... 61
B 5.5.2 Microscopic specimen processing and reporting ................................ 62
B 5.6 Lymph nodes ......................................................................................... 63
B 5.6.1 Macroscopic specimen processing ..................................................... 63
B 5.6.2 Microscopic specimen processing and reporting ................................ 64
B 6 Adjuvant Radiotherapy for Breast Cancer ............................................ 69
B 6.1 Radiotherapy after BCT ........................................................................ 69
B 6.2 Partial breast irradiation ....................................................................... 72
B 6.3 Radiotherapy after mastectomy ............................................................ 74
B 6.4 Irradiation of the regional lymphatic drainage system .......................... 77
B 6.5 Radiotherapy for advanced tumors ...................................................... 80
B 6.6 Sequencing of chemotherapy, antibody therapy and hormonal therapy 82
B 7 Systemic Adjuvant Therapy (Endocrine Therapy, Chemotherapy, Immune Therapy) ................................................................. 85
B 7.1 Selection of adjuvant therapy and risk assessment ............................... 86
B 7.2 Endocrine therapy ............................................................................... 87
B 7.3 Chemotherapy ...................................................................................... 90
B 7.4 Neoadjuvant (primary systemic) therapy ............................................. 91
B 7.5 Immune therapy ................................................................................... 93
B 8 Management of Locally and Locoregionally Advanced Breast Cancer ... 99
B 8.1 Primary systemic therapy .................................................................... 99
B 8.2 Inflammatory breast cancer ................................................................. 99
B 8.3 Inoperable patients ............................................................................... 99

Section C Recurrent or Metastatic Breast Cancer ............................................ 101
C 1 Definition and Prognosis......................................................................... 102
C 1.1 Definition ............................................................................................. 102
C 1.2 Incidence and prognosis ..................................................................... 102
C 2 Diagnostic Procedures for a Local or Locoregional Recurrence .......... 105
C 3 Treatment of Local or Locoregional Recurrence ................................ 106
C 3.1 Local (in-breast) recurrence ................................................................. 106
C 3.2 Local recurrence after mastectomy ..................................................... 107
C 3.3 Locoregional recurrences and isolated supraclavicular lymph node recurrences ................................................................. 107
C 3.4 Pharmacotherapy ................................................................................. 108
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>C 3.5</td>
<td>Radiotherapy</td>
<td>108</td>
</tr>
<tr>
<td>C 4</td>
<td>Distant Metastases</td>
<td>111</td>
</tr>
<tr>
<td>C 4.1</td>
<td>General principles</td>
<td>111</td>
</tr>
<tr>
<td>C 4.2</td>
<td>Diagnostic measures in patients with distant metastases</td>
<td>112</td>
</tr>
<tr>
<td>C 4.2.1</td>
<td>Skeletal metastases</td>
<td>112</td>
</tr>
<tr>
<td>C 4.2.2</td>
<td>Hepatic metastases</td>
<td>112</td>
</tr>
<tr>
<td>C 4.2.3</td>
<td>Pulmonary metastases</td>
<td>113</td>
</tr>
<tr>
<td>C 4.3</td>
<td>Systemic therapy of metastatic breast cancer</td>
<td>113</td>
</tr>
<tr>
<td>C 4.3.1</td>
<td>Systemic endocrine therapy</td>
<td>113</td>
</tr>
<tr>
<td>C 4.3.2</td>
<td>Endocrine therapy in postmenopausal patients</td>
<td>114</td>
</tr>
<tr>
<td>C 4.3.3</td>
<td>Endocrine therapy in premenopausal patients</td>
<td>115</td>
</tr>
<tr>
<td>C 4.4</td>
<td>Chemotherapy for metastatic breast cancer</td>
<td>115</td>
</tr>
<tr>
<td>C 4.5</td>
<td>Targeted therapies</td>
<td>117</td>
</tr>
<tr>
<td>C 4.5.1</td>
<td>HER-2 inhibitors (trastuzumab, lapatinib)</td>
<td>117</td>
</tr>
<tr>
<td>C 4.5.2</td>
<td>Anti-angiogenesis: VEGF inhibitors (bevacicumab)</td>
<td>119</td>
</tr>
<tr>
<td>C 4.6</td>
<td>Specific treatment of skeletal metastases</td>
<td>119</td>
</tr>
<tr>
<td>C 4.6.1</td>
<td>Indications for radiotherapy</td>
<td>119</td>
</tr>
<tr>
<td>C 4.6.2</td>
<td>Operative therapy</td>
<td>120</td>
</tr>
<tr>
<td>C 4.6.3</td>
<td>Bisphosphonates</td>
<td>120</td>
</tr>
<tr>
<td>C 4.6.4</td>
<td>Specific treatment of brain metastases</td>
<td>121</td>
</tr>
<tr>
<td>C 4.7</td>
<td>Special treatment of visceral distant metastases</td>
<td>122</td>
</tr>
<tr>
<td>C 4.7.1</td>
<td>Hepatic metastases</td>
<td>122</td>
</tr>
<tr>
<td>C 4.7.2</td>
<td>Pulmonary metastases</td>
<td>122</td>
</tr>
<tr>
<td>C 4.7.3</td>
<td>Malignant pleural effusion</td>
<td>123</td>
</tr>
<tr>
<td>C 4.7.4</td>
<td>Cutaneous and soft-tissue metastases</td>
<td>123</td>
</tr>
</tbody>
</table>

**Section D** | **Treatment, Care, Support** | 127  |
| D 1      | General Concept | 128  |
| D 2      | Psychosocial Aspects and Psychooncology | 130  |
| D 2.1    | Basic principles of psychooncological care | 130  |
| D 2.2    | Psychooncological care strategies and interventions | 130  |
| D 3      | Supportive Therapy | 136  |
| D 3.1    | Definition | 136  |
| D 3.2    | Significance and quantification of side effects | 136  |
| D 3.3    | Basic principles of supportive therapy | 136  |
| D 3.4    | Nausea and vomiting induced by chemotherapy | 137  |
| D 3.5    | Nausea and vomiting induced by radiation therapy | 139  |
| D 3.6    | Neutropenia – febrile neutropenia – infections | 139  |
| D 3.6.1  | Risk factors for febrile neutropenias | 140  |
| D 3.6.2  | Relative dose intensity of chemotherapy | 141  |
| D 3.6.3  | When is prophylactic use of G-CSF to prevent febrile neutropenia indicated in chemotherapy? | 141  |
| D 3.6.4  | G-CSF: Dosages and duration of therapy | 142  |
| D 3.6.5  | Infections in neutropenic patients | 142  |
| D 3.6.6  | Clinical work-up at commencement of therapy | 142  |
| D 3.6.7  | Treatment strategies | 143  |
| D 3.7    | Anemia in oncology | 146  |
| D 3.7.1  | Diagnostic workup of anemia | 147  |
| D 3.7.2  | Treatment of anemia | 147  |
| D 4      | Rehabilitation | 151  |
D 5 Follow-up Care Including Diagnostic Workup of Recurrences and Metastases and Support During Therapy .............................................. 154
D 5.1 Objectives.............................................................................................. 154
D 5.2 Examinations to detect locoregional and intramammary recurrences and contralateral breast cancer ............................................................ 155
D 5.3 Examination to detect metastases.......................................................... 156
D 5.4 Diagnostic workup and treatment of side effects and sequelae of primary and long-term treatments......................................................... 157
D 5.5 Frequency of follow-up examinations .................................................. 160
D 6 Palliative Medicine ............................................................................... 164

Section E Quality Management and Coordination of Patient Care ............. 165

Appendix 1: Diagnostic Chain for the Early Detection of Breast Cancer:
Clinical Algorithm................................................................................. 169
Appendix 2: Breast Reconstruction: Options/Indications......................................................... 170
Appendix 3: Pathomorphological Examination......................................................... 171
3.1 Histological classification .............................................................................. 171
3.1.1 Normal findings and benign lesions...................................................... 171
3.1.2 Benign epithelial proliferation .............................................................. 172
3.1.3 Papilloma .............................................................................................. 173
3.1.4 Myoepithelial lesions ............................................................................ 173
3.1.5 Fibroepithelial tumors .......................................................................... 174
3.1.6 Intraductal proliferative lesions.............................................................. 174
3.1.7 Lobular neoplasia (LN) ....................................................................... 177
3.1.8 Ductal carcinoma in situ (DCIS).......................................................... 178
3.1.9 Invasive breast cancer ........................................................................... 181
3.2 Special supplemental investigations .............................................................. 187
3.2.1 Hormone receptor status ....................................................................... 187
3.2.2 HER-2/neu testing ................................................................................. 188
3.2.3 Further special investigations .............................................................. 190
3.3 Processing and reporting of surgical specimens after primary (neoadjuvant) chemotherapy............................................................................. 190

Appendix 4: Recommendations on Adjuvant Systemic Treatment of Breast Cancer 200
Appendix 5: Algorithm for Systemic Treatment of Metastatic Breast Cancer ...... 204
Appendix 6: Dosage Recommendations for Palliative Chemotherapy .............. 206
Appendix 7: TNM and pTNM Classification and UICC Staging .................... 207
Appendix 8: Standards for a Quality Management System for Breast Cancer .... 209
8.1 Quality Indicators relating to the S3 Guidelines ........................................ 209
8.1.1 Updating and reaching of a consensus on the quality indicators..... 209
8.1.2 Quality indicators and assessment results ............................................. 211
8.1.3 Indicators of outcome quality used in the S3 Guidelines .................... 216
8.2 Sequential procedure for the management of women with breast cancer ................................................................................... 217
8.3 Variable set for breast cancer documentation ............................................. 219
Appendix 9: Members of the Guidelines Group .................................................. 220
Appendix 10: List of Statements ........................................................................... 224

Methodology Report ................................................................................ 257
By means of its comprehensive quality assurance program, the German Cancer Society has been working for many years to raise the level of care received by patients with cancer throughout the Federal Republic of Germany. At the Information Center for Standards in Oncology (ISTO) founded in 1995, the measures required to achieve this end are coordinated and implemented. In this context the elaboration of guidelines for the diagnosis, treatment and follow-up care of malignancies plays a central role. This is because only the development of new diagnostic and therapeutic concepts, as well as the consistent application of proven methods, can improve the chances of recovery for an increasing number of patients with malignant neoplasms.

In recent years the requirements for the elaboration of therapeutic guidelines have changed. Increasingly, methods from the field of evidence-based medicine (EBM) are used and, in fact, demanded by healthcare policy-makers. The German Cancer Society has devoted intensive study to this methodology and has created the requisite structures and methods for its implementation in cooperation with other organizations and individuals involved on the national level; in so doing it has taken account of applicable international standards.

The updated Stage 3 Breast Cancer Guidelines presented here lay the foundation for the nationwide implementation of a multidisciplinary, quality-assured and cross-sectoral approach to the treatment of breast cancer. The objective of the nationwide distribution and implementation of the S3 Guidelines is to optimize the diagnostic chain and the stage-appropriate treatment of the first occurrence of the disease as well as any recurrences and/or metastases. In the medium and long term this is expected to result in lower mortality rates and an enhanced quality of life for women with breast cancer.

The Guidelines, which conform to the highest quality standards, also constitute the foundation for the revision of the Breast Cancer Disease Management Program and the certification procedures for breast cancer centers developed by the German Cancer Society and the German Society of Senology.

The German Cancer Society thus hopes that these Guidelines will make a contribution to improving the care of women with breast cancer. However, that in itself is not enough. What is more importance is that all parties involved – but especially physicians – bring their actions into line with these Guidelines. Together with the patient, they can select and carry out the optimal therapy. The German Cancer Society hopes, in addition, that the Guidelines will lead not only to a further improvement of therapeutic outcomes but that – in particular by means of the planned patient version of the Guidelines – they will also serve as a source of orientation and security for the women involved.

We would like to thank, in particular, Guidelines Coordinator Prof. Dr. R. Kreienberg, the working parties participating in the project, the Scientific Medical Societies in Germany
(AWMF), the professional associations and, last but certainly not least, the patient representatives for the commitment they have shown.

The German Cancer Society will continue to be active in the future in drawing up the necessary scientific guidelines and in conducting the public education campaign that is a vital part of the battle against cancer. This will now also be carried out within the framework of the program “Guidelines in Oncology” recently instituted together with the AWMF and German Cancer Aid. The patient is at the center of all these activities and it is up to all of us to ensure that she receives the best care possible.

Prof. Dr. M. Bamberg  
President of the German Cancer Society  
(Deutsche Krebgesellschaft e.V.)
Section A
General
A 1 Introduction

Almost 60,000 women develop breast cancer each year in the Federal Republic of Germany. Carcinoma of the breast is thus the most common form of cancer in women in Germany and is responsible for 26.8 % of all new malignancies diagnosed in women in this country. The mean age at which women develop breast cancer is approx. 62 years. A woman has an approx. 12 % risk of developing breast cancer at some time in her life.

According to information supplied by the Federal Office of Statistics, just under 17,455 women died of breast cancer in Germany in 2005. Breast cancer is the form of cancer with the highest mortality rate – 17.8% - among women in Germany. It is ahead of both colorectal and lung cancer in this respect. Every second death occurring among women between the ages of 35 and 60 was caused by cancer. Carcinoma of the breast was responsible for 27 % of all deaths due to cancer in this age group. The 5-year survival rate for women with a diagnosis of breast cancer is approx. 76 %. The tumor-dependent survival for the first five years is around 83 % (GeKiD 2006; Kreienberg, R et al. 2004; Statistisches Bundesamt 2006).

A 1.1 Objectives and tasks of the S3 Guidelines

The S3 Guidelines for the Diagnosis, Treatment and Follow-up Care of Breast Cancer in Women are an evidence- and consensus-based instrument for the care of women with a confirmed diagnosis of breast cancer. The Guidelines have been drawn up in order to offer breast cancer patients scientifically based, up-to-date and economic procedures for diagnosis, treatment and rehabilitation appropriate to the particular stage of the disease. The recommendations and Statements laid down by the Expert Panel on Breast Cancer for the national S3 Guidelines are based, in particular, on publications upholding high standards of methodology. As part of this process, the statements found in the current literature were evaluated by the Expert Panel according to the usual criteria of evidence-based medicine (EBM). For this purpose, recommendations and results prepared from evidence published in secondary sources (international guidelines or metaanalyses) as well as evidence from primary publications in the form of prospective randomized clinical studies are classified as especially relevant whereas data from observational studies and case series are taken into account only when necessary.

To ensure the transparency of both the process of drawing up the S3 Guidelines and the accompanying evidence, all recommendations and Statements have been linked in a plausible manner to the sources in the literature, the levels of evidence (LOE), and the grades of recommendation of the Expert Panel which serve as the basis for the Guidelines. The objectives and tasks of the Guidelines, as well as the process of preparing the Guidelines, have also been described in detail in the accompanying Methodology Report.

The present Guidelines are intended to provide a basis for medical decision-making processes. It is expected that the Guidelines will help to ensure that appropriate healthcare measures are
taken in the areas of diagnosis and treatment for women with breast cancer and provide a firm foundation for individually adapted, quality-controlled therapy. Therapeutic interventions can be tailored, by applying the Statements formulated in the Guidelines, to the individual patient’s risk, the therapeutic objective, the physician’s assessment of the case, the weighing of risks and benefits, and the patient’s preferences. It is thus possible to take the situation of the individual patient into account when selecting a therapy appropriate for the particular stage of the disease from among the various therapeutic options and the various diagnostic and therapeutic interventional strategies available. The possible early and late sequelae of each type of therapy are presented insofar as these are known from the literature published to date. In this way, mistakes can be avoided during the planning and administering of therapy for breast cancer. It must be pointed out, however, that late sequelae of therapy can also occur years or decades later. During each revision of the Guidelines, such sequelae will have to be evaluated separately for each form of therapy and incorporated in the Guidelines.

The individual measures that can be taken by doctors for the diagnosis, treatment and follow-up care of breast cancer in women are arranged according to the current state of scientific literature: resources are named and interfaces defined. The Guidelines enable physicians participating in the patient’s care who are not specialized in the treatment of breast cancer to advise the patient entrusted to their care on the approach taken by the specialists, the therapeutic outcome, and the possible adverse reactions. The most important steps in the therapy are presented in the form of flow charts. In addition to stipulating the (minimum) scope of the documentation, the Guidelines specify the quality indicators, the methods to be used, the aims of the short- and long-term parameters used for reviewing and adapting the therapy, and the evaluation times.

During the elaboration of these national S3 Guidelines, statements and recommendations made in a number of international guidelines were included. Moreover, the results of international studies and metaanalyses on the diagnosis and treatment of breast cancer have been taken into account. The process of drawing up the Guidelines is described in detail in the accompanying Methodology Report.

The structural quality, definition of the points of intersection and minimum requirements for communication among all parties involved have not been set down in the S3 Guidelines; instead, these parameters have been defined by the requirements for accreditation of breast centers (German Cancer Society/German Society of Senology).

The present S3 Guidelines lay the foundation for the nationwide implementation of a multi-disciplinary, quality-assured and cross-sectoral approach to the treatment of breast cancer. The objective of the nationwide distribution and implementation of the S3 Guidelines is to optimize the diagnostic chain and the stage-appropriate treatment of the first occurrence of the disease as well as of any recurrences and/or metastases. In the medium and long term this is expected to result in lower mortality rates and an enhanced quality of life for women with breast cancer.

The diagnosis, treatment and follow-up care of breast cancer in men have not been discussed separately in these Guidelines. Breast cancer in men is, on the whole, diagnosed and treated in the same manner as breast cancer in women. Deviations from these Guidelines in individual points must be decided upon by experts in the particular case.
A 1.2 Preliminary remarks

Appropriate, scientifically based, up-to-date and economic procedures for the diagnosis and treatment of breast cancer, and for the rehabilitation of breast cancer patients, have been compiled in these Guidelines. The observance of these Guidelines is expected to result in a high quality of care for women with breast cancer.

The quality of the outcomes achieved in this way is to be made transparent continuously, and without regard to any time limits, by the long-term results. Overall survival, disease-related survival, locoregional recurrences and progression, and the time intervals between these events, substantiate the quality of care as a function of the diagnostic constellations and the treatments administered. They serve as the basis for institutional, regional and international comparisons.

Relevant findings and treatments, both primarily and in the course of the disease, are to be recorded by the hospitals, doctors in office practice and institutions providing care and transmitted to the regional clinical cancer registries with jurisdiction in the particular case.

Operational clinical cancer registries link the cooperating hospitals and physicians into networks. These registries collate the transmitted data including data on events taking place in the course of the disease and data on second malignancies. The life status is systematically incorporated. In this way the registries support the care of breast cancer patients and make it transparent. Simultaneously, the results are evaluated by external parties. The institutions providing care receive their own evaluated results. Many of the German states have already assigned clearly demarcated catchment areas for the clinical cancer registries and, in so doing, defined their jurisdiction. With this step, a development process has been initiated that will result in a lasting infrastructure for the support and quality assurance of patient care.

Literature


A 2 Patient Information

As a result of the further development of communication technology and the media and the increasing utilization of new information technologies such as the Internet, providing patients with adequate and appropriate information plays a more important role than ever before. Numerous studies have confirmed the importance of this issue for the doctor-patient relationship (Gysels, M et al. 2007; Wofford, JL et al. 2005). Patient information and patient decisions constitute the basis for action by doctors. Two ethical principles are at work in this interaction: the patient’s self-determination (autonomy) and the physician’s duty of care (Beauchamp, TL et al. 2001). The patient’s autonomy takes priority in this context. A decision made by a patient is always voluntary and binding for action taken by doctors. Patients can make decisions for or against diagnostic and therapeutic measures or can decide in favor of “not wanting to know.” Any existing information deficits are to be remedied by the physician so that the patient can make informed decisions (informed consent). The consultation between the patient and the doctor takes on special importance as the basis for a decision-making process based on mutual trust and respect. Increasing emphasis is being placed in this context on patient participation in decisions about treatment (“shared decision-making”). This kind of decision-making is characterized by an intensive exchange of information between doctor and patient and culminates in the woman making a decision both she and her doctor support with regard to the performance of medical procedures (Beauchamp, TL et al. 1994; Sieber, WJ et al. 2000; Weinstein, JN 2000).

The precondition for this is the patient-centered consultation. The information provided by the doctor should be comprehensive, unbiased and complete with respect to the type of measures envisaged, their purpose, and the benefits and the risks. In particular, the information should be easily understood (e.g. giving frequencies instead of relative percentages) (NHS 2000; Wright, EB et al. 2004). The consultation should be conducted in a manner that takes account of the individual patient’s somatic, psychological and social situation, age and any comorbidities. The doctor should directly address the patient’s anxieties and worries, any specific problems, and particularly her need for information and her expectations and preferences regarding the treatment (Jansen, SJ et al. 2005; Katz, SJ et al. 2005; Steinbach, K et al. 2004; Wagner, K et al. 1998). If the patient wishes, she should be allowed to have a person of her choice (e.g. partner, family member, patient advocate) with her at this or future consultations. The information provided by the doctor should include: information about the disease, results of examinations and tests, the treatment course to date, diagnostic and therapeutic options, available alternatives, and estimations of the respective prognoses and the influence on the patient’s life planning (Albert, US et al. 2004; Chouliara, Z et al. 2004; Hagerty, RG et al. 2005).

 Provision of printed material and access to such material are useful supportive measures to help the patient come to a decision (Albert, U et al. 2003; O’Connor, AM et al. 1999). Such decision aids include qualified, competent, accurate and easily understood information material which meets the quality standards of the Leitlinie Fraueninformation [Guideline Women’s Information] (www.leitlinien.net).
Statement Info-1

The provision of qualified, competent and accurate information material (printed or Internet material) should meet the quality standards of the *Leitlinie Fraueninformation* and should provide the patient with easily understood risk information (e.g. specification of absolute risk reduction instead of relative percentages) to help women arrive at a self-determined decision for or against a particular medical procedure.

**GCP** (Albert, U et al. 2003; Albert, US et al. 2008)

### A 2.1 Informing the patient of the diagnosis

As soon as the histopathological diagnosis of breast cancer is confirmed, the patient should be informed of the diagnosis by the physician treating her or by another doctor familiar with her case. It is up to the patient to decide whether her partner, a family member or a representative of a self-help group should be involved in the consultation(s). The consultation should take place in an appropriate setting and the information should be presented in a manner that is comprehensible to the patient and appropriate to her level of understanding. (NHS 2000; Wright, EB et al. 2004). The doctor must inform the patient truthfully, without painting an overly rosy picture and without depriving her of the hope of recovery or relief. The doctor should ensure that the information he gives the patient keeps pace with the course of the therapy.

Statement Info-2

When conveying information to the patient doctors should follow the following basic principles of patient-centered communication:

- Display empathy and listen actively.
- Address difficult topics directly and with empathy.
- Whenever possible, avoid medical terminology. If medical terms cannot be avoided they should be explained.
- Employ strategies that improve understanding (e.g. repeating, summarizing the salient points, using graphics, etc.).
- Encourage the patient to ask questions.
- Allow and even encourage her to express her feelings.
- Offer further assistance (Cf. Psycho-oncology).

**LOE 1b Grade of Recommendation A** (Bruera, E et al. 2002; Butow, P et al. 2007; Elkin, EB et al. 2007; Ford, S et al. 2006; Politi, MC et al. 2007)

### A 2.2 Informing the patient about the treatment

The physician informing the patient should present the rationale behind the recommendations for a special form of treatment, especially if a case-related consensus-based recommendation for treatment has been made at a multidisciplinary conference, and explain the principles of the treatment and the associated benefits and risks. Alternative forms of treatment which can be offered to the patient within the framework of clinical studies should also be explained. The impact of the proposed treatment on the patient’s life style and quality of life should be discussed.
The explanations provided should always include the following items. If surgical treatment is planned, possibilities for breast-conserving surgery and obligatory radiotherapy should be presented as therapeutic alternatives of equal value with mastectomy. When presenting the option of mastectomy, the physician should explain the various options for primary and secondary reconstruction as well as the option of an external breast prosthesis. If systemic therapy (endocrine therapy, chemotherapy, immunotherapy) or radiotherapy is planned, he or she should explain the principles and therapeutic objectives of these therapies as well as possibilities for participating in clinical studies. Furthermore, the patient should be told how long the therapy will take and how it will be carried out, what adverse reactions and possible late sequelae it has, and how these can be managed.

The patient should also be informed about measures for preventing lymphedema, about the necessity of oncological follow-up-care, about rehabilitation (see below), and about social, financial and psycho-oncological support (see below). If necessary, the patient should be advised to obtain further professional information and advice in the areas mentioned above (rehabilitation, social counseling and psycho-oncology), and the necessary arrangements made.

Any treatment requires the patient’s cooperation. The aspects which are the patient’s own responsibility should be discussed at the consultation.

**Statement Info-3**

<table>
<thead>
<tr>
<th>The consultation to inform the patient about the treatment should cover at least the following points:</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Surgical therapy: possibilities for breast-conserving therapy (surgery followed by radiation therapy), possibilities for reconstruction or external prostheses following mastectomy</td>
</tr>
<tr>
<td>– Systemic therapy: principles of adjuvant or palliative therapy (endocrine therapy, chemotherapy, immunotherapy).</td>
</tr>
<tr>
<td>– Radiotherapy: underlying principles, duration and follow-up surveillance, possible acute and late sequelae</td>
</tr>
<tr>
<td>– Participation in clinical studies, principles behind the treatment, duration and mode of administration of the therapy; treatment targets, effects and side-effects known to date, special features (e.g. monitoring, additional measures, cooperation, data storage and processing)</td>
</tr>
<tr>
<td>– Miscellaneous: possibilities for prevention and treatment of therapy-related side-effects (e.g. emesis, osteoporosis, lymphedema, etc.), necessity for follow-up care, possibilities for rehabilitation and psycho-oncological support as well as services offered by self-help groups, aspects that are the responsibility of the patient and the need for cooperation (e.g. reporting symptoms and problems, treatment compliance)</td>
</tr>
</tbody>
</table>

**GCP**

In the case of premenopausal women the influence of the treatment on fertility and questions of contraception should also be addressed. Questions related to the treatment of therapy-induced ovarian insufficiency in premenopausal women (e.g. symptoms and therapeutic options) should also be discussed.
The physician is to take account of the somatic, psychological and social situation of the individual patient, her age, and any comorbidities when talking to the patient. The patient’s anxieties, worries, specific problems, need for information, expectations concerning the treatment and personal preferences are to be addressed by the physician (Jansen, SJ et al. 2005; Katz, SJ et al. 2005; Steinbach, K et al. 2004; Wagner, K et al. 1998). This also includes informing the patients of “normal” and “unremarkable” test results to provide reassurance and providing prognostic information to facilitate the patient’s life planning (Albert, US et al. 2004; Chouliara, Z et al. 2004; Hagerty, RG et al. 2005).

Breast cancer is not an emergency. The patient must always be allowed sufficient time for decision making. She has the right to reject a particular procedure or treatment or to withdraw previously granted consent to participation in a therapeutic trial or clinical study. Moreover, she has the right to review the clinical documentation at any time and to receive copies of her medical records. Patients always have the right to choose their doctor and hospital freely, to change doctors and/or hospitals, and to obtain a second opinion.

(http://www.bmg.bund.de/cln_040/nn_600110/DE/Themenschwerpunkte/Gesundheit/Patientenrechte/Patientenrechte-in-Deutschland-2191.html)

Patients should be supported in their desire for further information and should be given direct and practical assistance (Albert, U et al. 2003; O’Connor, AM et al. 1999). Such assistance includes tips on where to obtain written information (in particular Patient Guidelines), addresses of self-help groups, phone numbers of help lines, and Internet addresses. Each patient should be urged to keep a file of her own medical records.

The desire to obtain information and to be involved in medical decisions varies greatly from patient to patient and can change over the course of time (Butow, PN et al. 1997; Degner, LF et al. 1997; Leinster, SJ et al. 1989). For this reason, the provision of information and the involvement of the patient in medical decisions should be tailored to the patient’s individual needs and the requirements of the therapy along the entire chain of diagnosis, treatment and care.

**Literature**


A 3 Early Detection, Mammographic Screening

Next to the further improvement of treatment, the early detection of breast cancer (secondary prevention) is the most promising possibility for optimizing the diagnosis and treatment of breast cancer, for consequently reducing breast cancer mortality, and for improving both the health-related and disease-related quality of life of women. The objective is to detect breast carcinoma in its preinvasive form or at an early invasive stage for which the 5-year survival rate in patients receiving adequate therapy is above 90% (Engel, J et al. 2002; Michaelson, JS et al. 2002; Michaelson, JS et al. 2003a; Michaelson, JS et al. 2003b; Verschraegen, C et al. 2005). The increasing detection of preinvasive lesions gives reason to hope that preventive measures will help to lower the incidence of breast cancer (Ries, L et al. 2006). The improved prospects of a cure opened up by secondary prevention can be realized at early stages of the disease, when it is possible to employ methods which are less radical and place less stress on the patient (Albert, US et al. 2004; Engel, J et al. 2004; Michaelson, JS et al. 2003b).


The objective of the updated Stage 3 Guidelines on Early Breast Cancer Detection in Germany is to help doctors, as well as healthy women and women affected by breast cancer, to make medical decisions along the diagnostic chain for the early detection of breast cancer by providing evidence-based recommendations reached by formal consensus. The updated Stage 3 Guidelines on Early Breast Cancer Detection in Germany, 1st revision 2008, lay the foundation for the development of an effective and efficient screening program for early breast cancer detection meeting the requirements set down by the Council of Europe (Council of Europe 2001) and the World Health Organization (WHO 2002; WHO 2005) for cancer control programs. The core element of an early detection program is mammography; the quality of the results can be markedly improved by embedding it in a quality-assured diagnostic chain (Groot, MT et al. 2006; Katalinic, A et al. 2007; Lash, TL et al. 2000; Nystrom, L 2000; Palmieri, C et al. 2000; Schreer, I et al. 2007). The Guidelines present the current state of scientific knowledge, in an evidence- and consensus-based form and across the boundaries of the medical disciplines, for all parts of the diagnostic chain consisting of history-taking, advising on risk, and providing information on health-related behavior, the clinical examination, apparative diagnostics, interventional tissue biopsy techniques, surgical exploration and pathohistological interpretation of results. It includes the quality indicators serving as indexes for assuring the structural, process and outcome quality of the diagnostic chain (cf. Annex 1).

The examinations performed to achieve early breast cancer detection by no means confer only benefits; instead, they also pose risks. This fact deserves all the more attention since most of the women who undergo examinations aimed at early detection are healthy. Only in individ-
ual cases do these examinations reveal breast lesions requiring further diagnostic exploration or, in the case of malignant lesions, treatment. In particular, false positive and false negative findings must be taken into consideration as stressful components of the overall concept. Informed self-determination and participation in the doctor’s decision-making processes have an especially high priority for the women interested in taking part in these programs.


Taking consideration of the available study data, the Cochrane analysis performed in 2006 showed that mammographic screening was associated with an approx. 15 % relative reduction of the risk of dying from breast cancer (Gøtzsche, PC et al. 2006).

For information on the various aspects of the diagnostic and medical care chain, the reader is referred to the Stage 3 Guidelines on Early Breast Cancer Detection in Germany (Albert, US et al. 2008).

**Literature**


Nothacker, M., Lelgemann, M., Giersiepen, K., Weinbrenner, S. Evidenzbericht 2007 zur S3-Leitlinie Brustkrebs-
Früherkennung in Deutschland. Ärztliches Zentrum für Qualität in der Medizin (ÄZQ), Berlin. 2007.
Palmieri C., Fishpool S. Breast cancer screening. Screening has to be combined with good surgical and oncological
Hayat B., Edwards B. SEER Cancer Statistics Review 1975-2003; based on November 2005 SEER data sub-
2006.
Schreer I., Katalinic A. Is high quality breast imaging and diagnosis possible in a decentralized system? Breast Care
2007; accepted.
WHO. National Cancer Control Programs: Policies and Managerial Guidelines, Health and Development Networks
A 4 Women at Increased Risk of Developing Breast Cancer

A 4.1 Familial breast cancer

About 5% of all carcinomas of the breast occur on the basis of a hereditary predisposition. Women with germline mutations in one of the predisposing genes, i.e. BRCA1 and BRCA2, have a 50-80% risk of developing carcinoma of the breast during their lifetimes, a 60% risk of developing carcinoma in the contralateral breast, and a 10-40% risk of developing ovarian carcinoma (Antoniou, A et al. 2003; Goldberg, JI et al. 2006).

A 4.1.1 Counseling and genetic testing

Statement Risk-1

Multidisciplinary counseling and genetic testing should be carried out at special centers and offered to every woman with one or more of the following constellations in her family:

- at least three women who developed breast cancer
- at least two women (including one below age 50) who developed breast cancer
- at least one woman who developed breast cancer and one who developed ovarian cancer
- at least two women who developed ovarian cancer
- at least one woman who developed breast and ovarian cancer
- at least one woman who developed breast cancer before age 36
- at least one woman who developed cancer in both breasts before age 51
- at least one man who developed breast cancer and one woman who developed breast or ovarian cancer.

GCP

A woman who has developed breast cancer later in life, and is the only person in her family with this disease, most probably does not carry the respective gene mutation. However, some women have several people with the disease in their families or have developed the disease themselves at an early age. In these cases genetic testing may be worthwhile. For this reason, inclusion criteria were established in Germany to identify women with an over 10% probability of carrying a mutation in the high-risk genes. In about 25% of the families satisfying these inclusion criteria, a causal mutation is found (Data collected by the German Consortium from more than 3,500 families).

Genetic testing must be preceded by comprehensive counseling at a specialized and interdisciplinary clinical unit (NICE-guideline 2004, HTA-Report Erblicher Brust- und Eierstock-
krebs, Gerhardus et al. 2005). In Germany 12 interdisciplinary centers have been established – at the Universities of Berlin, Düsseldorf, Dresden, Hannover, Kiel, Cologne/Bonn, Leipzig, Munich, Munster, Ulm and Wurzburg – for this purpose. Their addresses can be obtained from the German Cancer Aid (Deutsche Krebshilfe).

A 4.1.2 Treatment of BRCA-associated carcinoma of the breast

Statement Risk-2

The treatment of BRCA-associated carcinoma of the breast is based on the therapeutic guidelines for sporadic carcinoma of the breast.

GCP

Mastectomy can be performed in the contralateral breast to reduce the patient’s risk of developing a second carcinoma in this breast as well; however, an advantage of this approach in terms of survival is not substantiated by empirical evidence.

LOE 3a, Grade of Recommendation 0 (Hartmann, LC et al. 2001; Meijers-Heijboer, H et al. 2001; Rebbeck, TR et al. 2004)

Bilateral oophorectomy can be performed to reduce the risk of a second carcinoma of the breast and the ovaries. However, an advantage of this approach in terms of survival has also not been substantiated by empirical evidence.

LOE 3a, Degree of Recommendation 0 (Metcalfe, K et al. 2004; Pierce, LJ et al. 2006)

If a woman with a mutation in the genes BRCA1 or BRCA2 develops carcinoma of the breast, treatment is currently based on the therapeutic recommendations for sporadic carcinoma of the breast.

On the basis of current knowledge, the incidence of metachronic ipsilateral second carcinoma does not appear to be elevated. Consequently, breast-conserving therapy is adequate (Robson, M et al. 2005).

However, mutation carriers have a 30-40% higher risk of developing carcinoma in the contralateral breast within 10 years (Metcalfe, KA et al. 2005; Robson, M et al. 2005). It has been shown in several observational studies that performing prophylactic bilateral mastectomy in healthy women reduces the incidence of, and mortality due to, BRCA-associated carcinoma of the breast (Hartmann, LC et al. 2001; Lostumbo, L et al. 2004; Meijers-Heijboer, H et al. 2001; Rebbeck, TR et al. 2004). However, insufficient data are available from women who already have breast cancer. Whereas bilateral mastectomy has been shown to reduce the incidence of second carcinoma of the breast, no effect on overall survival has been demonstrated to date (Lostumbo, L et al. 2004; van Sprundel, TC et al. 2005).

The risk of developing a second breast cancer in the contralateral breast can also be reduced by 60% by bilateral prophylactic salpingo-oophorectomy (Metcalfe, K et al. 2004; Pierce, LJ et al. 2006). In women with Stage I or II carcinoma of the breast, a survival advantage has been described through the reduced incidence of ovarian carcinoma (Metcalfe KA et al. 2005).

A reduction of risk postulated for the administration of tamoxifen has not been clearly demonstrated. Whereas a significant reduction of 70% in the incidence of contralateral second car-
cinoma was described in one study (Pierce, LJ et al. 2006), in another study the multivariant analysis of the results revealed no significant lowering (Metcalfe, KA et al. 2004).

There is evidence that BRCA-associated tumors, in particular, respond well to treatment with platinum derivatives (Husain, A et al. 1998; Quinn, JE et al. 2003; Tassone, P et al. 2003; Yun, J et al. 2005). On this topic the results of clinical studies must be awaited.

A 4.1.3. Pathology of hereditary carcinoma of the breast

Statement Risk-3

<table>
<thead>
<tr>
<th>BRCA1-associated carcinomas of the breast frequently exhibit a characteristic histopathological and immunohistochemical phenotype:</th>
</tr>
</thead>
<tbody>
<tr>
<td>– invasive carcinoma (NOS) with a growth pattern similar to that of medullary carcinoma</td>
</tr>
<tr>
<td>– G3 morphology</td>
</tr>
<tr>
<td>– negativity for estrogen receptors, progesterone receptors and HER2/neu (triple negative)</td>
</tr>
</tbody>
</table>

LOE 2a (Honrado, E et al. 2006; Lakhani, SR et al. 1998; Lakhani, SR et al. 2005)

In cases where these characteristics are present, the pathologist should draw attention to the possibility of an inherited susceptibility to breast cancer.

GCP

Whereas BRCA2-associated carcinomas of the breast present the same picture as sporadic carcinomas, BRCA1-associated carcinomas display a special phenotype (Foulkes WD 2003, Lakhani SR 2002, Karp SE 1997, Palacios J 2005). Carriers of the latter mutation more frequently develop a type of carcinoma with the characteristics of medullary carcinoma although not in the typical form described in the WHO classification. These special characteristics include: relatively well-defined borders upon macroscopic examination with a displacing rather than invasive and marrowy rather than compact appearance, G3 morphology with high-grade nuclear atypia, high mitotic activity and absence of tubule formation, a syncytial growth pattern, no expression of steroidal hormone receptors or HER2 (triple negative), a Ki-67 value above 30%, and expression of high-molecular-weight cytokeratins (basal phenotype, cytokeratins 5/6). In the adjacent tumor-free breast tissue, so-called lymphocytic lobulitis is frequently encountered; however, this constitutes a weaker pointer. The presence of these features should prompt consideration of the possibility of a genetic predisposition and elicitation of a family history.

Literature


Section B
Locoregional Primary Disease
The incidence of breast cancer rose in Germany until the end of the 1980s; it is only in recent years that it has displayed a marked decline. Since 1990 the mortality rate has also been falling. In the U.S. and England as well a reduction in mortality of over 20% has been observed; this has been linked to consistent early detection and the use of adjuvant systemic therapy. It is hoped that the screening projects – as part of which asymptomatic women aged 50 to 69 are personally invited to take part in mammographic screening – which are currently being instituted all over Germany on the basis of the Cancer Early Detection Guidelines (KFÜ) and the nationwide agreements entered into for this purpose – will result in earlier detection of breast cancer and a further lowering of mortality over the medium term.

Decisive advances have been made in diagnostic imaging of both palpable lesions and clinically unclear or suspicious lesions as well as in the establishment of interventional procedures as part of the preoperative diagnostic workup.

In addition to meticulous clinical examination, the following diagnostic procedures are available to patients with breast cancer, unclear or suspicious findings, or precancerous lesions:

- mammography including supplementary mammographic studies (e.g. magnification mammography)
- breast sonography using high-frequency probes (7.5–10 MHz)
- interventional methods such as core biopsy and vacuum-assisted biopsy
- magnetic resonance imaging (MRI) with the administration of contrast medium
- galactography
- pneumocystography, a technique that is now rarely used and has largely been replaced by high-frequency sonography
- fine-needle biopsy, a technique employed only in special individual cases (e.g. axillary lymph-node biopsy)

The above invasive and non-invasive methods make up a diagnostic arsenal which, in combination with the histological workup of the preoperative core biopsies (including immunohistochemical determination of estrogen and progesterone receptors and HER-2 status), lays the groundwork for the targeted surgical planning carried out at the pretherapeutic consultation. At this time the extent of the planned operation (taking into account the oncological safety margins), any oncoplastic procedures that may be necessary for reconstruction of the surgical defect, and the patient’s wishes, can be merged to create an overall surgical concept.

In addition to this comprehensive surgical planning at an early date, the introduction of sentinel node biopsy, in particular, has resulted in advances in the operative therapy of primary breast cancer. The practice of limiting conventional axillary lymph-node dissection to cases
with clinically or sonographically demonstrated axillary involvement means that nearly 60% of our patients now undergo distinctly less radical surgery in the axilla and experience a marked reduction of short-term and long-term morbidity. The surgical standard has changed substantially in this area.

The same applies to the surgical techniques used for oncoplastic reconstruction. The increased use of intramammary reconstruction procedures including the use of the glandular rotation-flap technique to prevent larger tissue defects and of local flap techniques to cover defects – in particular the use of thoracoepigastric sliding flaps or latissimus dorsi flaps with and without skin islands – today make breast conservation possible even in cases where major tissue resection has been carried out. This approach achieves acceptable cosmetic results and restored physical integrity while maintaining a maximum degree of oncological safety.

The diagnostic and surgical advances in the treatment of primary breast cancer are supplemented by the successes achieved by primary systemic therapy. In this context the use of chemotherapy has led to impressive rates of histopathologically demonstrated complete remission in patients with receptor-negative tumors. With the help of this primary systemic therapy breast carcinomas previously considered inoperable can now be treated surgically and the percentage of patients treated with breast-conserving operations can be raised.

Postoperative radiotherapy leads to improved local tumor control: metaanalyses have shown that it also results in a relevant reduction of mortality. The effects are independent of the patient’s age. This is true both of percutaneous radiotherapy administered after breast-conserving surgery and after mastectomy. The effects of radiotherapy on regional lymph drainage have not yet been definitively explored.

Adjuvant systemic therapy has been assigned a new role – especially after the Consensus Meetings in 2005 and 2007 in St. Gallen, Switzerland – as a result of the renaissance of adjuvant endocrine therapy for postmenopausal women with receptor-positive tumors. For postmenopausal patients with tumors that respond to endocrine therapy, in particular, promising results have been achieved with the administration of aromatase inhibitors as an upfront therapy, as a sequential therapy (i.e. a switch to aromatase inhibitors following an abridged tamoxifen therapy of 2–3 years and a total therapy duration of 5 years), and as extended adjuvant therapy following regular 5-year tamoxifen therapy.

The data available to date from large multicenter prospective randomized studies must be substantiated by long-term therapeutic results. This is necessary, in particular, to obtain a better picture of the as yet unidentified late sequelae of long-term treatment with aromatase inhibitors.

With respect to adjuvant systemic chemotherapy as well, the optimal use of taxanes or of dense-dose and dose-intensified chemotherapy is expected to result in further therapeutic success over the short-term and medium-term. The results achieved with adjuvant therapy with trastuzumab (Herceptin®) have attracted special attention. Two international and two U.S. studies revealed a significant prolongation of the recurrence-free period and a lower rate of metastases – as well as improved overall survival – in patients who received this antibody.

On the whole the doctors treating patients with breast cancer now have recourse to a large arsenal of diagnostic and therapeutic modalities. Treating our patients in accordance with the recommendations contained in these Guidelines will undoubtedly play a decisive role in achiev-
ing improved overall results. Under-treatment or over-treatment, i.e. therapy that does not conform to the Guidelines, results in poorer outcomes as measured by disease-free survival and overall survival.
B 2 Pretherapeutic Diagnostic Measures to Assess the Spread of Cancer in Symptomatic Patients

B 2.1 Basic diagnostic measures

An algorithm for the early detection of breast cancer in symptomatic patients with breast findings is provided in Annex 1.

Statement Stag-1: Basic diagnostic measures

<table>
<thead>
<tr>
<th>The following examinations are considered essential elements of a basic diagnostic workup:</th>
</tr>
</thead>
<tbody>
<tr>
<td>– clinical examination of the breast: inspection and palpation of both breasts and the efferent lymphatic system</td>
</tr>
<tr>
<td>– mammography</td>
</tr>
<tr>
<td>– diagnostic ultrasound</td>
</tr>
</tbody>
</table>

If the clinical breast examination produces abnormal findings, diagnostic imaging and histological examination should be performed to complete the diagnostic workup.

**Grade of Recommendation A** (Calman, K et al. 2002; NBCC 2001; NBCC 2006a; NBCC 2006b; NCCN 2007; SIGN 2005)

For the investigation of symptomatic findings in women under age 40, sonography is the imaging method of first choice.

**LOE 3b, Grade of Recommendation A** (Nothacker, M et al. 2007)

The effects of endogenous and exogenous hormones are to be taken into account during the performance and interpretation of diagnostic procedures.

**LOE 2b, Grade of Recommendation B** (Calman, K et al. 2002; NBCC 2006b; NHMRC 2004; Schulz, KD et al. 2003)

The *Stage 3 Guidelines on Early Breast Cancer Detection in Germany 2008* should be consulted when determining the steps in, and documentation of, the clinical breast examination (Albert, US et al. 2008).
B 2.2 Imaging methods

Statement Stag-2: Mammography

At present mammography is the only method generally recognized to be effective for the detection of precursor or early stages of breast cancer.

**LOE 1a, Grade of Recommendation A** (Calman, K et al. 2002; NBCC 2006a; NCCN 2006; NCCN 2007; SIGN 2005)

High mammographic density (ACR 3 and 4) is, next to the BRCA1/2 mutation, the highest-ranking individual risk factor; consequently, the limited sensitivity of mammography in this situation should be countered by performing sonography as a supplementary study.

**LOE 3b, Grade of Recommendation B** (Nothacker, M et al. 2007)

Statement Stag-3: Sonography

Sonography is a supplementary study performed to investigate indeterminate lesions.

**Grade of Recommendation A** (Calman, K et al. 2002; NBCC 2006a; NBCC 2006b; NCCN 2007; Schulz, KD et al. 2003; SIGN 2005)

Sonography should be used to investigate clinically non-palpable mammographic lesions with the classifications BI-RADS 0, III, IV and V.

**LOE 2b, Grade of Recommendation B** (Nothacker, M et al. 2007)

The aim of standardized breast sonography is the systematic and reproducible examination of both breasts and the axilla.

**LOE 2b, Grade of Recommendation B** (Madjar, H et al. 2006; NCCN 2007; Schulz, KD et al. 2003)

Structural and process quality, as well as quality of outcomes, should also be demonstrated as a prerequisite for the use of breast sonography.

**GCP** (DEGUM 2006)

Statement Stag-4: MRI with Contrast Medium

An MRI scan with contrast medium (CM-MRI) should be recommended preoperatively for the local staging (excision margins) of lobular breast carcinoma.

**LOE 3b, Grade of Recommendation B** (Schwartz, GF et al. 2006)

To realize the benefits associated with this recommendation, strict coupling of CM-MRI and the possibility of performing MRI-guided interventions should be assured.

For other indications (e.g. multicentricity, occult breast carcinoma, etc.), CM-MRI should be performed only if there are possibilities for MRI-guided interventions.

**GCP**

The quality requirements for the structural, process and outcome quality of the various imaging methods (e.g. mammography, sonography, magnetic resonance imaging) are set down in the *Stage 3 Guidelines for Early Breast Cancer Detection in Germany 2008* (cf. www.awmf-leitlinien.de, www.degum.de and www.ibus.org – guidelines for systematic examination,

### B 2.3 Diagnostic confirmation

#### Statement Stag-5: Imaging-guided minimally invasive biopsy

The histological diagnostic investigation of unclear findings should be carried out via core biopsy, vacuum-assisted biopsy or open biopsy. Percutaneous interventions should be carried out in accordance with the quality recommendations.

**LOE 3a, Grade of Recommendation A** (NCCN 2007; NICE 2006a; Perry N, et al. 2006; Schulz, KD et al. 2003)

Fine-needle biopsy should not be employed as the standard biopsy method.

**LOE 2b, Grade of Recommendation A** (NCCN 2007; NICE 2006a; Schulz, KD et al. 2003)

Intervention-guided tissue biopsy for histopathological confirmation of the diagnosis and for therapeutic planning should be performed in patients with the following findings: mammographic classification BI-RADS IV and V and/or sonographic classification US-BI-RADS IV or V and/or MRI classification MRT-BI-RADS IV or V.

**LOE 3a, Grade of Recommendation A** (NCCN 2007; Schulz, KD et al. 2003)

During intervention-guided (preferably sonography-guided) core biopsy, ≥ 3 representative specimens should be taken at ≤ 16G.

**LOE 3b–2b, Grade of Recommendation B** (Crystal, P et al. 2004; Fishman, JE et al. 2003)

In the presence of microcalcifications, stereotactically guided vacuum-assisted biopsy should preferably be performed.

**LOE 3b–2b, Grade of Recommendation A** (Nothacker, M et al. 2007)

Vacuum-assisted biopsy should also be used for MRI-guided tissue sampling.

**GCP**

Following minimally invasive imaging-guided tissue sampling, the results should be verified by correlating the results of the imaging diagnostic studies with the histopathological findings.

**Grade of Recommendation A** (NBCC 2006a; NCCN 2007; NICE 2006b; Perry, N et al. 2006; Schulz, KD et al. 2003)

If the histopathological examination reveals a benign lesion, a follow-up imaging study should be performed with the appropriate imaging method in six months’ time.

**Grade of Recommendation B** (NCCN 2007; NICE 2006b)
Statement Stag-6: Open Excisional Biopsy

The operative quality assurance for the open diagnostic excision of screen-detected lesions should take place in conformance with the guidelines of the European Commission. The surgical objective (diagnostic or therapeutic) should be defined in a non-ambiguous manner.

**Grade of Recommendation A** (O’Higgins, N et al. 2006; Schulz, KD et al. 2003)

During the preoperative wire marking of non-palpable lesions, the wire should penetrate the focal lesion and project beyond the lesion by less than 1 cm. In cases where the wire does not penetrate the focal lesion, the distance between the wire and the margin of the lesion should be ≤ 1 cm. In non-space-occupying processes, marking of the surgically relevant target volume may be useful.

**LOE 3b, Grade of Recommendation A** (O’Higgins, N et al. 2006; Schulz, KD et al. 2003)

In the case of non-palpable changes, it is always important to perform preoperative marking and to demonstrate adequate resection via imaging methods.

**LOE 3b, Grade of Recommendation A** (NBCC 2001; O’Higgins, N et al. 2006; Schulz, KD et al. 2003)

The material collected during the operation should be clearly marked and sent to the pathologists without any incision of the tissue material obtained.

**Grade of Recommendation A** (Carlson, RW et al. 2006; Perry N, et al. 2006; Schulz, KD et al. 2003)

Intraoperative determination of malignancy by frozen section should be the exception. Frozen section of breast specimens can be performed in cases satisfying the following criteria:
- The lesion is palpable intraoperatively and in the specimen.
- The lesion is large enough (in general > 10 mm).

**Grade of Recommendation A** (O’Higgins, N et al. 2006; Schulz, KD et al. 2003)

The quality requirements for the structural, process and outcome quality of the various diagnostic methods (e.g. imaging-guided core and vacuum-assisted biopsies, open excisional biopsy) are set down in the *Stage 3 Guidelines for Early Breast Cancer Detection in Germany 2008* (Albert US et al. 2008) (Cf. AWMF Reg. No. 077/001; www.awmf-leitlinien.de).

B 2.4 Staging

Statement Stag-7

In patients with locally advanced carcinomas and in cases where metastasis is suspected, the following individual studies should be performed for staging prior to the institution of treatment:
- chest x-ray
- ultrasound examination of the liver
- bone scan

**LOE 5, Grade of Recommendation B** (Alderson, PO et al. 1983; Crump, M et al. 1996)
All patients with breast cancer should receive a complete physical examination and undergo clinical classification according to the TNM system developed by the International Union Against Cancer (IUCC). Mammographic examination of the contralateral breast is mandatory. In patients with locally advanced disease, in particular, the signs of local tumor growth must be described precisely (e.g. inflammatory component, ulceration, satellite metastases, involvement of the thoracic wall, etc.). In patients with primary breast carcinoma, it is recommended that staging studies undertaken to evaluate any metastatic disease should be performed before starting systemic primary treatment (Harder F et al. 1997).

The following studies are suitable for staging:
- blood count
- chest x-ray
- ultrasound examination of the liver
- bone scan

As a rule these apparative studies can be useful for determining the baseline situation in patients with confirmed invasive carcinoma; however, they are generally not indicated for patients with pT1pN0 tumors.

Tumor marker assays are not necessary (ASCO 1998).

**Literature**


Harder F, Zuber M, Oertli D. Apparative Diagnostik zur Therapieentscheidung - was ist möglich und wünschenswert, was unverzichtbar und was überflüssig - in der Mammachirurgie. (Kongressbericht 1997). Langenbecks Arch Chir 1997; (suppl II:391-393.

NHMRC. Clinical practice guidelines for the management and support of younger women with breast cancer. NBCC, NHMRC, National Health and Medical Research Council, Camperdown, NSW, Australia. 2004.
NICE. Breast Cancer: Diagnosis and Treatment. NICE (http://www.nice.org.uk), UK. 2006a.
NICE. Image-guided vacuum-assisted excision biopsy of benign breast lesions. NICE (http://www.nice.org.uk/IPG156), UK. 2006b.
B 3  Preinvasive Lesions

B 3.1  Preliminary remark

As a result of the improved diagnostic methods and the introduction of the Mammographic Screening Program in Germany, there is also increased detection of benign and preinvasive lesions of the breast accompanied by microcalcifications or architectural abnormalities. The data position on the potential of these lesions to become malignant or on the risk of progression is very heterogeneous. As the result, the basis for therapeutic decisions or further management is not always supported by a high degree of scientific evidence. For this reason it is all the more important that decisions on further treatment or follow-up should be made on an individual basis at an interdisciplinary tumor conference; the procedures followed here should be identical to those for patients with invasive breast carcinoma.

The list of benign or preinvasive lesions which are either associated with an elevated risk of cancer or should be viewed as precancerous according to the strict definition of the term includes: usual (intra)ductal hyperplasia (UDH), atypical (intra)ductal hyperplasia (ADH), ductal carcinoma in situ (DCIS), and lobular neoplasia (LN – formerly atypical lobular hyperplasia and lobular carcinoma in situ). (For details on classification, cf. Pathology)

B 3.2  Risk of developing breast cancer

The risk of developing breast cancer for a woman with a previously diagnosed preinvasive lesion depends on the presence of atypia or the type of in situ lesion (Hartmann, LC et al. 2005; Singletary, SE et al. 2002).

Lobular neoplasia (LN) is now viewed as a risk marker and not as a true precancerous lesion (Lakhani, SR 2003). The special feature of LN is its frequent multicentric (46–85%) and bilateral occurrence (30–67%) (Lakhani, SR 2003). Accordingly, the risk of developing breast cancer is elevated in both the ipsilateral and contralateral breast. Following mean observation periods of at least 14 years, cancer subsequently developed in the ipsilateral and contralateral breast in 14–23% and 9–19%, respectively, of patients (Page, DL et al. 2003).

In particular in women with additional risk factors, such as young age and a familial predisposition, UDH and ADH are associated with an increased probability of developing breast cancer. Because UDH of itself raises the risk by only a factor of 1.5, it is currently not viewed as a significant risk factor or precursor lesion. ADH, in contrast, is deemed a potential precursor lesion since it results in a 4–5-fold higher risk of developing breast cancer (Hartmann, LC et al. 2005).

DCIS is a precancerous condition (Burstein, HJ et al. 2004). Women with untreated DCIS have a 30–50% risk of subsequently developing invasive carcinoma (Lebeau, A 2006). The nuclear
grade, architecture, size and distribution pattern of the DCIS, the presence or absence of necrosis, and the resection margin status (including safety distances) are decisive factors for the prognosis regarding the development of secondary invasive breast carcinoma and for treatment planning (Lagios, MD 2002).

Knowledge concerning the risk of breast cancer developing in the natural course of the preinvasive lesion is important, in particular, when counseling patients seeking advice and during interdisciplinary treatment planning. LN should be viewed in this context as a risk marker for both the ipsilateral and contralateral breast. DCIS, in contrast, is a genuine risk factor only for the ipsilateral breast (Boyages, J et al. 1999; Silverstein, MJ et al. 1995). The probability of progression is higher, and the development time shorter, for high-grade DCIS. In patients with low-grade DCIS the development can extend over decades (Sanders, ME et al. 2005). At present there are no known predictors enabling us to reliably assess the risk of progression associated with DCIS.

**B 3.3 Pathomorphological examination**
(cf. also Chapter B 5 and Annex 3)

In the updated WHO classification the traditional terminology of intraductal proliferative lesions, which differentiates between usual ductal hyperplasia (UDH) and both atypical ductal hyperplasia and DCIS, was not replaced by the term “ductal intraepithelial neoplasia” (DIN) (Tavassoli, FA 2005). Nevertheless, the DIN classification can be used optionally in addition to the traditional terminology (DIN grade 1A: flat epithelial atypia; DIN grade 1B: ADH; DIN grade 1C: DCIS grade 1; DIN grade 2: DCIS grade 2; DIN grade 3: DCIS grade 3) (Bani MR 2006; Bani MR et al. 2006).

In accordance with the current WHO classification, the term “lobular neoplasia” (LN) covers the groups of lesions which were previously designated as “atypical lobular hyperplasia” or “lobular carcinoma in situ.”

If the changes described above are demonstrated in a core biopsy or vacuum-assisted biopsy as part of the mammographic screening process, they are also classified according to the B-classification of the National Coordinating Group for Breast Screening Pathology (NHSBSP), Great Britain (Maxwell, AJ et al. 2001; NHSBSP 2001), and the E. C. Working Group on Breast Screening Pathology (EC Working Group on Breast Screening Pathology 2001). Assignment to the categories B2–B5 is made on the basis of the underlying lesion (cf. also Table 1 and Pathology).

<table>
<thead>
<tr>
<th><strong>Table I. B-Classification (NHSBSP).</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>B2</td>
</tr>
<tr>
<td>B3</td>
</tr>
<tr>
<td>B4</td>
</tr>
<tr>
<td>B5</td>
</tr>
</tbody>
</table>

Changes which cannot be clearly identified as either lobular neoplasia or DCIS are classified as B4 or B5.
The distribution pattern displayed by these precancerous lesions is of great importance for the surgical procedure. The study performed by Faverly et al. (Faverly, DR et al. 1994) in which the distribution and/or growth pattern of intraductal carcinomas was reconstructed in 3D showed that DCIS is usually monocentric (i.e. in more than 90% of cases) but also frequently displays a multifocal discontinuous growth pattern. A multicentric distribution, which is defined as a distance of at least 4 cm between two foci, was observed in only one out of 60 cases. However, 30 cases of intraductal carcinoma (50%) exhibited discontinuous growth. A multifocal distribution was found in the majority (70%) of the cases of low-grade highly differentiated DCIS. High-grade DCIS, in contrast, exhibited a continuous growth pattern in nearly all (90%) cases. Intermediate-grade DCIS displayed no preference with respect to growth pattern.

In 19 (63%) of the 30 cases of DCIS with discontinuous growth, the distance between foci was less than 5 mm. In 25 (83%) of the 30 cases, the distance between foci was less than 1 cm. Altogether a gap between foci exceeding 1 cm was found in only 8% (5 out of 60) of all cases of DCIS examined.

If we extrapolate these results to the evaluation of resection margins, it follows that the determination of resection margin status will theoretically be more reliable for high-grade than for low-grade DCIS. However, the probability of an excision margin being placed exactly between two foci, thus creating a false impression of complete removal of the lesion, is low. This is because the tumor foci are generally uniformly distributed with narrow gaps between any two foci. Nevertheless, these observations provide an explanation for those cases in which a recurrence takes place within a short time even though the resection margins were reported to be clear. In cases with a safety distance greater than 1 mm, tumor residues are still found in 43% of the subsequently resected specimens and secondary mastectomy specimens. The 3-dimensional extent of DCIS within the milk duct system can only be visualized in an approximate manner by embedding the tissue and preparing 2-dimensional tissue sections. Even with meticulous and complete embedding of DCIS along with the corresponding resection margins, the tissue will usually be examined only at intervals of approx. 2–3 mm in the tissue sections; in individual cases, a positive resection margin can be overlooked during the histological evaluation. The probability of finding a positive resection margin is increased by 30–50% when complete tissue embedding is carried out in comparison with random tissue sampling. Differences in the type of tissue preparation exert a significant effect on the results over the course of the disease in patients with DCIS who have received breast-conserving therapy (Page, DL et al. 1995; Sahoo, S et al. 2005).

### B 3.4 Prevention

The prevention of invasive breast carcinoma comprises both primary and secondary prevention. Primary prevention encompasses pharmacotherapeutic prevention for women with a low or medium risk, and surgical prevention for women with a high-risk, of developing the disease (cf. Familial Breast Cancer).

The studies on the drug prophylaxis of breast cancer were not primarily aimed at the end point of reduction of preinvasive lesions but rather at a possible reduction of the number of cases of invasive breast carcinoma (Cuzick, J et al. 2003; Fisher, B et al. 2001b). These data are valid for postmenopausal women; there are no data for premenopausal women. Nevertheless, the
studies carried out on the use of tamoxifen to prevent breast cancer showed that tamoxifen treatment also significantly reduced the incidence of preinvasive lesions including DCIS (Cuzick, J et al. 2003). This preventive advantage was not shown for raloxifen (MORE Study: Raloxifen versus Placebo; STAR Study: Raloxifen versus Tamoxifen). There are currently no published data from prospective randomized studies on DCIS prevention.

**B 3.5 Therapeutic decisions and options**

Local treatment strategies are available for benign lesions and lesions suggestive of malignancy.

The optimal local therapeutic strategy for DCIS has still not been adequately defined because of DCIS's biological heterogeneity and the unsatisfactory data position.

**Statement DCIS-1**

In cases where a potential precursor lesion or preinvasive lesion is suspected on the basis of the radiological studies or has been demonstrated by core biopsy or vacuum-assisted biopsy, the therapeutic strategy should be elaborated by an interdisciplinary team consisting of a specialist in diagnostic radiology, a surgeon and if necessary a pathologist.

GCP

The therapeutic decision or recommendation should be made at an interdisciplinary tumor conference. The radiological extent of the excised lesions, the histopathological data and information from the history, as well as the patient's personal preferences, should serve as the basis for making a decision on further treatment or follow-up (Albert, US et al. 2007).

The therapeutic options comprise therapeutic excision following interventional radiological diagnostics, therapeutic repeat resection subsequent to open diagnostic excision, postoperative radiotherapy and pharmacotherapy. The surgical options include breast-conserving procedures and mastectomy, if necessary in combination with sentinel node biopsy and primary or secondary plastic reconstructive procedures.

Radiotherapy is administered only in connection with breast-conserving procedures or in the (very rare) cases of R1 resection after mastectomy in which repeat resection cannot be performed.

Adjuvant drug therapy, if performed, should be carried out in the form of endocrine therapy with the anti-estrogen agent tamoxifen (Fisher, B et al. 1999; Fisher, B et al 2001a).

Sufficient data are not available to support the use of GnRH analogs in premenopausal women, the use of aromatase inhibitors in postmenopausal women, or the use of chemotherapy or immune therapy.
When making a therapeutic decision or recommendation, the physician should present in detail the advantages and disadvantages of the individual methods and of combinations of these methods. In particular, the difference between a local non-invasive recurrence and local invasive carcinoma, possible metastasis, and the effect of various therapeutic modalities on overall survival and possible subsequent therapies, must be explained in detail to the patient to enable her to make an independent decision when selecting the initial therapy from among the various therapeutic options available.

**Statement DCIS-2**

<table>
<thead>
<tr>
<th>An individualized treatment strategy should be elaborated for and offered to every patient with ductal carcinoma in situ (DCIS). The patient must be briefed on the arguments for and against the particular therapies and combinations of these therapies (including possible adverse reactions), possible subsequent therapies, the effect of each therapeutic option on the frequency of recurrence, and the absence of an effect on the probability of survival (Houghton, J et al. 2003).</th>
</tr>
</thead>
</table>

**GCP**

Histopathological studies on the growth pattern of DCIS show that DCIS is usually a monocentric, potentially multifocal lesion which can theoretically be removed by surgery alone. This would require performance of a targeted (i.e. segmental) therapeutic surgical procedure with sufficiently wide resection margins (MacDonald, HR et al. 2006; Solin, LJ 2006).

The presently available prospective randomized studies on the value of radiotherapy for patients with DCIS (Bijker, N et al. 2006; Clarke, M et al. 2005; Emdin, SO et al. 2006; Fisher, B et al. 1998; Julien, JP et al. 2000) undergoing breast-conserving surgery have not demanded adherence to the elaborate diagnostic-therapeutic algorithm (high-resolution target radiograph, measurement of the precise histologically determined extent of the DCIS (not only the mammographically determined extent), segmental operation, complete embedding of the DCIS with meticulous examination of the resection margins) that would have been required in order to achieve targeted and as complete as possible removal of the DCIS lesion.

The same applies to the previously published studies on treatment of DCIS by surgery alone (Wong, JS et al. 2006). It has thus not been possible to date to identify any groups of women with DCIS whose risk of recurrence is so low that postoperative RT can be dispensed with following treatment by excisional biopsy alone.

One retrospective analysis (MacDonald, HR et al. 2005) showed that, if an adequate chain of diagnostic and therapeutic modalities is in place, a local recurrence rate of 4.6 % can be achieved over a follow-up period of 57 months. This is lower than the recurrence rate recorded for patients who received BCT with radiotherapy.

Since no prospective randomized studies have been published to date which have systematically transferred the knowledge gained during histopathological basic research to clinical trials, DCIS can be treated with surgery alone only in isolated cases and/or after a comprehensive briefing of the patient or under study conditions.
B 3.6 Therapeutic methods

B 3.6.1 Surgery

Most preinvasive lesions are not detected by palpation. Diagnostic exploration is usually carried out by mammographically-guided interventional procedures (i.e. stereotactically guided core or vacuum-assisted biopsy) (Silverstein, MJ et al. 2005). In exceptional cases (e.g. unfavorable position of the lesion, technically difficult access), an open diagnostic excision can be performed following wire marking and with intraoperative specimen radiography. In the case of interventional procedures the correlation between the screen-detected lesion and the histopathological findings should be checked.

In cases where there is a favorable relationship between breast size and extent of lesion, a breast-conserving procedure with segmental resection can be performed as a therapeutic excision (Solin, LJ 2006; Wong, JS et al. 2006). Precise 3-dimensional marking of the specimen and specimen radiography should be performed intraoperatively; the site of the specimen should be marked preoperatively.

If there is an unfavorable relationship between breast size and size of lesion, or the patient requests, mastectomy (including removal of the mammilla-areola complex) should be performed.

The histological demonstration of ADH in a core biopsy or vacuum-assisted biopsy is generally an indication for surgery (open diagnostic excision).

The diagnosis of classic LN in the core biopsy or vacuum-assisted biopsy is usually an incidental finding and does not mandate surgery if histopathological examination of the core biopsy reveals a different type of lesion that explains the imaging findings. If no histopathological correlate is found that explains the lesion seen in the imaging studies, a repeat core biopsy (ideally a vacuum-assisted biopsy) or a diagnostic excisional biopsy must be performed in the presence of LICS (LIN). The demonstration of LN in a surgical specimen is generally not an indication for further excision. According to the current WHO classification (2003), massive widening of the acinus or the demonstration of pleomorphic, signet-ring cell variants or necrotic variants of the LN directly on or near the resection margin constitute exceptions to this rule.

In patients with DCIS, factors such as young age (< 45 years), positive resection margins or margins close to the tumor (not ventrally or dorsally), positive amputation margins and higher-grade lesions are associated with a significantly higher rate of recurrence (Bijker, N et al. 2001; Bijker, N et al. 2002; Chan, KC et al. 2001; Lebeau, A 2006; Vargas, C et al. 2005). If these factors are present, a more far-reaching surgical method (e.g. repeat resection or mastectomy) must be discussed; radiotherapy is mandatory in these cases.

In patients with DCIS, axillary staging is frequently performed without any malignant cells being demonstrated in the excised lymph nodes (BQS data).
Statement DCIS-3

Axillary staging (sentinel node biopsy or axillary dissection) is generally not indicated for patients with DCIS.

GCP

Sentinel lymph node biopsy is indicated if mastectomy was performed because of an extensive primary lesion or if occult invasion is suspected or has been demonstrated.

B 3.6.2 Radiotherapy

Statement DCIS-4

Postoperative radiotherapy after breast-conserving surgery for DCIS lowers the rate of invasive and non-invasive local recurrences.

**LOE 1a** (Bijker, N et al. 2006; Clarke, M et al. 2005; Cutuli, B et al. 2002)

There is evidence that the effect of radiotherapy depends on individual factors such as patient age, extent of tumor, grading, surgical procedure and resection status.

GCP

Adjuvant radiotherapy is not indicated in patients with ADH or LN.

Adjuvant percutaneous irradiation of the entire remaining breast is indicated after breast-conserving surgery with R0 resection or after R1 resection in cases where repeat resection after mastectomy is not an option (Organgruppe Mammakarzinom der DEGRO 2006).

Radiotherapy significantly lowers the rate of non-invasive in-breast recurrences and invasive breast carcinoma following standard surgical procedures (Bijker, N et al. 2006; Clarke, M et al. 2005; Cutuli, B et al. 2002).

Adjuvant radiotherapy has no effect on overall survival.

The heterogeneous study results on the value of radiotherapy for patients with DCIS who receive breast-conserving treatment indicate that younger women, women with high-risk lesions, and women with narrow resection margins (< 1 cm) derive the most benefit from adjuvant radiotherapy (Vargas, C et al. 2005).

With advancing patient age an increasingly critical attitude should be taken toward radiotherapy because of the lack of an effect on overall survival and the decreasing benefits.

For all other constellations, the indication for radiotherapy, in combination with an additional anti-hormonal therapy if appropriate, should be critically evaluated during the discussion with the patient.
B 3.6.3 Drug therapy

On the subject of adjuvant drug therapy, data are available on the use of tamoxifen (Fisher, B et al. 1999; Fisher, B et al. 2001b; Houghton, J et al. 2003). No data are available on the effect of aromatase inhibitors.

For patients with ADH or LH no recommendation can be made at present on adjuvant drug therapy.

Two prospective randomized studies have been published on the use of tamoxifen and radiotherapy after breast-conserving treatment for DCIS. In the NSABP-B-24 study (Fisher, B et al. 1999; Fisher, B et al. 2001b), patients were accepted independently of the status of the excision margins (i.e. patients with R0 and R1 status were enrolled). In this study a reduction of both ipsilateral and contralateral invasive carcinoma was achieved by the administration of tamoxifen in combination with radiotherapy. In the four-arm English-Australian-New Zealand study (Houghton, J et al. 2003), patients were examined who displayed a clear excision margin of at least 1 mm. In this study the administration of tamoxifen brought about a reduction of ipsilateral preinvasive recurrences but not of ipsilateral or contralateral invasive recurrences. After weighing the positive effects and side effects (e.g. thrombosis, embolism, endometrial carcinoma), the authors do not see any indication for the routine use of tamoxifen in patients who have received BCT for DCIS. Since the guideline-conforming treatment of DCIS pursuant to the present S3 Guidelines foresees an R0 status with a clear excision margin of 5 mm, the employment of tamoxifen should be carefully weighed in each individual case. Since both randomized studies showed a strong correlation between recurrence and both grading and patient age, the use of tamoxifen can be recommended – following consideration of the features of the individual case – in patients meeting all of the following criteria: age < 50, G3 and insufficient resection margins.

B 3.7 Treatment, support and continuing care

During the subsequent treatment, support and continuing care, a mammogram and manual breast examination should be performed every six months during the first five years – in particular in women who have received no adjuvant therapy (e.g. radiotherapy, drug therapy). Any changes detected by radiodiagnostic methods should be investigated by core biopsy or surgery.

Locoregional changes (e.g. fibrosis, edema and circumscribed dysesthesia) should be treated.

B 3.8 Preinvasive recurrence or invasive breast carcinoma

Non-invasive recurrences and invasive breast carcinoma can occur after the diagnosis of a preinvasive lesion as well as after the occurrence of DCIS treated by surgery alone or by a combination treatment. In this context no distinction can be made in the individual case between an in-breast recurrence and the metachronous development of a new carcinoma.

If ADH or LN is diagnosed again in the breast that was previously operated on, a breast-conserving procedure can again be carried out if breast volume is sufficient.
In patients with recurrent DCIS, the therapeutic decision should take account of the type of treatment that was previously administered.

In patients previously treated by surgery alone, renewed breast-conserving therapy together with additional adjuvant radiotherapy can be discussed if there is an adequate correlation between the extent of the recurrent lesion or invasive breast cancer and the size of the breast.

Following a previous operation and irradiation, mastectomy is indicated.

Drug therapy should be discussed if it has not been employed already during the primary therapy.

Literature


Bani MR. Gutartige und präinvasive Läsionen der Brust. Teil 2. Geburtsh Frauenheilk 2006; 2006;R147-R162.


B 4 Surgical Treatment of Invasive Breast Cancer

B 4.1 General recommendation

Statement Gen-1

<table>
<thead>
<tr>
<th>Excision of the tumor with a negative resection margin (R0) is the basis of therapy for all non-advanced breast carcinomas.</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOE 1b, Grade of Recommendation A (Blichert-Toft, M et al. 1998; Renton, SC et al. 1996)</td>
</tr>
</tbody>
</table>

Statement Gen-2

<table>
<thead>
<tr>
<th>The microscopically measured safety distance between the tumor and the resection margin should be 1 mm or more for invasive carcinoma.</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCP (NHMRC 2001; NHSBSP et al. 2003; O’Higgins, N et al. 1998; O’Higgins, N et al. 2006)</td>
</tr>
</tbody>
</table>

Statement Gen-3

<table>
<thead>
<tr>
<th>The microscopically measured safety distance between the tumor and the resection margin should be 5 mm or more for intraductal carcinoma (DCIS).</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCP</td>
</tr>
</tbody>
</table>

Complete removal of the tumor minimizes the risk of local recurrence. In line with various international guidelines, complete removal of the tumor calls for histologically negative resection margins with a border of normal breast tissue surrounding the primary tumor (NHMRC 2001; NHSBSP et al. 2003; O’Higgins, N et al. 1998; O’Higgins, N et al. 2006. The background to this demand is the effect of involvement of the resection margin on the rate of local recurrence. Differences in local treatment, which considerably influence the rate of local recurrence, can significantly lower the 15-year overall mortality (EBCTCG 2005). However, there is still a lack of clear-cut data indicating what safety margins are necessary in the case of invasive and intraductal carcinoma to ensure complete removal. Until such time as reliable data are available, it is recommended that a safety margin of 1 mm for invasive carcinoma and of 5 mm for DCIS should be used as a general standard with the aim of quality assurance of the surgical procedure.
In the case of invasive carcinoma the presence of an intraductal component can increase the risk of local recurrence if the associated DCIS is extensive and goes beyond the limits of the invasive tumor (Freedman, GM et al. 2002; Schnitt, SJ et al. 1984; Smitt, MC 2004). This is because of the increased likelihood that the tumor has not been completely removed. Therefore, in the case of invasive carcinoma with extensive intraductal component (EIC (Schnitt, SJ et al., 1994)); see Chapter B 5.2. for definition) it would appear advisable to maintain a minimum safety distance of 5 mm for the intraductal component, even though there are no unequivocal data to support this.

The topography should also be taken into account when considering the acceptable safety distances. If a segmental resection has been performed to the level of the pectoral fascia a safety margin in the direction of the fascia of less than 1 mm or 5 mm, respectively, is also acceptable provided that the resection margin is microscopically negative (R0).

Thus it is an essential prerequisite for breast-conserving therapy to specify the macroscopic and microscopic status of the resection margin as well as the minimum safety distance taking into account the topographic orientation and the tumor type (DCIS or invasive).

**B 4.2 Breast-conserving treatment**

Randomized clinical studies have shown that, if certain clinical and histological parameters are taken into consideration, breast-conserving treatment achieves survival rates identical to those of mastectomy. Patients whose findings make them eligible for breast-conserving treatment must be informed of this option (Antoniades J et al. 1993; van Dongen, JA et al. 1992; van Dongen, JA et al. 2000).

**Statement Gen-4**

| The objective of surgical treatment is removal of the tumor. Breast-conserving therapy (BCT) with subsequent radiotherapy is equal, with respect to survival, to modified radical mastectomy (MRM) alone. |
| LOE 1a (EBCTCG 1995; Fisher, B et al. 2002a; Veronesi, U et al. 2002; Wald, NJ et al. 1995; Weaver, DL et al. 2000) |
| For this reason, all patients should be briefed on the options of breast-conserving therapy (BCT) or modified radical mastectomy (MRM) with the possibility of primary or secondary reconstruction. The patient’s preference is decisive. |

**GCP**

In the normal case the following constitute indications for breast-conserving treatment of breast cancer:

- locally confined non-invasive carcinomas of the breast (DCIS, LCIS)
- invasive carcinomas with a favorable ratio of tumor size to breast volume
- invasive carcinomas with a concomitant intraductal component, provided that the resection margins are negative.
The tumor must be excised completely; the resection margins should be negative (R0) upon histopathological examination (Renton, SC et al. 1996). The microscopically measured safety distance should be more than 1 mm for the invasive and intraductal tumor components (Morrow, M et al. 1995; Schnitt, SJ et al. 1994). Breast-conserving treatment should not be administered to patients with multicentric carcinoma, inflammatory breast carcinoma or a very unfavorable ratio between tumor and breast size. Mastectomy is also indicated in cases where negative resection margins cannot be achieved despite repeated resection or when postoperative radiotherapy is technically not possible or is refused by the patient. Moreover, a preference for mastectomy expressed by the patient must be respected. When treating breast cancer patients under 40 displaying an extensive intraductal component (EIC) in addition to invasive carcinoma, it is important to bear in mind that this group has an enhanced risk of local recurrence after BCT in comparison with MRM (Jaeger K et al. 2000).

If the lesion cannot be palpated preoperatively, its location must be identified by wire marking; it can then be excised on the basis of this marking (Blamey, RW 1998; Blichert-Toft, M et al. 1998; O’Higgins, N et al. 1998). The excised piece of tissue should be examined using an imaging method compatible with the type of preoperative marking (e.g. specimen radiography) in order to verify complete removal of the lesion in concordance with the preoperative findings.

**B 4.3 Mastectomy**

**Statement Gen-5**

<table>
<thead>
<tr>
<th>The following constitute indications for modified radical mastectomy:</th>
</tr>
</thead>
<tbody>
<tr>
<td>– diffuse, extensive calcifications of the malignant type</td>
</tr>
<tr>
<td>– multicentricity</td>
</tr>
<tr>
<td>– incomplete removal of the tumor (including the intraductal component), even after repeat excision</td>
</tr>
<tr>
<td>– inflammatory carcinoma of the breast, possibly following pre-treatment</td>
</tr>
<tr>
<td>– likelihood of an unsatisfactory cosmetic result</td>
</tr>
<tr>
<td>– postoperative radiotherapy clinically contraindicated after breast-conserving treatment</td>
</tr>
<tr>
<td>– informed preference for mastectomy voiced by the patient</td>
</tr>
</tbody>
</table>

**LOE 2b, Grade of Recommendation A** (Fisher, B et al. 1994; Voogd, AC et al. 2001)

Modified radical mastectomy is performed in all cases where a breast-conserving approach according to the criteria set out above is not possible. A transverse or oblique incision is made; this incision should take account of future reconstruction possibilities. The entire breast tissue, the skin and nipple-areola complex and the pectoral fascia are removed. The pectoralis muscles are left intact.
**B 4.4 Plastic reconstructive procedures**

**Statement Gen-6**

Every patient who undergoes a breast amputation should be informed about the possibility of immediate or later breast reconstruction or of not having any reconstructive procedure performed at all; contact to a support group should also be offered.

**GCP**

Breast reconstruction appears to have no influence on the oncological course of the disease or on the detection of local recurrences (SIGN 2005). However, there are insufficient data available to allow a conclusive statement on this issue.

Plastic reconstructive procedures can be carried out at the time of primary operation or some time later. These procedures are performed to correct the breast defect and replace the missing tissue volume as well as to satisfy the patient’s wish for restoration of her physical integrity. Breast reconstruction does not appear to be associated with an increased rate of local recurrence (Vandeweyer, E et al. 2003).

The decision of whether to perform immediate breast reconstruction or plastic surgery at a later date depends on the situation of the individual patient and her particular preferences (Audretsch W et al. 1998). Immediate reconstruction may result in less emotional trauma for the patient. However, some women prefer to be given time to consider the various reconstructive options at their own pace following the diagnosis and primary treatment of the breast cancer. The question of which reconstructive measures are options in the individual case hinges on several factors; apart from the patient’s personal preferences; these include the size of the breast, the scar situation and tissue status, and whether radiotherapy is planned or has already been administered. In patients who have already received radiotherapy, preference should be given to use of autologous tissue instead of expanders or breast implants since irradiated tissue can be stretched and shaped to only a limited extent (Calabrese C et al. 2001). If a tissue expander has already been implanted prior to planned radiotherapy, the best course is to fill this expander completely and then wait and see how the tissue reacts after radiotherapy before deciding whether definitive implant insertion or flap transposition is likely to produce the better result (Bohmert H et al. 1997; Kroll SS et al. 1999; Krupp S (Ed.) 1994). It may be necessary to perform adaptive surgery on the contralateral breast in order to achieve a symmetrical appearance. The nipple is restored either by reconstruction of the nipple-areola complex or by tattooing.

Refer also to the figure showing the possibilities and indications for plastic reconstruction in Appendix 2.
B 4.5  Surgical treatment of the axilla

Statement Gen-7

Determination of the histological node status (pN status) is part of the surgical treatment of invasive breast cancer. It should be performed by means of sentinel node biopsy (SNB).

**GCP, Grade of Recommendation A** (Kuehn, T et al. 2005; Lyman, GH et al. 2005; Veronesi, U et al. 2003).

Sentinel node biopsy is equal to axillary dissection with regard to local control. **LOE 1b** (Palesty, JA et al. 2006; Smidt, ML et al. 2005; Veronesi, U et al. 2005a; Zavagno, G et al. 2005)

The morbidity after SNB is significantly reduced compared with axillary dissection. **LOE 1a** (Fleissig, A et al. 2006; Mansel, RE et al. 2006; Veronesi, U et al. 2003)

In patients in whom SNB is not possible or in whom the sentinel node is positive, axillary dissection with removal of at least 10 lymph nodes from levels I and II must be carried out.

**GCP**

Statement Gen-8

If the sentinel node is excised, the quality criteria set out by the medical associations must be satisfied.

**GCP** (Kuehn, T et al. 2005; Lyman, GH et al. 2005)

SNB is a surgical procedure designed specially for determination of the node status in breast cancer. The procedure is used to identify node-negative patients who require no further local treatment in the region of the lymph drainage areas.

Provided it is performed in a standardized and quality-assured fashion, SNB is characterized by a high staging accuracy (Bergkvist, L et al. 2001; Kim, T et al. 2006; Krag, D et al. 1998; Kuehn, T et al. 2004; Tafra, L et al. 2001) and considerably reduced shoulder morbidity (Fleissig, A et al. 2006; Veronesi, U et al. 2003). SNB is associated with reliable local control (axillary recurrences <1%) (Palesty, JA et al. 2006; Smidt, ML et al. 2005; Veronesi, U et al. 2005a; Zavagno, G et al. 2005).

Suitable patients for SNB are women with T1 and T2 tumors (Veronesi, U et al. 2003) (6). If the surgeon has sufficient experience SNB can also be performed in patients with larger tumors (Kuehn, T et al. 2005; Lyman, GH et al. 2005).

SNB is not indicated if there is clinical suspicion of advanced lymph node involvement and infiltrated lymph nodes (Kuehn, T et al. 2005; Lyman, GH et al. 2005).

Functional studies of the patterns of lymph drainage from the breast as well as initial clinical data indicate that SNB also permits reliable prediction of node status in patients with multicentric carcinomas (Borgstein, PJ et al. 2000; Ferrari, A et al. 2006; Gentilini, O et al. 2006;
Knauer, M et al. 2006; Nathanson, SD et al. 2001). Therefore SNB can also be performed in these cases, although the limited supporting evidence must be borne in mind.

SNB is not recommended after neoadjuvant chemotherapy (Bauernfeind, I et al. 2007; Kuehn, T et al. 2005; Lyman, GH et al. 2005). This applies particularly to patients who have suspicious lymph nodes before chemotherapy. Participation in clinical studies is recommended.

SNB is possible after smaller excisional biopsies (Kuehn, T et al. 2005; Lyman, GH et al. 2005). In the case of larger excisions (e.g. quadrantectomy) the results are not reliably reproducible.

In women with positive node status surgical clearance of the axillary lymph nodes is indicated. This is because of the significance of the quantitative node status for the choice of systemic therapy as well as the better local control of axillary dissection compared with radiotherapy (Goldhirsch, A et al. 2003; Louis-Sylvestre, C et al. 2004; Veronesi, U et al. 2005b). In exceptional cases (patient’s age, no relevance for choice of systemic therapy) irradiation of the axilla for local control can be discussed.

The optimal procedure in patients with a positive SN has not yet been conclusively established and is currently the subject of ongoing studies.

A decision to refrain from axillary intervention altogether may be made in exceptional circumstances (e.g. microinvasion, age) (Fisher, B et al. 2002b; Rudenstam, CM et al. 2006; Veronesi, U et al. 2005b). Axillary staging is not indicated in patients with stage M1 disease.

**Literature**


B5 Pathomorphological Examination

B 5.1 Foreword

The “Instructions on Breast Pathology” presented here are based on internationally recognized publications and protocols such as the Quality assurance guidelines for pathology of the European guidelines for quality assurance in mammography screening (Amendoeira, I 2006a; Amendoeira, I 2006b), the Guidelines for non-operative diagnostic procedures and reporting in breast cancer screening and the NHSBSP guidelines for pathology reporting in breast disease of the National Coordinating Group for Breast Screening Pathology (NHSBSP), UK (NHSBSP 2001; NHSBSP 2006), and the monograph Histopathology Reporting by D.C. Allen (Allen DC 2000) and further literature on this subject (Deutsche Krebsgesellschaft 2000; Fitzgibbons, PL et al. 2000; Fitzgibbons, PL et al. 2005; Wagner G et al. 2001).

The presentation begins with the “General Principles” which are valid for all tissue specimens. Special aspects of the examination of “Percutaneous biopsies performed within the framework of interventional diagnostics,” “Excisional biopsies,” “Mastectomy specimens” and “Axillary lymph nodes” are presented separately; these are broken down into the following topics:

– processing of specimens for macroscopic examination (“cutting to size”) with removal of tissue for histological examination
– preparation of specimens for microscopic examination (section levels, stains, special methods) and interpretation (including criteria for classification)

These instructions, which are also part of the S3 Guidelines on the Early Detection of Breast Cancer in Germany, are supplemented by the recommended classification and grading systems, special aspects of interpretation and reporting after neoadjuvant systemic therapy, and proposed standard forms, e.g. the “Pathology Request Form” and the “Pathology Reporting Form.” This information is presented in the Appendices (cf. Appendix 3 and Appendix 7).

B 5.2 General principles

Statement Patho-1: General principles for surgical specimens

Normally the material removed during the operation is to be furnished with unambiguous topographical markings and sent to the pathologist without any prior taking of specimens by the clinician, surgeon or other physician.

GCP (Amendoeira, I 2006b; Carlson, RW et al. 2006a)
Well-organized collaboration among the various disciplines involved is a vital prerequisite for effective pathomorphological diagnostics.

To make a pathomorphological diagnosis that is as precise as possible, the biopsy and surgical specimens have to meet certain requirements; these are listed below.

– The material removed during the operation is to be sent to the pathologist without any prior taking of specimens by the clinician, surgeon or other physician.

– The surgeon should attach unambiguous topographical markings to the excised tissue and/or mastectomy specimens (e.g. using different-colored suture material); the position of the markings should be noted on the Pathology Request Form accompanying the specimen (cf. Appendix: Form 1).

– Any removal of specimen material from the tumor or from other tissues (e.g. for scientific studies, tumor bank) should be carried out under the supervision of the pathologist. For this purpose the surgical specimens are to be sent to the pathologist immediately after removal and without prior fixation.

– During removal of specimen material, care must be exercised not to do anything that would impede the necessary classification of the tumor (in particular, the R classification, pTNM classification, tumor heterogeneity).

– The tissue should be fixed in 4% neutral buffered formalin. A fixation time of between 6h and 48h is recommended.

B 5.2.1 General patient data, previous findings, information from the history

The most practical way to convey the patient data, previous findings and other information to the pathologist is to use a standard form (cf. Appendix: Form 1) containing spaces for entering the following items:

– patient data (name, date of birth, sex, identification number if available)

– responsible physician

– date specimen was taken or tissue removed

– additional clinical information

– site from which the tissue specimen was taken (e.g. right breast, upper outer quadrant)

– type of tissue removal (e.g. high-speed core biopsy, modified radical mastectomy)

– clinical/mammographic findings (e.g. lesion palpable/not palpable; microcalcifications present/not present; with specimen radiograph if appropriate)

– previous findings and relevant information from the medical history

B 5.2.2 Documentation of the macroscopic processing

With respect to the documentation of the processing of specimens for macroscopic examination, please refer to the chapters on the respective types of tissue specimens.

B 5.2.3 Documentation of the microscopic processing and reporting

The following information is recorded; a standard form may be used for this purpose (cf. Appendix: Forms 2A and 2B):
- type of tissue specimen
- side
- most important pathological changes (e.g. invasive carcinoma, non-invasive carcinoma, atypical ductal hyperplasia, ductal hyperplasia, fibrocystic mastopathy, mastitis)
- carcinoma
  - histological type
  - grading (for invasive carcinomas and DCIS)
  - extent of associated intraductal carcinoma/DCIS
  - tumor size* (DCIS and invasive carcinomas)
  - (For invasive carcinomas with extensive intraductal component [cf. Extent of intraductal component for definition]: state the size of the invasive portion and additionally the size of the associated DCIS.)
- information on additional malignant foci if present (multifocality, multicentricity)*
- resection margin* (for invasive carcinomas and DCIS):
  - tumor directly on the resection margin
  - tumor not directly on the resection margin; in this case minimum distance of the tumor from the resection margin in mm together with specification of the location (specify separately for intraductal component, if appropriate)
- peritumoral vascular invasion (if visible by light microscopy)
- pTNM classification*(UICC 2002) (if necessary after evaluating additional tissue specimens)
- special supplementary studies:
  - ER / PgR status (for DCIS and invasive carcinomas)
  - HER-2 status (for invasive carcinomas)
  - other studies if appropriate (e.g. Ki-67 for invasive carcinomas)
- microcalcifications, if present: location and/or specification of association with a benign or malignant lesion
- commentary
  - correlation with results of frozen section provided intraoperatively
  - correlation with clinical/radiological findings (particularly microcalcifications: e.g. “finding compatible with” or “correlation not certain”)
  - correlation with findings from other tissue specimens and/or previous studies (when evaluating surgical specimens following percutaneous breast biopsy, it must be stated whether or not the biopsy cavity is included in the surgical specimen)

**Statement Patho-2: Histological classification of invasive carcinomas**

All invasive carcinomas are classified histologically (according to WHO 2003).


* not provided for percutaneous biopsies
Statement Patho-3: Grading of invasive carcinomas

All invasive carcinomas are to be graded according to the WHO system (Elston and Ellis modification of the Bloom and Richardson grading; Elston and Ellis 1991).


DCIS grading

In all cases of DCIS the grading must include the following parameters:

– nuclear grade according to the Consensus Conference on the Classification of DCIS, Philadelphia, 1997 (The Consensus Conference Committee 1997) (c.f. Appendix 3: Table I)
– comedo-type necrosis present/not present

The grading can currently be based on either the WHO grading system (WHO 2003) or the Van Nuys classification (Silverstein, MJ et al. 1995). There is insufficient evidence at present to permit a decision in favor of one or the other of the two grading systems as there are no published data on the prognostic relevance of the WHO grading system and the prognostic value of the Van Nuys classification has only been analyzed retrospectively (Bijker, N et al. 2001; Silverstein, MJ et al. 1995).

Extent of intraductal tumor component

If a breast-conserving procedure is planned: estimation of the proportion of intraductal tumor involvement; if appropriate, specification of an extensive intraductal component (EIC) (according to Schnitt (Schnitt, SJ et al. 1994): intraductal tumor component of at least 25% of the tumor area with extension beyond the boundaries of the invasive tumor component).

If the intraductal component extends beyond the boundaries of the invasive carcinoma: specification of the distance between the intraductal tumor component and the nearest resection margins in mm.

Multifocality/multicentricity

There are currently no internationally uniform definitions of the terms “multifocality” and “multicentricity.” The following definitions are recommended:

– Multifocality: occurrence of separate carcinoma foci in one quadrant or according to Faverly (Faverly DR et al. 1994) with a distance of less than 4 cm between the foci.
– Multicentricity: occurrence of separate carcinoma foci in more than one quadrant or according to Faverly (Faverly DR et al. 1994) with a distance of at least 4 cm between the foci.
Statement Patho-4: Hormone receptor (ER/PgR) and HER2 status of invasive carcinomas

In patients with invasive breast carcinoma the primary diagnostic procedures should include determination of the estrogen and progesterone receptor status and the HER2 status.

**LoE 2a Grade of Recommendation A** (Carlson, RW et al. 2006a; ICSI Institute for Clinical System Improvement 2005; NHMRC 2001) re hormone receptor status, (Carlson, RW et al. 2006a; ICSI Institute for Clinical System Improvement 2005; NCRI Breast Clinical Studies Group 2005; Wolff, AC et al. 2007) re HER2 status.

The estrogen and progesterone receptor status should be determined by immunohistochemistry assay, preferably in the core biopsy already. The percentages of tumor cell nuclei positive for estrogen and progesterone receptors, respectively, should be stated; this may be done by giving summation scores, in which case the procedure used should be specified (Allred (Quick) Score, Immunoreactive Score of Remmele and Stegner).

**GCP** (Goldhirsch, A et al. 2005)

HER2 positivity as precondition for trastuzumab therapy is defined as protein overexpression with a score of 3+ demonstrated by immunohistochemistry assay or gene amplification demonstrated preferably by fluorescence in situ hybridization (FISH) or chromogenic in situ hybridization (CISH).

**LoE 1b; Grade of Recommendation A** (Carlson, RW et al. 2006b; Carlson, RW et al. 2006a; Crump M 2005; NCRI Breast Clinical Studies Group. 2005; Wolff, AC et al. 2007)

The reliability of the detection method used for determination of the hormone receptor and HER2 status must be ensured. For this purpose internal test validation, the use of standardized protocols and internal controls and the regular successful participation in external quality assurance measures are necessary.

**GCP** (Carlson, RW et al. 2006b; Wolff, AC et al. 2007)

The reliability of the detection procedure used must be ensured (Carlson, RW et al. 2006b; Wolff, AC et al. 2007). It should be noted that the diagnostic equivalence of immunohistochemical HER2 determination in the core biopsy and the excised tumor has not yet been confirmed. For this reason use of the immunohistochemical HER2 status determined in the core biopsy as a decision base for trastuzumab therapy can only be recommended if it has been demonstrated for the particular institution that there is a reliable agreement between core biopsy and excision specimen with respect to negative and positive results (Kappa > 0.81 or concordance >95%). In addition, measures must be taken to ensure that artificially altered tissue (edge, retraction or crush artifacts) are excluded from the evaluation (Carlson, RW et al. 2006b; Wolff, AC et al. 2007)

The validity and reproducibility of HER2 determination is easier to ensure with standardized test kits; the use of such test kits is therefore recommended. In this case the manufacturer’s instructions must be exactly followed.

In order to ensure the reliability of the hormone receptor and HER2 determination, internal test validation, the use of standardized protocols and internal controls and the regular successful participation in quality assurance measures (at least once a year), e.g. proficiency surveys
of the Deutsche Gesellschaft für Pathologie/ Berufsverband Deutscher Pathologen e.V. (ER, PgR, HER2) or PEER review, are expressly recommended.

**Interpretation of hormone receptor status**

The definition of cut-off values is currently under discussion. According to the St. Gallen Consensus 2005 a distinction is made between hormone-sensitive and non-hormone-sensitive breast carcinomas (Goldhirsch, A et al. 2005). However, it is not clear at present what exact cut-off value should be used to distinguish between these two categories. Tumors with a low percentage of positive tumor cell nuclei (upwards of about 1% of the tumor cells) can show a certain response to endocrine therapy (Harvey, JM et al. 1999). On the basis of empirical considerations the following classification is therefore currently recommended for ER and/or PgR (Goldhirsch, A et al. 2005):

- No response to endocrine therapy: 0 positive tumor cell nuclei
- Uncertain response to endocrine therapy: 1–9% positive tumor cell nuclei
- Responsive to endocrine therapy: >10% positive tumor cell nuclei

In addition to the percentage of positive tumor cell nuclei the internationally accepted Allred Score (Harvey, JM et al. 1999) or the immunoreactive score (IRS) of Remmele and Stegner (Remmele W et al. 1987) may also be given (cf. Appendix 3: Table IX).

**Test algorithm for interpretation of the HER2 status**

(adapted from the guidelines of the American Society of Clinical Oncology (ASCO), of the College of American Pathologists (CAP) and of the National Comprehensive Cancer Network (NCCN), USA (Carlson, RW et al. 2006a; Wolff, AC et al. 2007):

- Positive HER2 status:
  - IHC score 3+ (uniform intensive circular membrane reaction in more than 30% of the invasive tumor cells)
  - or FISH/CISH positive:
    - HER2/CEP17 ratio > 2.2
    - or average HER2 gene copy numbers > 6 per nucleus

- Borderline HER2 status:
  - IHC score 2+ (irregular or weak circular membrane reaction in more than 10% of the invasive tumor cells or strong circular membrane reaction in ≤30% of the invasive tumor cells)
  - or FISH/CISH borderline:
    - HER2/CEP17 ratio 1.8–2.2
    - or average HER2 gene copy numbers 4–6 per nucleus
  - In the case of a borderline test result further diagnostic procedures for determination of the HER2 status are necessary (see below)

- Negative HER2 status:
  - IHC score 0/1+ (no membrane reaction or weak incomplete membrane reaction)
  - or FISH/CISH negative:
    - HER2/CEP17 ratio < 1.8
    - or average HER2 gene copy numbers < 4 per nucleus
The immunohistochemical cutoff of 30% recommended in the ASCO/CAP and NCCN guidelines for the score 3+ reflects essentially an endeavor to lower the rate of false positive findings. Cases with an immunohistochemical result in the doubtful range (score 2+) require confirmation by another analytical procedure, i.e. FISH or CISH, if they are to serve as a prerequisite for trastuzumab therapy. Further analytical procedures should also be employed in the case of a FISH or CISH result in the newly introduced ‘borderline’ category (HER2/CEP17 ratio 1.8–2.2 or average number of HER2 gene copies 4–6 per nucleus), e.g. counting of further invasive tumor cells or, if appropriate, repetition of the FISH/CISH test. If the result remains unclear performance of an immunohistochemistry assay is recommended (if this has not already been done). In addition, in the case of FISH/CISH assays which only contain the HER2 probe, an additional CEP17 control can be helpful in order to rule out polysomies.

The reason for the introduction of this borderline range for FISH/CISH assays too is that its biological significance is unclear (Carlson, RW et al. 2006a; Wolff, AC et al. 2007). This is an insufficiently studied subgroup in which it is uncertain how many of the patients will profit from trastuzumab therapy. With regard to the clinical consequences it should be pointed out that according to the conventional criteria patients with a HER2/CEP17 ratio of 2.0–2.2 were classed as positive and treated with trastuzumab in the context of the adjuvant studies (Piccart-Gebhart, MJ et al. 2005; Romond, EH et al. 2005). Consequently, in the view of the authors of the ASCO/CAP guidelines the available data on the efficacy of trastuzumab in adjuvant therapy do not justify withholding the treatment from these patients even if it is not possible to give a high level of evidence for this manner of proceeding. This means in practice that in patients with a HER2/CEP17 ratio of 1/-2.2 additional cell counting or retesting may be helpful. However, if the result is then still in this range a test result with a ratio >2 should currently be regarded as positive and justifies treatment with trastuzumab. In analogy to this, a similar procedure is recommended in the case of results of 4–6 signals per nucleus on average in FISH/CISH assays without CEP17 control, in which case a cutoff of >5 copies per nucleus should be used for the final evaluation. Alternatively, additional CEP17 control can be used in order to determine the corresponding ratio.
Statement Patho-5

Documentation of the tumor characteristics and the patient’s situation are necessary in order to be able to assess the course of the disease (prognosis) and the expected effect of systemic therapies (prediction).

The following prognostic factors are to be documented:

- **pTNM status (tumor size, axillary lymph node involvement, distant metastasis)**  
  **LoE 1a, Grade of Recommendation A** (Bundred, NJ 2001; Carter, CL et al. 1989; Page, DL et al. 1992; Page, DL et al. 1998; Rosen, PP et al. 1991; Rosen, PP et al. 1993)

- **Resection margin (R classification) LoE 1b, Grade of Recommendation A** and safety distances  
  **GCP** (Bundred, NJ 2001; Kurtz, JM et al. 1989; Park, CC et al. 2000)

- **Histological type**  
  **LoE 2b, Grade of Recommendation A** (Fisher, ER et al. 1990)

- **Grading**  
  **LoE 2a, Grade of Recommendation A** (Elston, CW et al. 1991)

- **Lymphatic and vascular invasion (Lx, Vx)**  
  **LoE 1b, Grade of Recommendation B** (Colleoni, M et al. 2007; Gasparini, G et al. 1994; Goldhirsch, A et al. 2007; Kato, T et al. 2003)

- **Age**  
  **GCP**

Documentation of the following predictive factors is mandatory:

- **Estrogen/progesterone receptor status for hormone therapy**  
  **LoE 1a, Grade of Recommendation A** (Bundred, NJ 2001; EBCTCG 1992; EBCTCG 1998; Osborne, CK 1998)

- **HER2/neu status for treatment with trastuzumab**  
  **LoE 1b, Grade of Recommendation A** (Bundred, NJ 2001; Cobleigh, MA et al. 1999; Piccart-Gebhart, MJ et al. 2005; Romond, EH et al. 2005; Slamon DJ et al. 2001; Wallgren, A et al. 2003) (Nabholtz)

- **Menopausal status for use of GnRH analogs**  
  **LoE 1c, Grade of Recommendation A** (EBCTCG 2000)

In the case of node-negative breast carcinomas the invasion factors uPA and PAI-1 can provide additional prognostic information.

**LoE 1a** (Harris, L et al. 2007; Janicke F et al. 2001; Look, MP et al. 2002)

The use of gene expression analyses – PCR-based or by microarray – for evaluation of the prognosis or response to treatment (prediction) is not yet validated for routine use and can therefore not be recommended.

**LoE 5, Grade of Recommendation B** (Paik, S et al. 2004; Paik, S et al. 2006)
With the help of the invasion factors uPA/PAI-1 the risk of recurrence for patients with node negative breast cancer can be better estimated. Patients with low uPA/PAI-1 concentrations, particularly patients with an unclear risk of recurrence according to traditional criteria (G2), can be spared adjuvant chemotherapy (Harbeck, N et al. 2002; Janicke, F et al. 2001). The prognostic value of uPA and PAI-1 is only validated if determined by ELISA in tissue extracts prepared from fresh or deep-frozen tumor tissue (200-300 mg), determination in the tumor core biopsy is currently being tested. Immunohistochemical determination does not provide reliable results for methodological reasons (extracellular factors). The multiparameter gene assay Oncotype DX has been validated in several retrospective studies. It is based on the extraction of RNA fragments from paraffin-embedded material. A recurrence score is calculated which can be used to predict the risk. The method is not yet sufficiently validated and cannot therefore be recommended for routine use (Paik, S et al. 2004; Paik, S et al. 2006).

**B 5.2.4 Investigation of mammographically detected microcalcifications**
- Correlation of the histopathological findings with the imaging findings (specimen radiography required).
- In the absence of evidence of radiologically relevant microcalcifications (> 100 μm) in the initial sections: additional step sections, possibly examination under polarized light to demonstrate calcium oxalate (weddelite) or use of special stains (Kossa); if necessary radiographic examination of the paraffin blocks or the remaining, not yet embedded tissue.
- If radiologically relevant microcalcifications are detected: reporting of the localization in relation to the histopathological changes.

**B 5.2.5 Frozen section examination**

**Statement Patho-6: Frozen section examination**

<table>
<thead>
<tr>
<th>The decision as to whether a lesion is benign or malignant should only be made intraoperatively on the basis of a frozen section in exceptional cases.</th>
</tr>
</thead>
<tbody>
<tr>
<td>The following are prerequisites for intraoperative frozen section examination of breast specimens:</td>
</tr>
<tr>
<td>– The lesion must be palpable intraoperatively and in the specimen.</td>
</tr>
<tr>
<td>– The lesion must be sufficiently large (generally &gt;10 mm).</td>
</tr>
<tr>
<td><strong>GCP</strong> (Amendoeira, I 2006b; NHMRC 2001; O’Higgins, N et al. 1998)</td>
</tr>
</tbody>
</table>

A decision to perform frozen section examination should be made circumspectly and only if the results of the section would have intraoperative consequences. Frozen section examination of tissue cores obtained via interventional diagnostic procedures is not advisable.

The objective of intraoperative frozen section examination of surgical specimens from the breast is to evaluate those criteria which have a direct impact on the further surgical procedure:
- benign or malignant nature of the lesion (DCIS or invasive carcinomas)
– size and extent of the tumor (possibly identification of multiple tumor foci)
– safety distances to the resection margins (optional)

Intraoperative examination of the sentinel nodes (SN) permits axillary dissection in the same operation if the node is positive. However, in the case of a negative result it must be borne in mind that the subsequent work-up of the remaining material after formalin-fixation and paraffin-embedding results in subsequent detection of metastases in the sentinel lymph nodes in up to 21% of the cases. (Cserni, G et al. 2003) Intraoperative processing of the lymph nodes in step sections is not justified in view of the limited evaluability of frozen sections and the work involved.

As an alternative to frozen section examination, imprint cytology can also be performed for orienting examination of the SN status if the examiner has the necessary expertise (Kuehn, T et al. 2005).

The specimen material examined by frozen section should be embedded in paraffin for further examination.

**B 5.3 Percutaneous biopsies performed within the framework of interventional diagnostics**

Methods currently available for interventional diagnostics:
– high-speed core biopsy (e.g. 14 gauge)
– vacuum-assisted biopsy (Mammotome®) (e.g. 11 gauge)
– fine-needle biopsy/aspiration cytology (e.g. 21 gauge)

**B 5.3.1 Percutaneous biopsy (high-speed core biopsy, vacuum-assisted biopsy)**

Indications: confirming the diagnosis for the purpose of therapeutic planning, investigation of unclear findings and findings suggestive of malignancy.

**B 5.3.1.1 Specimen processing for macroscopic examination**

Description
– High-speed core biopsy: number and total length of the biopsy cores or core portions;
  vacuum-assisted biopsy: number of biopsy cores/core portions; if appropriate, further description (color, consistency)

Tissue embedding
– Complete embedding of the submitted tissue specimens

**B 5.3.1.2 Specimen processing for microscopic examination and reporting**

Processing
– Step sections (H&E, supplementary studies if required)
– Special supplementary studies if invasive carcinoma is detected (hormone receptors; possibly HER2/neu, Ki-67).
Reporting

– The information is recorded as described in Chapter 5.2.3; a standard form may be used (cf. Appendix 3: Form 2A).

Within the framework of core biopsies seeding of benign or malignant epithelial cell aggregates into the stroma and/or the blood vessels is possible; it may be difficult in the individual case to distinguish between this seeding and genuine invasion of the stroma and/or blood vessels.

It may be necessary to call attention to the necessity for further diagnostic biopsy in the following situations:

– absence of a morphological correlate for the imaging findings
– questionable malignancy of the detected lesion (e.g. detection of atypical ductal hyperplasia (ADH) or fibroepithelial neoplasia which cannot be reliably distinguished from a fibroadenoma or phyllodes tumor).

In addition, in the context of mammographic screening the pathomorphological findings are classified on the basis of the 5 categories of the B-Classification of the National Coordinating Group for Breast Screening Pathology (NHSBSP), United Kingdom (NHSBSP 2001) and the E.C. Working Group on Breast Screening Pathology (Amendoeira, I 2006a). For a comprehensive explanation of the interpretation criteria readers should refer to the Guidelines for non-operative diagnostic procedures and reporting in breast cancer of the NHSBSP (NHSBSP 2001); these are available on the internet at the following address: http://cancerscreening.org.uk/breastscreen/publications/nhsbsp50.pdf.

Table 1. B Classification.

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>Not usable or consisting exclusively of normal tissue</td>
</tr>
<tr>
<td>B2</td>
<td>Benign e.g. fibrocystic disease, fibroadenoma, sclerosing adenosis, periductal mastitis, etc.</td>
</tr>
<tr>
<td>B3</td>
<td>Benign but with unclear biological potential e.g. atypical intraductal epithelial proliferation (e.g. atypical ductal hyperplasia: depending on the extent and degree of atypia possibly also Category B4); lobular neoplasia (LN); papillary lesions (in cases of a strong suspicion of papillary DCIS: possibly also Category B4); radial scar or complex sclerosing lesion; suspicion of phyllodes tumor.</td>
</tr>
<tr>
<td>B4</td>
<td>Suspected malignancy e.g. specimens with probably malignant changes where interpretation is limited for technical reasons; atypical intraductal epithelial proliferation depending on the extent and severity of the atypia (cf. also Category B3).</td>
</tr>
<tr>
<td>B5</td>
<td>Malignancy e.g. DCIS, invasive carcinomas, malignant lymphomas</td>
</tr>
</tbody>
</table>

B 5.3.2 Fine-needle biopsy/aspiration cytology

Not recommended in Germany for confirmation of diagnosis in the case of suspicion of breast cancer, among other things because the method does not allow a reliable distinction between non-invasive and invasive changes.
B 5.4  **Excisional biopsies**

All forms of excisional biopsies are generally treated like specimens obtained during breast-conserving surgery (unless “diagnostic excisional biopsy” has been noted on the Request Form).

Types of excisional biopsy

– Open biopsy/diagnostic excisional biopsy following preoperative localization of a nonpalpable lesion with marking wire (guidance via mammography, ultrasound or MRI);
– Tumorectomy/lumpectomy/segmental resection of a palpable lesion.

**B 5.4.1  Macroscopic specimen processing**

Description

– Total tissue specimen received
  – size (3 dimensions) and weight
  – cut open/not cut open
  – size and consistency of attached skin portions
  – markings for topographic orientation of the tissue specimen (if made by the operating surgeon)
  – location of marker wire (if used)
– Palpable tumor
  – size (3 dimensions)
  – cut surfaces: borders (distinct/blurred), consistency, color
  – correlation with marker wire and specimen X-ray if applicable
  – minimum distance to resection margin (in mm) taking account of specimen topography
  – other abnormalities

Specimen workup

– Marking of the surface of the specimen with ink, latex or other suitable material in order to evaluate the excision margins.
– Slicing of the specimen by making parallel incisions perpendicular to the longitudinal axis of the specimen from one end of the specimen to the other (slice thickness approx. 5 mm); in the case of spherical-like geometry and appropriate topographic markings, the nipple is used for orientation. (Decker, T et al. 1997)

Tissue biopsies are taken from nonpalpable lesions or palpable tumors to obtain information on:

– non-palpable lesion or palpable tumor (see below)
– resection margins
– other changes/surrounding tissue
– special questions (additional studies)
Remark

The number of tissue blocks depends on the size and nature of the submitted material, the number and size of the lesions detected by mammography and/or palpation as well as the underlying process (e.g. carcinoma that is clearly recognizable upon macroscopic examination vs. DCIS without clearly demarcated boundaries).

Nonpalpable lesions

Embedding of the entire screen-detected lesion is necessary for exact identification of the localized and marked changes, the resection margins and dense tissue outside the mammogram-detected abnormal area (low-grade DCIS in particular can be far more extensive than suggested by the radiologically visible microcalcifications). Orientation of the tissue specimens in order to reconstruct the size and topography or the lesion in relation to the resection margins if necessary; possibilities for doing this include:

– systematically placing the specimen slices on a piece of foil after slicing and then obtaining a specimen radiograph or photocopy. In the case of radiologically visible microcalcifications, performing a specimen radiograph of the tissue slices makes it possible to remove and examine the microcalcifications in such a way that the histological and radiological findings can be precisely correlated. The sites of tissue sampling are entered on the radiograph or photocopy with the corresponding block designations.

– use of previously prepared sketches for recording tissue sampling with block designations (cf. Fig. 1).

Palpable tumor

– Size of tumor is decisive for extent of embedding.

– Small carcinomas up to about 1 cm in diameter: embedding in toto.

– Larger invasive carcinomas: embedding of at least three tumor blocks or a complete tumor cross-section is desirable (cf. Fig. 2); if possible the tumor margin together with the nearest excision margin should be included in at least one block.

– Always also examine surrounding fibrous tissue that appears to be free of malignancy.

Specimen processing if DCIS is present

– Objectives: determination of size, evaluation of resection margins, exclusion of invasive growth.

– Tissue excision: procedure depends on type of lesion (nonpalpable or palpable, see above).

B 5.4.2 Microscopic specimen processing and reporting

Processing

– If invasive carcinoma has been detected: special additional studies (hormone receptors, HER2/neu) unless already performed in pretherapeutic core biopsy.

Reporting:

– The information is recorded as described in Chapter 5.2.3; a standard form may be used (cf. Appendix 3: Form 2B).
Orientation of the specimen (see *)

Site of biopsy: Breast  Ø right  Ø left

*e.g. cranial

*e.g. lateral

Diameter 1 (D1) = _______ mm/cm
Diameter 2 (D2) = _______ mm/cm
Diameter 3 (3rd dim.) = _______ mm/cm

Number of slices: _______

Number the slices starting from the left margin of the above sketch.

State the orientation of the slices (as above, see *)

Indicate where samples were taken (with block designation):

*e.g. ventral

*e.g. dorsal

Figure 1. Sketch of tissue sampling
B 5.5 Mastectomy specimens

Mastectomy is usually performed after a carcinoma has been confirmed by an interventional diagnostic method or excisional biopsy. It leads to definitive tumor classification and grading with determination of the extent of the tumor; if applicable, identification of further changes.

In order to obtain rapid fixation of the tissue it is advisable to send the specimen to the pathologist immediately after the operation so as to accelerate preservation of the tissue by slicing the specimens.

The types of mastectomy are simple mastectomy, skin-sparing mastectomy, modified radical mastectomy (Patey), radical mastectomy (Rotter-Halstedt) or extended mastectomy.

B 5.5.1 Macroscopic specimen processing

Description

- Mastectomy specimen:
  - size (3 dimensions) and weight
  - attached tissue (e.g. intact pectoral fascia, pectoral muscles, axillary fatty tissue)
  - size and consistency of the attached skin portions, position of the nipple (e.g. central, eccentric)
  - orientation of the tissue specimen (if performed by the surgeon)
  - location of previous biopsy, tissue excision or tumor (quadrant, position relative to the resection margins)

Figure 2. Tissue biopsy in patients with a palpable focal lesion
– Tumor
  – size (3 dimensions)
  – cut surfaces: borders (distinct/blurred), consistency, color
  – position relative to the resection margin
– Other abnormalities (e.g. breast implant, fibrocystic changes)

Specimen workup
– if necessary marking of the specimen with ink or pigments to identify the resection margins
– slicing of the specimen from lateral to medial in parallel slices with a thickness of 5-10 mm, with the slices remaining in contact with the skin.

Tissue biopsy is carried out to gain information on the following items:
– mamillary/submamillary tissue (2 blocks)
– tumor (number of paraffin blocks depending on size)
– margins of previous biopsy or excision cavity (3-4 tissue specimens in total)
– resection margins
– additional breast tissue from the 4 quadrants (at least 1 block per quadrant)
– further changes
– special questions/additional studies

If the mastectomy was performed because of DCIS or if extensive radiographically identifiable microcalcifications were present it can be helpful to obtain a specimen radiograph of the tissue slices in order to precisely localize the changes and remove them in such a way that the extent and relation to the resection margins can be precisely determined.

B 5.5.2 Microscopic specimen processing and reporting
The information is recorded as described in Chapter 5.2.3; a standard form may be used (cf. Appendix 3: Form 2).
B 5.6 Lymph nodes

Statement Patho-7: Lymph node status

<table>
<thead>
<tr>
<th>Lymph node status is determined on the basis of the histological examination of all lymph nodes removed.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documentation of the following is mandatory: number of lymph nodes removed and involved, capsule penetration, pN category (according to TNM classification, 6th Edition, UICC 2002).</td>
</tr>
</tbody>
</table>


Axillary lymphadenectomy
- Traditional procedure for determination of lymph node status. Determination of the number of positive lymph nodes in relation to the total number removed, of the maximum extent of metastatic infiltration and of any perinodal tumor infiltration.
- The aim of the histological examination is to detect all macrometastases (> 2 mm)

Sentinel node biopsy (SNB)
- Removal of the so-called sentinel node (marking with dye and/or radionuclide)
- Currently the preferred procedure for determination of node status. Observation of the recommended quality criteria (Kuehn, T et al. 2005) is essential.
- The minimum aim of the histological examination is to detect all macrometastases (> 2 mm) (Amendoeira, I 2006b; Kuehn, T et al. 2005; Lyman, GH et al. 2005)) In addition, identification of micrometastases (< 2 mm but > 0.2 mm) is desirable, but not mandatory, since if micrometastases are present involvement of further lymph nodes can be expected in about 20% of cases (Cserni, G et al. 2004), in the case of metastases > 1 mm in as many as approx. 30% of cases (Viale, G et al. 2005). The histological examination of the sentinel nodes is not performed with the intention of discovering isolated tumor cells (ITC). If ITCs are found, attention should be paid to their correct classification (see below).

B 5.6.1 Macroscopic specimen processing

Description
- size (3 dimensions) and weight of the total tissue specimen
- orientation (if marked)
- number of lymph nodes
- size of the largest lymph node (if visible)

Specimen workup
- meticulous examination of axillary fatty tissue for the presence of lymph nodes
- histological examination of all lymph nodes found:
  - lymph nodes seen to contain malignancy upon macroscopic examination and nodes adhering to each other: examination of a representative cross section.
– lymph nodes not clearly identifiable as containing malignancy upon macroscopic examination: complete embedding for histological examination:

– If the size of the lymph nodes permits, these should be halved along the longitudinal axis or cut into slices with a thickness of 2–3 mm.

**B 5.6.2 Microscopic specimen processing and reporting**

**Processing**

– Axillary dissection specimens

– Lymph nodes seen to contain malignancy upon macroscopic examination: one H&E section per block.

– Lymph nodes not clearly identifiable as containing malignancy upon macroscopic examination: According to international guidelines one H&E section is sufficient (A mendoeira, I 2006; Fitzgibbons, PL et al. 2000). However, depending on the thickness of the total lymph node tissue in the block, preparation of at least 2-3 sections (100-500 μm apart) is recommended in order to ensure that all macrometastases (> 2 mm) are detected.

– Special features of sentinel lymph nodes (Kuehn, T et al. 2005; Lyman, GH et al. 2005)

– Step sections (100-500 μm apart) with H&E staining; number for reliable detection of all macrometastases depends on thickness of tissue.

– Immunohistochemical reactions with antibodies to cytokeratins are not recommended as standard procedure but can be diagnostically helpful in individual cases (e.g. invasive lobular carcinoma).

**Reporting**

The following information is recorded; a standard form may be used for this purpose (cf. Appendix 3: Form 2):

– type of tissue specimen

– side

– number of lymph nodes examined (with location if marked)

– number of positive lymph nodes

– extent of the largest metastatic infiltration

– extranodal infiltration, if present

– pTNM stage (if necessary after examining further tissue specimens) (cf. Chapters 5.4 and 5.5)

**Remarks**

– If only sentinel lymph node biopsy is performed: add (sn) to pN category (UICC 2002).

– Number of lymph nodes normally removed and histologically examined for staging purposes in the case of axillary dissection:

– at least 6 lymph nodes from level I according to the currently valid TNM classification (UICC 2002).

– at least 10 lymph nodes in the case of dissection of levels I and II according to the specifications of the EORTC Breast Cancer Cooperative Group (EORTC Breast Cancer Coop-
ervative Group 2000). Even if this number is not achieved the pN stage is stated (e.g. pN0 (0/9 LN) (Sobin, LH et al. 2001).

- Isolated single tumor cells or small tumor cell aggregates not larger than 0.2 mm (ITC) are classified as pN0 and should not be considered micrometastases (Hermanek P et al. 1999; Singletary, SE et al. 2003; UICC 2002); their occurrence is documented as pN0 (i+).

**Literature**


NCRI Breast Clinical Studies Group. UK Clinical Guidelines for the use of adjuvant Trastuzumab (Herceptin®) with or following chemotherapy in HER2-positive Early breast Cancer. 2005.


NHSBSP Guidelines for Non-Operative Diagnostic Procedures and Reporting in Breast Cancer Screening (NHSBSP Publication No. 50). Non-operative Diagnosis Subgroup of the National Coordinating Group for Breast Screening Pathology (NHSBSP) NHS Cancer Screening Programmes 2001; Publication No. 50.


Remmele W, Stegner HE. Recommendation for uniform definition of an immunoreactive score (IRS) for immunohistochemical estrogen receptor detection (ER-ICA) in breast cancer tissue. Pathologe 1987; 8:138-140.


B 6  Adjuvant Radiotherapy for Breast Cancer

B 6.1  Radiotherapy after BCT

Statement RT-1: Radiotherapy after BCT (general)

In patients with invasive carcinoma, irradiation of the affected breast is indicated after breast-conserving surgery.


Percutaneous high-volt radiotherapy brings about improvements in local tumor control and overall survival.


This applies, in particular, to patients in whom adjuvant radiotherapy achieves a reduction of the risk of recurrence of > 10 %. Statistically, this means that, as a result of the prevention of four local recurrences, one death caused by cancer can be prevented over a period of 15 years (Clarke, M et al. 2005; Peto, R 2006; Whelan, T et al. 2007).

In elderly patients and patients whose tumors have favorable morphological and biological properties, this effect – and with it the indication for radiotherapy – becomes relative. Like adjuvant radiotherapy after breast-conserving surgery, irradiation of the breast is also indicated, despite the insufficient body of evidence, in patients with a histopathologically confirmed total remission following primary (neoadjuvant) systemic (chemo)therapy (ypT0) (Huang, EH et al. 2006).
Statement RT-2: Administration of radiotherapy after BCT

The target volume of percutaneous adjuvant radiotherapy encompasses the entire residual breast and the adjoining thoracic wall.


The dose should amount to approx. 50 Gy fractionated in the conventional manner (5 x 1.8–2.0 Gy/week).

**LOE 1a, Grade of Recommendation A** (Clarke, M et al. 2005; EBCTCG 2000; EBMG 2006; NCCN 2007; NHMRC 2001; SIGN 2005; Whelan, T et al. 2002)

The application of a local boost dose to the tumor bed in addition to whole-breast irradiation reduces the rate of local recurrence in the breast in all age groups without conferring an advantage in terms of survival (Antonini, N et al. 2007; Bartelink, H et al. 2007; Romestaing, P et al. 1997). Boost irradiation is indicated as a rule. The recommended boost dose amounts to 10–16 Gy fractionated in the conventional manner (5 x 1.8–2.0 Gy/week).

**LOE 1b, Grade of Recommendation B** (Antonini, N et al. 2007; Bartelink, H et al. 2007)

In postmenopausal patients with a very low risk of local recurrence (in particular patients > 60 years of age and patients with small tumors), the advantage conferred by boost irradiation is small in absolute terms. In this subgroup the administration of boost irradiation can possibly be waived.

**LOE 2a, Grade of Recommendation B** (NCCN 2006; NCCN 2007; NHMRC 2003; SIGN 2005)

In two studies with low case numbers and short observation periods, alternative fractionation regimens were investigated with the aim of shortening the treatment time (e.g. 42.5 Gy in 16 fractions). Even though no differences were noted in terms of oncological results, these alternative strategies have not gained clinical acceptance (Owen, JR et al. 2006; Whelan, T et al. 2002; Yarnold, J et al. 2005).

The application of a boost dose reduces the rate of local recurrences in all age and risk groups (Antonini, N et al. 2007; Bartelink, H et al. 2007).

The greatest benefit from the application of a boost dose, as measured by the absolute reduction in the risk of a local recurrence, is realized by younger patients and patients with an elevated risk of a local recurrence. The type of radiation and the irradiation technique used do not affect the therapeutic outcome (Poortmans, P et al. 2004).

**Literature**


Peto R. Highlights from the 2005/6 EBCTCG worldwide overview of every women in all the trials in early breast cancer. 29th Annual San Antonio Breast Cancer Symposium 2006; Abstract book # 40.


B 6.2 Partial breast irradiation

Statement RT-3: Partial breast irradiation

The use of partial breast irradiation as the sole intraoperative or postoperative radiation treatment, without homogeneous irradiation of the entire breast, represents an experimental approach at present and should not be undertaken outside of studies.

LOE 3, Grade of Recommendation A (NCCN 2006; NCCN 2007)

At present there is no evidence-based risk-adapted strategy for partial breast irradiation. To date neither the optimal breast volume to be irradiated after breast-conserving surgery nor the dose required for tumor control has been determined with adequate certainty (Graham, P et al. 2006; McCormick, B 2005; Rosenstein, BS et al. 2004; Wallner, P et al. 2004; Wazer, DE et al. 2006).

The currently accepted indication for partial breast irradiation after breast-conserving surgery is circumscribed boost radiotherapy of the primary tumor region before or after homogeneous whole-breast irradiation (Antonini, N et al. 2007; Bartelink, H et al. 2007; Sauer, R et al. 2007). Suitable methods for this are: radiation treatment with electrons, interstitial radiotherapy with multicatheter or balloon catheter techniques, three-dimensional (3-D) conformal percutaneous irradiation and intraoperative radiotherapy (Arthur, DW et al. 2005). The technique used for applying the boost dose has no impact on the therapeutic outcome (Poortmans, P et al. 2004). Partial breast irradiation with protons is an experimental method (Weber, DC et al. 2006).

The methods employed for intraoperative partial breast irradiation use electrons or x-rays (Vaidya, JS et al. 2006; Veronesi, U et al. 2005).

All of these accelerated methods derive their attractiveness mainly from the shortened treatment times they offer. However, their biological effectiveness, rate of adverse reactions, and rate of chronic complications cannot be estimated at present (Arthur, DW et al. 2005; Rosenstein, BS et al. 2004; Tai, P et al. 2005; Vaidya, JS et al. 2006; Wazer, DE et al. 2006).

At present it is thus not yet possible to answer the two questions of decisive clinical importance in this context: 1) Can the doses applied with the various techniques for partial breast irradiation be compared with respect to their biological effects (Rosenstein, BS et al. 2004; Sauer, G et al. 2005)? 2) Is there an equivalency between the different options for localized irradiation and percutaneous homogeneous whole-breast irradiation? The periods covered by observational studies published to date are still (too) short, exceeding 5 years in only a few individual cases (Arthur, DW et al. 2005). As a result, the use of partial breast irradiation as
the sole form of radiotherapy should be undertaken only within the framework of controlled clinical studies until valid long-term results are available (NCCN 2007; Sauer, R et al. 2005; Sauer, R et al. 2007).

**Literature**


B 6.3 Radiotherapy after mastectomy

Statement RT-4: Radiotherapy after mastectomy

Postoperative irradiation of the thoracic wall after mastectomy lowers the risk of a locoregional recurrence.

**LOE 1a** (Clarke, M et al. 2005; EBMG 2006; NCCN 2006; NCCN 2007; NHMRC 2001; Peto, R 2006; Shafiq, J et al. 2007; SIGN 2005; Whelan, T et al. 2007)

In patients with a high risk of a local recurrence, overall survival is also improved.

**LOE 1a** (Clarke, M et al. 2005; Gebski, V et al. 2006; Peto, R 2006; Whelan, T et al. 2007).

Postoperative irradiation of the thoracic wall after mastectomy is therefore indicated in the following situations:

- **T3/T4**
  
  **LOE 2a, Grade of Recommendation A** (NCCN 2007; SIGN 2005; Truong, PT et al. 2004)

- R1/R2 resection
  
  **LOE 2a, Grade of Recommendation A** (NCCN 2007; SIGN 2005; Truong, PT et al. 2004)

- pN+ (> 3)
  
  **LOE 1a, Grade of Recommendation A** (NCCN 2006; NCCN 2007; SIGN 2005; Truong, PT et al. 2004)

Patients with 1–3 positive lymph nodes can benefit from radiotherapy.

**LOE 1a, Grade of Recommendation 0** (NCCN 2007; Peto, R 2006; Truong, PT et al. 2005b)

After primary (neoadjuvant) systemic therapy the decision to institute radiotherapy should be made on the basis of the pretherapeutic T and N scores regardless of the degree of response to the primary systemic therapy.

**LOE 2a, Grade of Recommendation A** (Huang, EH et al. 2006; Kaufmann, M et al. 2003; NCCN 2007)

After mastectomy, as after breast-conserving surgery, postoperative radiotherapy can not only achieve improved locoregional tumor control but also exert a positive impact on breast-cancer-specific mortality and the probability of survival. In patients with a high risk of a local recurrence, additional radiation treatment can result in a substantial reduction of the probability of a local recurrence (Clarke, M et al. 2005; EBCTCG 1995; EBCTCG 2000; Truong, PT et al. 2004; Van de Steene, J et al. 2000; Van de Steene, J et al. 2004; Whelan, T et al. 2007).

In patients with locoregional lymph-node involvement and an increased risk of a local recurrence, the survival advantage is distinctly more pronounced: In the current metaanlysis performed by the EBCTCG, this advantage was found when the rate of local recurrence after 15 years was reduced by the additional radiation treatment from 24.3 to 5.3 % in the group of patients with 1-3 positive lymph nodes and from 40.6 to 12.9 % in the group with > 3 positive
lymph nodes (Clarke, M et al. 2005). In patients with positive regional lymph nodes, the administration of radiotherapy after mastectomy resulted in a 4.4% lower overall mortality and a 5.4% lower tumor-specific mortality over a 15-year period (Clarke, M et al. 2005). A point that merits consideration here is that these data are based largely on studies with comparatively negative overall results in terms of local recurrence rate and overall survival (Overgaard, M et al. 2007).

In patients without involvement of the locoregional lymph nodes who received additional radiotherapy after mastectomy, a negative effect on overall survival of 3.9% (p = 0.0005) was noted in the current EBCTCG metaanalysis (2006). Even if this negative effect is less pronounced when sophisticated irradiation techniques are used, the pros and cons of administering radiotherapy should be carefully weighed in such cases (NCCN 2007).

The value of post-mastectomy radiotherapy has not been sufficiently substantiated for the group of patients > 70 years of age since this patient group is under-represented in the prospective studies (Clarke, M et al. 2005; EBCTCG 2000; Smith, BD et al. 2006; Truong, PT et al. 2005a). In a current retrospective analysis of the SEER Medicare database for patients > 70 years age, a survival advantage was found for patients with a high risk of recurrence (T3/4 and/or N2/3) (Smith, BD et al. 2006).

In certain subgroups (e.g. age < 40 years, extensive lymphangiosis or hemangiosis, a classification of pT2 (> 3 cm), infiltration of the pectoral fascia or a safety margin < 1 mm), a benefit of radiotherapy after mastectomy appears plausible, especially for cases in which several of these factors are present, even though this has not yet been sufficiently substantiated by studies (NHMRC 2003; Truong, PT et al. 2004).

After primary (neoadjuvant) systemic therapy the decision to institute radiotherapy should be made on the basis of the pretherapeutic T and N category regardless of the degree of response to the primary systemic therapy (Buchholz T 2007; Huang, EH et al. 2006; Kaufmann, M et al. 2003; McGuire, SE et al. 2007; NCCN 2007).

**Literature**


Overgaard M., Nielsen H. M., Overgaard J. Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. Radiother Oncol 2007; 82 (3):247-253.

Peto R. Highlights from the 2005/6 EBCTCG worldwide overview of every women in all the trials in early breast cancer. 29th Annual San Antonio Breast Cancer Symposium 2006; Abstract book # 40.


B 6.4  Irradiation of the regional lymphatic drainage system

Statement RT–5: Irradiation of the regional lymphatic drainage system

So far the value of adjuvant irradiation of the regional lymphatic drainage system has not been substantiated by the results of prospective and randomized studies; as a result, the decision to irradiate the regional lymphatic drainage system must be made from case to case.

LOE 3b (EBMG 2006; NCCN 2007; NHMRC 2001; Recht, A et al. 2001; SIGN 2005; Truong, PT et al. 2004)

In patients with negative sentinel node biopsy results, irradiation of the axilla is not indicated.

LOE 1b, Grade of Recommendation A (Veronesi, U et al. 2005b; Veronesi, U et al. 2005a)

Irradiation of the axilla is recommended only in the following situations:

– residual tumor in the axilla

   LOE 2b, Grade of Recommendation A (NCCN 2007; SIGN 2005; Truong, PT et al. 2004; Truong, PT et al. 2005b)

– clear-cut clinical involvement or positive SN status in patients in whom no axillary dissection or only incomplete axillary dissection has been performed


No substantial body of data is available which could validate the advantage of irradiating the axilla in patients with histologically demonstrated tumor growth beyond the capsule. Irradiation of the axilla is thus not indicated in this group of patients.

Irradiation of the internal mammary nodes is generally not recommended (NCCN 2007). Irradiation of the supraclavicular and infraclavicular lymphatic drainage channels is recommended in the following situations:

– patients with > 3 positive axillary lymph nodes

   LOE 2a, Grade of Recommendation B

– involvement of Level III of the axilla

   LOE 3b, Grade of Recommendation B

– cases where irradiation of the axilla is indicated

   LOE 3b, Grade of Recommendation B

In cases where a decision is made to irradiate lymphatic drainage areas, radiotherapy is administered with approx. 50 Gy fractionated in the conventional manner (5 x 1.8–2.0 Gy/week). For irradiation of the supraclavicular lymphatic drainage region, preference should be given to a single dose of 1.8 Gy.
The value of adjuvant irradiation of the regional lymphatic drainage system has been substan-
tiated for cases with > 3 positive axillary lymph nodes and axillary resection with positive
resection margins. It should be taken into account in this context that the advantage of adju-
vant radiotherapy after adequately performed axillary dissection, with excision of at least 10
lymph nodes at Levels I and II, has not been clearly demonstrated.

The value of adjuvant radiotherapy for patients with extensive tumor growth beyond the cap-
sule in the axilla is not substantiated at present; consequently, radiotherapy is not indicated for
this group of patients (NCCN 2007; Recht, A et al. 2001; SIGN 2005; Truong, PT et al. 2004;
Truong, PT et al. 2005a; Wallgren, A et al. 2003; Wapnir, IL et al. 2006; Whelan, T et al. 2005).

The current metaanalysis performed by EBCTCG 2005/2006 on the administration of radio-
therapy after mastectomy and axillary dissection (Clarke, M et al. 2005; Darby, S et al. 2006;
McGale, P et al. 2006; Peto, R 2006) also reveals an advantage in terms of a higher probabil-
ity of survival in cases where radiotherapy can reduce the risk of a local or locoregional recur-
rence by > 10 % owing to the low axillary recurrence rate following adequate surgery in the
axilla, with excision of at least 10 lymph nodes, this is improbable. Adjuvant irradiation of the
axilla following adequate axillary dissection is limited to cases with R2 resection margins.

Prospective randomized studies now in progress are evaluating the value of adjuvant irradia-
tion of the internal mammary and supra- and infraclavicular lymphatics in patients with
tumors in a central or medial location as well as in patients with positive sentinel node biopsy
results in whom axillary dissection was not performed.

It should be borne in mind that, in the studies included in the EBCTCG metaanalysis in 2006,
the supraclavicular and infraclavicular (but not always the axillary) lymphatics were irradi-
ated (Clarke, M et al. 2005; Darby, S et al. 2006; McGale, P et al. 2006; Peto, R 2006; Ragaz,

Irradiation of the supraclavicular and infraclavicular lymphatics is recommended in cases with
demonstrated axillary lymph-node metastases or a high risk of occult tumor growth. This con-
stellation is present in the following cases:

– involvement of the axillary lymph nodes (mandatory in cases with > 3 positive lymph
  nodes; however, radiotherapy has only a marginal effect on the rate of regional recurrence
  in patients with 1–3 positive lymph nodes)

– involvement of Level III of the axilla

– patients in whom irradiation of the axilla is indicated

– patients with an indication for irradiation of the parasternal lymph nodes (controversial
  indication)

In cases where irradiation of the supraclavicular and infraclavicular lymphatics is indicated,
one should also examine whether irradiation of the internal mammary region is indicated.
(NCCN 2007; Truong, PT et al. 2004).
Literature


Peto R. Highlights from the 2005/6 EBCTCG worldwide overview of every women in all the trials in early breast cancer. 29th Annual San Antonio Breast Cancer Symposium 2006; Abstract book # 40.


B 6.5 Radiotherapy for advanced tumors

Statement RT-6: Radiotherapy for patients with locally very advanced tumors or primary inoperability

For patients with primarily inoperable carcinomas (Stage IIIB), primary systemic therapy is recommended followed by surgery and postoperative radiotherapy.

**LOE 1b, Grade of Recommendation A** (Kaufmann, M et al. 2003; NCCN 2007; Shenkier, T et al. 2004; SIGN 2005; Truong, PT et al. 2004)

If the systemic therapy fails to achieve operability, radiotherapy – possibly in combination with simultaneous systemic therapy – is indicated.

**Grade of Recommendation B** (Kaufmann, M et al. 2003; NCCN 2007; Shenkier, T et al. 2004; Truong, PT et al. 2004)

The following constellations are uniformly described as locally advanced breast cancer (LABC): tumors > 5 cm demonstrated by clinical, mammographic or sonographic examination, confirmed skin involvement (erythema, ulceration), infiltration of the thoracic wall (muscles or ribs), matted involved axillary lymph nodes, involved lymph node in the apical axilla or infracavicular region, clinical signs of inflammatory carcinoma (Giordano, SH et al. 2003; Giordano, SH 2003; Rutgers, EJ 2001; Shenkier, T et al. 2004).

Inflammatory carcinoma is usually viewed as a subgroup of LABC (Anderson, WF et al. 2003; Cristofanilli, M et al. 2003; Cristofanilli, M et al. 2004).

The locally advanced stages of breast cancer – IIB (T2, N1) and IIIA (T0, T1, N2) – are defined differently in the TNM classification system (UICC 2002) and the classification system of the American Joint Committee on Cancer (American Joint Committee on Cancer 2002), respectively (Giordano, SH 2003; Singletary, SE et al. 2002; UICC 2002).

Preoperative radiotherapy can increase the rate of breast-conserving therapies and apparently has no negative effect on cosmetic results; however, it is not a substitute for a subsequent necessary operation. The administration of radiotherapy alone does not achieve sufficient local tumor control and does not justify a decision to dispense with surgical removal of the tumor (Huang, EH et al. 2004; Ring, A et al. 2003; Shenkier, T et al. 2004; Toi, M et al. 2003; Truong, PT et al. 2004).

The question of whether to administer radiotherapy after primary systemic therapy and surgery should be discussed before the beginning of the primary systemic therapy (Shenkier, T et al. 2004; Toi, M et al. 2003; Truong, PT et al. 2004). This decision should be made on the basis of the pretherapeutic T and N category, regardless of the degree of response to the primary systemic therapy, and thus according to the same criteria that apply when systemic therapy is administered as adjuvant therapy after surgery (Kaufmann, M et al. 2003; NCCN 2007; Shenkier, T et al. 2004).

Patients with locally advanced operable tumors (Stage IIIA) should be offered chemotherapy in combination with radiotherapy – to be administered either postoperatively or as primary therapy with subsequent local therapy (surgery and radiotherapy) (Kaufmann, M et al. 2003; NCCN 2007; Shenkier, T et al. 2004; Truong, PT et al. 2004).
The decision on whether or not to irradiate the axilla as well can be made contingent upon the extent of the surgical therapy and the histopathological results after systemic primary therapy. It is recommended for patients in whom residual lymph-node metastases have been demonstrated postoperatively (Shenkier, T et al. 2004; Truong, PT et al. 2004). The value of irradiating the internal mammary nodes has not been definitely established (Kaufmann, M et al. 2003; NCCN 2007; Shenkier, T et al. 2004).

**Literature**


B 6.6 Sequencing of chemotherapy, antibody therapy and hormonal therapy

Statement RT-7: Sequencing of chemotherapy and radiotherapy

The superiority of a particular sequence of chemotherapy and radiotherapy has not been sufficiently established. As a basic rule the postoperative sequence depends on the type of recurrence most likely to occur, especially since the optimal time for starting adjuvant therapy is not substantiated by a sufficient body of data.


Surgery, chemotherapy and radiotherapy should be sequenced according to the stage of disease at the time of diagnosis in the individual case. This sequence should be set down by an interdisciplinary team after taking account of the individual risk factors present.

To date there is no sufficient body of data pointing to an optimal sequence of postoperative adjuvant chemotherapy and radiotherapy (Bellon, J et al. 2005; NCCN 2006; NCCN 2007; SIGN 2005; Truong, PT et al. 2004).

For this reason, the sequencing of postoperative systemic antineoplastic therapy or radiotherapy should be based on the type of recurrence most likely to occur (i.e. systemic or locoregional). The goal should be an interdisciplinary decision on a suitable sequence based on the risk factors present in the individual case (e.g. ulcerated or T4 carcinoma, R2 resection status which cannot be improved, etc.).

Radiotherapy should be instituted within 4–6 weeks after surgery or after completion of primary or adjuvant chemotherapy (NHS 2003; SIGN 2005).

Clinical and experimental data point – at least for subgroups of patients – to the advantages of administering radiotherapy as early as possible. With respect to the prognosis, preventing metastases by administering systemic therapy early on is clearly the top priority of adjuvant therapy.

Theoretically, the concurrent administration of chemotherapy and radiotherapy eliminates the delay in instituting oncologically necessary systemic and local measures. Moreover, radiotherapy may make the tumor cells more sensitive to cytotoxic agents (radiosensitization). In practice, however, the advantage of this approach is achieved at the price of higher acute and late toxicity, especially when cytotoxic agents containing anthracycline are used. Because of their duration, chemotherapeutic concepts that are even more aggressive heighten the dilemma of finding the right therapeutic sequence.

Whereas a sequential approach is worthwhile for (anthracycline) chemotherapy and radiotherapy, radiotherapy and systemic endocrine therapy (e.g. tamoxifen) can be carried out concurrently. The use of combination therapies is also an established approach for patients with invasive breast cancer or DCIS. So far retrospective and randomized clinical studies have not revealed any negative impact of tamoxifen on the effectiveness of radiotherapy (Hoeller, U et al. 2007). To the contrary, the combination therapy results in a higher rate of local tumor control in comparison with monomodal therapy regardless of whether tamoxifen is administered before, concurrently with or sequential to radiotherapy.
Statement RT-8: Sequencing of antibody therapy and radiotherapy

No sufficient body of data is available on the sequencing of trastuzumab and radiotherapy.

The concurrent administration of trastuzumab and radiotherapy does not appear to increase the side effects of radiotherapy dramatically and can be justified as long as no irradiation of the internal mammary nodes is planned.

**LOE 3a** (Belkacemi Y et al. 2006; Belkacemi Y et al. 2007; Halyard MY et al. 2006; Romond, EH et al. 2005)

Trastuzumab has become an established therapeutic modality in the adjuvant therapy of tumors that overexpress the HER-2/neu oncogene. During a clinical study, the simultaneous administration of trastuzumab was continued in a large number of patients receiving adjuvant radiotherapy (Halyard, MY et al. 2006; Romond, EH et al. 2005). However, co-irradiation of the internal mammary nodes was not permitted during this study. So far the data available from this study do not show any elevated cardiac or other kinds of toxicity.

Increased toxicity in connection with the simultaneous administration of trastuzumab and radiotherapy was observed in one small study in which the adjuvant radiotherapy included irradiation of the internal mammary nodes (Belkacemi, Y et al. 2006; Belkacemi, Y et al. 2007).

Statement RT-9: Sequencing of tamoxifen and radiotherapy

**Anti-estrogen treatment modalities can be carried out concurrently with or sequential to radiotherapy.**


**Literature**


B7 Systemic Adjuvant Therapy
(Endocrine Therapy, Chemotherapy, Immune Therapy)

Statement Adj-1

Pharmacotherapy for the primary disease is carried out before or after surgery in the form of chemotherapy, endocrine therapy, immune therapy or a combination of these forms of therapy.

LOE 1a (EBCTCG 2005; EBCTCG 2006; NCCN et al. 2006)

Statement Adj-2

The rate of recurrence and the mortality can be reduced by systemic therapy. This is true of polychemotherapy (in particular, the administration of anthracyclines and taxanes, pharmacological suppression of ovarian function, tamoxifen, aromatase inhibitors and trastuzumab). The magnitude of this effect in absolute terms depends on the level of risk.

LOE 1a (EBCTCG 1998a; EBCTCG 2005; EBCTCG 2006; NIH 2001)

Statement Adj-3

An optimal supportive therapy (e.g. anti-emetic medication, provision of wigs, etc.) is an integral part of all systemic therapies. All patients must be briefed on possible side-effects and late sequelae and offered prophylactic measures.

GCP

Statement Adj-4

Older patients should receive a systemic adjuvant therapy comparable to that given to younger patients. The altered organ function and comorbidities should be taken into account when establishing the indication for, and carrying out, adjuvant therapy measures.

GCP

The meta-analyses carried out by the Early Breast Cancer Trialist Cooperative Group (EBCTCG) has shown repeatedly that adjuvant systemic therapy in the form of cytotoxic poly-chemotherapy and/or endocrine therapy substantially improves both recurrence-free survival and overall survival in all age groups regardless of nodal status (EBCTCG 2005; EBCTCG 2006). Adjuvant endocrine therapy (tamoxifen) or chemotherapy (anthracyclines) alone can reduce the cumulative 15-year mortality rates by as much as 30%; the combination can apparently achieve more marked reduction.
Furthermore, the results of current studies substantiate the high effectiveness of adjuvant immune therapy with trastuzumab in patients with HER2-overexpressing tumors (Joensuu, H et al. 2006; Piccart, MJ et al. 2005; Romond, EH et al. 2005; Slamon, DJ et al. 2006a). With the short follow-up periods (i.e. two years) evaluated by these studies to date, the results have consistently shown that this therapy reduces the rate of recurrence by 45 to 50% in comparison with standard adjuvant therapy.

For this reason, an adjuvant systemic therapy adapted to the biology of the individual tumor must be considered for, and discussed with, every woman with invasive carcinoma of the breast.

Older patients should not be excluded from adjuvant systemic therapy on the basis of their age alone. The altered organ function found in older people, any comorbidities and any functional impairment should be taken into account when deciding whether a patient stands to benefit from adjuvant therapeutic measures (Allan, SG et al. 1985; Crivellari, D et al. 2003; de la Haba Rodriguez JR et al. 2003). If it appears likely from the start that it will not be possible to administer adjuvant chemotherapy at adequate doses, a decision should be made to forego chemotherapy entirely (de la Haba Rodriguez JR et al. 2003; DeMichele, A et al. 2003).

Effective concomitant measures, in particular adequate anti-emetic medication, are a part of every systemic therapy.

Despite the recognized benefits of adjuvant systemic therapy, many questions remain with respect to individual aspects of this therapy. For this reason, these therapies should be administered within the scope of clinical therapeutic trials whenever possible.

**B 7.1 Selection of adjuvant therapy and risk assessment**

The recommendation concerning adjuvant therapy for breast cancer take account of tumor size, node status, grading, hormone receptor status, HER2 status, menopausal status and age as these are the most important factors for deciding on the necessity for, and type of, adjuvant therapy (EBCTCG 2005; Goldhirsch, A et al. 2001; Goldhirsch, A et al. 2003; Peto R et al. 1998). In accordance with the St. Gallen Recommendations 2005 and 2007, patients are assigned to one of three groups on the basis of a risk assessment. The group with the lowest risk of recurrence is reserved for women who satisfy all of the following conditions: patients 35 years of age or older, tumor diameter less than 2 cm, grading I, positive estrogen and/or progesterone receptor status, negative HER2 status and axillary lymph nodes free of malignancy (N0). All other patients are to be assigned to the groups with an intermediate or elevated risk of recurrence, respectively.

In women with a low risk, adjuvant chemotherapy can be dispensed with. Adjuvant endocrine therapy should generally be carried out nevertheless.

Adjuvant chemotherapy is indicated in all cases with elevated risk and in which the sensitivity of the tumor to endocrine therapy is unclear or absent.

In women with an intermediate risk and a reliably demonstrated high sensitivity to endocrine treatment, the expected benefits of a sequence of chemotherapy and endocrine therapy must be weighed against the expected benefits of endocrine therapy alone in each individual case.
Factors associated with an unfavorable prognosis – e.g. lymph node involvement, unfavorable grading, age under 35, increased expression of uPA/PAI-1, slight hormone receptor expression (ER/PgR) and large tumor size – generally justify the use of adjuvant chemotherapy.

### B 7.2 Endocrine Therapy

**Statement Adj-5**

In patients with tumors positive for estrogen and/or progesterone receptors, endocrine treatment is indicated.

**LOE 1a, Grade of Recommendation A**

This treatment should not be initiated until after completion of the chemotherapy.

**LOE 2, Grade of Recommendation B** (EBCTCG 1998a; Fisher, B et al. 1997c; Thuerlimann B et al. 2001)

**Statement Adj-6**

Adjuvant anti-estrogen therapy with tamoxifen 20 mg per day is carried out over a period of 5 years or until recurrence.

**LOE 1a, Grade of Recommendation A** (EBCTCG 1998b)

If the duration of therapy is distinctly shorter than 5 years, it is worthwhile to reinitiate the therapy in order to complete the 5 years.

**LOE 2a, Grade of Recommendation B** (Gradishar, WJ et al. 2002; Peto, R 1996; Stewart, HJ et al. 1996; Swedish Breast Cancer Cooperative Group 1996)

**Statement Adj-7**

In premenopausal women, suppression of ovarian function via GnRH analogs, oophorectomy or ovarian ablation via radiotherapy can have a positive impact on the disease. This treatment is comparable in effect to CMF chemotherapy. Treatment with GnRH analogs should be carried out for at least 2 years.

**LOE 1b, Grade of Recommendation A** (Cuzick, J et al. 2007)

The efficacy of suppression of ovarian function after chemotherapy is uncertain.

**Statement Adj-8**

In women who are unmistakably postmenopausal, third-generation aromatase inhibitors are superior to tamoxifen. In women with a corresponding risk constellation, these can be administered as primary therapy for 5 years, for 2-3 years alternating after 2-3 years of tamoxifen therapy, or for 5 years after 5 years of tamoxifen therapy.

**LOE 1b, Grade of Recommendation A** (Boccardo, F et al. 2006; Coombes, RC et al. 2007; Goss, PE et al. 2005; Jakesz, R et al. 2005; Kaufmann, M et al. 2007; Thurlimann, B et al. 2005)
The data from the EBCTCG Overview show that tamoxifen therapy can distinctly lower the probability of a recurrence (40% relative reduction) or of death (31% relative reduction) over a 15-year period in patients with breast cancer (EBCTCG 2005; EBCTCG 2006). Adjuvant tamoxifen treatment is beneficial for women of any age regardless of nodal status, menopausal status or the administration of adjuvant chemotherapy; however, it is limited to women with hormone-receptor-positive breast cancer.

Suppression of ovarian function is an effective adjuvant treatment for premenopausal patients with hormone-receptor-positive breast cancer. In a meta-analysis, data from nearly 12,000 women enrolled in 16 studies on the pharmacological suppression of ovarian function using LHRH agonists, were analyzed (Cuzick, J et al. 2007). The addition of LHRH agonists to adjuvant systemic therapy can reduce the risk of recurrence by 12.7% (2.4-21.9, p=0.02) and the risk of death by 15.1% (1.8-26.7, p=0.03). However, this effect is limited to patients who are not taking tamoxifen concurrently. Only 365 patients received LHRH agonists in addition to chemotherapy and tamoxifen; in this group only a non-significant trend toward risk reduction was observed. A direct comparison of LHRH agonists with tamoxifen was not undertaken in any of the studies. LHRH agonists are equal in effectiveness to CMF chemotherapy (i.e. non-significant increase of +3.9% in the risk of recurrence (CI -7.7% - +17.0%, p=0.52) and a -6.7% lowering of the risk of death (CI -20.7% - +9.6%, p=0.4)). So far no studies have been carried out which compare the combination of chemotherapy + tamoxifen with the combination of LHRH + tamoxifen. LHRH agonists have no effect on hormone-receptor-negative tumors. The effect of ovarian suppression after chemotherapy in non-amenorrheic women has not been established.

Concerning the use of aromatase inhibitors in the adjuvant treatment of hormone-sensitive breast cancer, data are now available from various study groups which have explored the use of aromatase inhibitors either in a direct five-year comparison with tamoxifen (ATAC, BIG 1-98), or after 2–3 years of treatment with tamoxifen (ARNO, ABCSG 8, ITA, IES), or even after the completion of a five-year period of tamoxifen treatment (MA-17).

Option I: Administration of aromatase inhibitors up front (ATAC and BIG 1-98)

In the four-arm BIG 1-98 Study (5 years of letrozole versus 5 years of tamoxifen versus 2–3 years of letrozole followed by tamoxifen versus 2–3 years of tamoxifen followed by letrozole), the data recorded during a median follow-up period of 26 months revealed a distinct reduction of recurrences (Hazard ratio (HR) = 0.81, p=0.003), in particular for the occurrence of distant metastases (HR = 0.73, p=0.001) in comparison with tamoxifen (Thurlimann, B et al. 2005).

In the ATAC Study (5 years of anastrozole versus 5 years of tamoxifen versus 5 years of anastrozole + tamoxifen), which was the study with the longest follow-up period (68 months), the administration of anastrozole monotherapy was found to result in significantly improved disease-free survival (DFS) (HR = 0.87, p=0.01) (Howell, A et al. 2005).

Option II: Sequential and “switch“ therapies (ABCSG-8, IES, ITA)

A definitive statement on the optimal sequence of administration of the anti-hormonal agents now available will have to await the final analysis of the data from the BIG 1-98 Study.

Nevertheless, it appears to be important, especially in this context, to make a distinction between an initially sequential anti-hormonal therapy (Tam → AI) and a ”switch“ therapy. In
a “switch” therapy a patient with breast cancer who has already been taking tamoxifen for two to three years and is currently free of disease is switched to an aromatase inhibitor. In this comparison of study results the time of randomization and the “window” for data analysis is of decisive importance. Only in the ABCSG 8 Study was a genuine sequential therapy investigated: in this study randomization took place a priori and not after 2–3 years of tamoxifen therapy.

The Intergroup Exemestane Study (IES) involving 4,724 postmenopausal patients compared the results achieved by a “switch” to exemestane after 2–3 years of tamoxifen therapy (n=2,352) with those after a five-year tamoxifen therapy (2,372).

During a mean follow-up period of 55.7 months, 809 recurrences were observed. The benefit in absolute terms amounted to 3.3% (95% CI 1.6–4.9). A total of 222 and 261 fatalities were recorded in the exemestane and tamoxifen groups, respectively. The Hazard Ratio was 0.85 (95% CI 0.71–1.02, p=0.08) (Coombes, RC et al. 2007).

Following a median follow-up period of 64 months, the Italian ITA Study (n=448) noted an advantage in DFS for “switching” to anastrozole (HR = 0.57 (95% CI 0.38–0.85). Likewise, recurrence-free survival and overall survival were higher in the group of patients treated with anastrozole (HR = 0.56 (95% CI 0.35–0.89), p=0.01; as well as HR = 0.56 (95% CI 0.28–1.15), p= 0.1) (Boccardo, F et al. 2006). The Arimidex-Nolvadex 95 Study (ARNO 95) and the Austrian Breast Cancer Study Group 8 Study (ABCSG-8) compared 2 years of tamoxifen treatment followed by 3 additional years of tamoxifen treatment with 2 years of tamoxifen treatment followed by 3 years of anastrozole treatment; patients were randomly assigned to the tamoxifen and anastrozole groups after the first 2 years. After a follow-up period of 28 months, a 40% reduction of risk was noted in 3,224 patients who had been switched to anastrozole. The rate of recurrence was 0.60 (95% CI 0.44–0.81) p=0.0009 (Jakesz, R et al. 2005a). In the ARNO Study the aromatase inhibitors were found to confer a survival advantage (Kaufmann, M et al. 2007).

The administration of extended adjuvant endocrine therapy with an aromatase inhibitor after 5 years of tamoxifen therapy to a patient who has been free of disease to date can significantly reduce the risk of both ipsilateral and contralateral recurrence (HR = 0.58, 95% CI = 0.45 – 0.76; p < 0.001) as well as the risk of distant recurrence (HR = 0.60, 95% CI = 0.43 – 0.84; p = 0.002). An improvement in overall survival has been demonstrated so far only for patients with axillary lymph-node involvement (HR = 0.61, 95% CI = 0.38 – 0.98; p = 0.04). Treatment with aromatase inhibitors is accompanied by a significant increase in adverse reactions induced by the hormone withdrawal (Goss, PE et al. 2005).

During treatment with aromatase inhibitors – in comparison with tamoxifen treatment – fewer side-effects such as heat flushes, thromboembolic events and endometrial carcinoma occur. However, treatment with aromatase inhibitors is associated with a higher rate of arthralgia and myalgia. Furthermore, greater lose of bone density and (among other sequelae) a higher rate of osteoporotic fractures are to be expected in these patients.
**B 7.3 Chemotherapy**

**Statement Adj-9**

Chemotherapy should be administered at the recommended dosages.

**LOE 1a, Grade of Recommendation A** (Budman, DR et al. 1998; Fisher, B et al. 1997a; French Adjuvant Study Group 2001; Fumoleau, P et al. 2003)

A reduction of either the dosage or the number of cycles may result in a loss of effectiveness.

**LOE 1a, Grade of Recommendation A** (Bonadonna, G et al. 1995; Budman, DR et al. 1998; Cady, B et al. 1993; Fisher, B et al. 1990; French Adjuvant Study Group 2001)

Increasing the doses of cyclophosphamide or doxorubicin does not improve effectiveness.

**LOE 1b, Grade of Recommendation A** (Fisher, B et al. 1999; Fumoleau, P et al. 2003; Henderson, IC et al. 2003)

**Statement Adj-10**

Cytotoxic agents can be administered concurrently or sequentially.

For patients with an elevated risk of recurrence, dose-dense treatments should be administered; however, these therapies should be carried out only at experienced centers.

**LOE 1b, Grade of Recommendation B** (Bonadonna, G et al. 1995; Citron, ML et al. 2003; Henderson, IC et al. 2003; NIH 2001; Wilking, N et al. 2000)

**Statement Adj-11**

An adjuvant combination chemotherapy (three-drug combination) should contain an anthracycline.

The decision to institute this therapy should not be influenced by nodal status or receptor status.

**LOE 1a, Grade of Recommendation A** (EBCTCG 2005; EBCTCG 2006; EBM Reviews 2003; NIH 2001)

**Statement Adj-12**

Patients with axillary lymph-node involvement should receive an adjuvant combination therapy with taxanes.

**LOE 1b, Grade of Recommendation B** (Bria, E et al. 2006; Citron, ML et al. 2003; Clavarezza, M et al. 2006; Estevez, LG et al. 2007; Henderson, IC et al. 2003; Mamounas, EP et al. 2005; Roche, H et al. 2006)

The positive effects of adjuvant chemotherapy on the risk of recurrence or death demonstrated by the data published by the Oxford Overview (EBCTCG) are most pronounced in women under 50. This kind of therapy is also beneficial for postmenopausal women (EBCTCG 2005; EBCTCG 2006)
In the same overview (EBCTCG 2005; EBCTCG 2006), the superiority of anthracycline-containing regimens over CMF could be demonstrated solely for three-component combinations (e.g. FAC/FEC); both the dose and number of cycles (6) must be adequate. No enhanced efficacy over CMF was demonstrated for the administration of 4 or 8 cycles of the two-component combinations EC or AC (Fisher, B et al. 1990; Piccart, MJ et al. 2001). A treatment duration of more than 6 months does not confer any additional benefits.

Epirubicin should be administered at a dosage of at least 30 mg/m² per week and doxorubicin at a dosage of at least 20 mg/m² per week. FAC is administered every three weeks with a dosage of doxorubicin of 60 mg/m². FEC is administered in an analog manner either according to the French regimen (100 mg/m² of epirubicin every three weeks (Bonneterre, J et al. 2005)) or the Canadian regimen (60 mg/m² of epirubicin on Days 1 and 8 every four weeks (Levine, MN et al. 2005)).

The data position on adjuvant chemotherapy with taxanes is buttressed by recent study results. In particular, women with lymph node involvement and patients with negative hormone receptor status benefit from the employment of taxanes in the adjuvant therapy (Bria, E et al. 2006; Clavarezza, M et al. 2006; Estevez, LG et al. 2007; Henderson, IC et al. 2003; Mamounas EP 2000; Martin, M et al. 2005; Roche, H et al. 2006).

The list of acceptable therapeutic regimens is not yet definitive. According to the present state of published knowledge, FEC x 3-Doc x 3 (PACS-01) and DocAC (“TAC,” BCIRG 006) are the most effective therapeutic regimens (Roche, H et al. 2006).

The sequence of 4 cycles of AC/EC followed by taxanes (“Henderson-like“ approach) does not appear to display optimal efficacy according to recently published data from the Canadian MA-21 Study. The results of this study showed that this sequence is only slightly superior to 4 cycles of AC! (Burnell M et al. 2006).

Recent studies have demonstrated the enhanced effect achieved by dose-intensified chemotherapy protocols in patients with node-positive breast cancer. In contrast, high-dose myeloablative therapies should still be used only in clinical studies (Citron, ML et al. 2003; Henderson, IC et al. 2003; Kummel, S et al. 2006; Möbus VJ et al. 2004; Wilking, N et al. 2007).

**B 7.4 Neoadjuvant (primary systemic) therapy (NACT or PST)**

**Statement Adj-13**

Neoadjuvant (primary, preoperative) systemic therapy is now deemed the standard treatment for patients with locally advanced, primarily inoperable or inflammatory breast carcinoma. This treatment should be administered within the framework of a multimodal therapeutic strategy.

**LOE 1c, Grade of Recommendation A** (Brito, RA et al. 2001; Fisher, B et al. 1997b; Kaufmann, M et al. 2006)
Statement Adj-14

Neoadjuvant chemotherapy represents an alternative treatment option in cases where mastectomy is indicated but the patient wants to have a breast-conserving operation.

**LOE 1b, Grade of Recommendation 0** (Kaufmann, M et al. 2006)

This kind of therapy has the greatest effect on hormone-receptor-negative carcinoma.

**LOE 2b** (Bear, HD et al. 2006; von Minckwitz, G et al. 2005)

Resection according to the new tumor margins is a possibility if RO resection with a sufficient safety distance can thereby be achieved.

**LOE 3b, Grade of Recommendation 0** (Kaufmann, M et al. 2003)

Statement Adj-15

Primary hormonal therapy represents an option for postmenopausal patients with receptor-positive tumors in cases where an operation is contraindicated or is refused by the patient.

**Grade of Recommendation 0**

Numerous studies have shown that there is no difference of any kind in terms of long-term survival between the neoadjuvant and adjuvant administration of chemotherapy. The risk of local recurrence appears to be elevated in several studies; it must be noted, however, that inferior chemotherapies or chemotherapy regimens which are no longer up to today’s standard were used in part in these studies (Mauri, D et al. 2005).

Reasons for neoadjuvant chemotherapy (NACT) apart from improving the operability of breast cancer or increasing the frequency of breast-conserving operations are to gain more information about the effectiveness of the treatment and to enable faster development of individual treatment strategies within the framework of the neoadjuvant studies (Kaufmann, M et al. 2006).

The NACT should contain an anthracyline and a taxane and be administered for at least 6 cycles (all of them prior to surgery). In patients with HER2-overexpressing tumors, trastuzumab therapy should be carried out postoperatively. The preoperative administration of trastuzumab concurrently with chemotherapy can significantly raise the histological complete remission rate (pCR); however, at present, this use of NACT should be confined to clinical studies (Buzdar, AU et al. 2005).

The demonstration of pCR, which is defined as the absence of tumor cells in the breast and axilla following NACT, has gained currency in clinical trials as a valid surrogate marker for long-term survival. Patients who have not responded to NACT by the time of the operation or already showed no response after the first chemotherapy cycles have an unfavorable prognosis (Bear, HD et al. 2006; von Minckwitz, G et al. 2005).

The most important predictive marker for response to a regimen containing both taxane and anthracyline is negative hormone-receptor status. In this subgroup of patients a PCR of up to 40% can be achieved.

In postmenopausal patients with highly hormone-receptor-positive breast cancer, neoadjuvant endocrine therapy can be carried out in cases where surgery and chemotherapy are not options.
Third-generation aromatase inhibitors are recommended for this group of patients (Ellis, MJ et al. 2001; Smith, IE et al. 2005).

After completion of the NACT, the patient should receive a typical operative therapy as described above. Excision can be performed according to the new tumor boundaries. In patients with radiologically demonstrated complete remission after primary systemic therapy, an excision should be made at the former tumor site to determine whether there are still vital tumor cells in the tumor bed. The indications for postoperative radiotherapy are the same as those described for the adjuvant situation and are based on the pretherapeutic baseline findings (Kaufmann, M et al. 2006).

### B 7.5 Immune therapy

#### Statement Adj-16

<table>
<thead>
<tr>
<th>Patients with HER2-positive (immunohistochemical score 3+ and/or FISH positive) tumors should receive trastuzumab treatment for one year. Trastuzumab can be administered concurrently with a taxane or sequential to anthracycline/taxane-containing chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LOE 1b, Grade of Recommendation A</strong> (Joensuu, H et al.; Piccart-Gebhart, MJ et al. 2005; Romond, EH et al. 2005; Slamon, DJ et al. 2006)</td>
</tr>
</tbody>
</table>

The results of five separate and unrelated studies have shown that adjuvant treatment with trastuzumab either sequentially or in combination with a standard chemotherapy consistently reduces the rate of recurrence by 45% to 50% and the mortality rate by about 30% in patients with HER2-overexpressing tumors (relative reduction of the risk of recurrence) (Joensuu, H et al. 2006; Piccart-Gebhart, MJ et al. 2005; Romond, EH et al. 2005; Slamon, DJ et al. 2006).

Consequently, adjuvant treatment with trastuzumab is always indicated for patients with node-positive tumors or node-negative tumors > 1 cm in diameter with HER2-overexpression. The duration of this therapy is one year. The infusions can be carried out weekly or at three-week intervals.

Quality-assured determination of HER2 status (for algorithm cf. Pathology) and adequate cardiac function are prerequisites for trastuzumab therapy. Monitoring of the left ventricular ejection fraction is obligatory since trastuzumab can induce clinically relevant cardiac insufficiency (NYHA III/IV) in as many as 4.1% especially when administered in combination with anthracyclines (Romond, EH et al. 2005; Tan-Chiu, E et al. 2005). In the retrospective analysis this appeared to affect mainly older patients (> 50 years) with previous cardiac disease. The three-year analysis of the American studies revealed no elevated late cardiac toxicity; after three years this figure was 2.5%.
Literature


Bonadonna G., Zambetti M., Valagussa P. Sequential or alternating doxorubicin and CMF regimens in breast cancer with more than three positive nodes. Ten-year results. JAMA 1995; 273 (7):542-547.


Thueerlim B., Price K. N., Castiglione M., Coates A. S., Goldhirsh A., Gelber R. D., Forbes J., Holmberg S., Verno A., Bernhard J., Zahrich D. Randomized controlled trial of ovarian function suppression plus tamoxifen versus the same endocrine therapy plus chemotherapy: Is chemotherapy necessary for premenopausal women


The term “locally advanced breast cancer” is usually used to describe T3 and T4 tumors with or without axillary involvement which have not yet produced systemic metastases. For some patients with this diagnosis, initial surgical therapy is an option and should be performed in conformance with the preceding statements (NCCN 2007; Shenkier, T et al. 2004). For more information on primary systemic therapy, refer also to Chapter B 7.4 and Statement Adj-13; for more information on radiotherapy, the reader is referred to Chapter B6.

### B 8.1 Primary systemic therapy

For most of these patients, systemic chemotherapy is the treatment of choice. A response rate of more than 60% can be expected. The objective of chemotherapy is to achieve operability. Primary radiotherapy alone is not recommended; however, it can be employed in combination with systemic chemotherapy (De Lena, M et al. 1981; Hortobagyi GN et al. 1987).

### B 8.2 Inflammatory breast cancer

In patients with inflammatory breast cancer, primary (preoperative, neoadjuvant) systemic therapy must be administered as part of a multimodal therapeutic strategy (Lucas, FV et al. 1978; NCCN 2007; Thomas, F et al. 1995; Thoms, WW, Jr. et al. 1989; Ueno, NT et al. 1997). A five-year survival rate of max. 50 % can be achieved for inflammatory breast cancer only with optimal chemotherapy. This disease thus represents a subgroup of breast cancer with an especially unfavorable prognosis (Genet, D et al. 2007). The best local control and the best survival rates are achieved in these patients by a combination of chemotherapy, mastectomy and radiotherapy.

### B 8.3 Inoperable patients

The majority of inoperable patients are older women with substantial comorbidity or a poor functional status. The objective of treatment in these cases is to preserve the best possible quality of life while achieving local tumor control.

Systemic endocrine therapy should be given a try in these patients. Most patients in this group will respond to treatment with anti-estrogens or aromatase inhibitors. The administration of radiotherapy alone represents a supplementary and/or alternative treatment option, especially in patients with actual or impending tumor ulceration (De Lena, M et al. 1978; De Lena, M et al. 1981; NCCN 2007; NHS 1994).
Literature


Section C
Recurrent or Metastatic Breast Cancer
C 1 Definition and Prognosis

C 1.1 Definition

The following are designated as local or locoregional recurrences: recurrence of breast cancer in the ipsilateral breast, in the ipsilateral chest wall including the overlying skin, in the regional lymph nodes of the axilla, in the supra- and infraclavicular region and along the internal mammary vessels.

A local or locoregional recurrence can occur in isolation or in combination with distant metastases in other organ systems ((Bruce, J et al. 1970), (Kurtz, JM et al. 1989), (Recht A et al. 1996).

Early detection of an isolated local or locoregional recurrence has a positive impact on survival. Regular examination for the presence of local or axillary recurrence is thus an important objective of follow-up care. Accordingly, therapy for local and locoregional recurrences is administered with curative intention in the majority of cases (50-70%) and with palliative intention in only about 30% (Dunst, J et al. 2001).

C 1.2 Incidence and prognosis

The incidence of local recurrence after breast-conserving surgery and radiotherapy is 5-10% (after 10 years). Median 5-year survival is 65 (45-79)% (Haffty, BG et al. 1991). Recurrences in the chest wall and axilla after mastectomy are observed in 4 (2-20) % and 1(0.1-8) %, respectively. These patients have a 5-year survival rate of 50 (24-78)% and 55 (31-77)%, respectively (Haffty, BG et al. 1991). The incidence of locoregional recurrences appearing simultaneously at different locations is 16 (8-19)%; this constellation is associated with a 5-year survival of 21 (18-23)% (Karabali-Dalamaga, S et al. 1978). Intramammary recurrence following BCT and local recurrence following MRM do not differ substantially in their clinical course and biological behavior ((Halverson, KJ et al. 1992a), (Jobsen, JJ et al. 2001), (Katz, A et al. 2001), (van Tienhoven, G et al. 1999)). The prognostic factors for the clinical course are identical for both constellations. After a local recurrence the primary prognostic factors continue to apply. The only differences here are between “early” (< 2 years) and “late” (> 2 years) local recurrences. “Early” recurrences can be cured to a lesser degree; moreover, they correlate with higher rates of second recurrences and distant metastases ((EBCTCG 1998), (Haylock, BJ et al. 2000a), (Huang, E et al. 2002), (Newman LA et al. 1998), (Taylor, ME et al. 1995)).
Prognostic factors for a local or locoregional recurrence after MRM or BCT:
- number of positive lymph nodes
- tumor size (maximal diameter)
- tumor grade
- hormone receptor status
- resection status (R0/R1/R2)
- focality (unifocal > multifocal > inflammatory LR)

Local and locoregional recurrences are treated with local therapy. In operable cases the goal should be complete excision of the tumor recurrence. The administration of postoperative radiotherapy following tumor excision can improve local tumor control (Schwaibold, F et al. 1991). If local tumor control is achieved by this therapy, long-term survival is possible (Halverson, KJ et al. 1992b). In inoperable cases, radiotherapy is the therapeutic modality of choice (Schwaibold, F et al. 1991). Owing to the high risk of subsequent systemic progression, systemic therapy can also be considered in addition to local treatment of the recurrence with surgery and/or radiotherapy ((Borner, M et al. 1994), (Haylock, BJ et al. 2000b)). It should be noted, however, that the effect of systemic chemotherapy in this context has not yet been substantiated by prospective randomized studies (Haylock, BJ et al. 2000b).

Prognostic factors for the clinical course after local or locoregional recurrence following MRM or BCT:
- resection status of the local recurrence (R0, R1, R2)
- tumor size of the local recurrence
- location (proximity to scars)
- focality
- tumor grade
- hormone receptor status
- length of disease–free interval
- primary lymph node status

Literature


C 2  Diagnostic Procedures for a Local or Locoregional Recurrence

In cases where a recurrence is suspected following BCT but it is not possible to differentiate clearly between scar tissue and malignancy on the mammogram, a magnetic resonance imaging (MRI) study of the breast should be performed. In patients who have undergone mastectomy, ultrasound diagnostic procedures to detect a recurrence should be performed regularly in addition to the clinical examination; in cases with unclear findings, MRI should additionally be performed. In both cases the diagnosis should be confirmed histologically via core biopsy. Following histological confirmation, mammographic and sonographic examination of the contralateral breast should also be performed and restaging should be undertaken. This restaging should be based on at least an x-ray of the lungs, a bone scan and an ultrasound examination of the liver. These methods can be supplemented by additional imaging studies if necessary. The performance of these additional studies is required during restaging in order to determine whether a curative or only a palliative approach is appropriate before starting the therapy (Hölzel D et al. 2001; Veronesi, U et al. 1995).

Literature

C 3 Treatment of Local or Locoregional Recurrence

C 3.1 Local (in-breast) recurrence

Statement Rec-1

In patients with an in-breast recurrence (DCIS or invasive carcinoma), the best local tumor control is achieved by secondary mastectomy.

LOE 3b (Borner, M et al. 1994; Dalberg, K et al. 1998)

In patients with a favorable baseline, e.g. patients with DCIS or invasive carcinoma with a long recurrence-free interval, no skin involvement and a large spatial distance between the site of the first tumor and the recurrence, an organ-conserving surgical procedure can be performed in cases where this is deemed justified.

LOE 4, Grade of Recommendation 0 (Deutsch, M 2002; Haffty, BG et al. 1996; Kurtz, JM et al. 1991; Whelan, T et al. 1994)

Patients who undergo organ-conserving surgery must be advised of the associated higher risk for a repeat in-breast recurrence.

GCP

The treatment of local recurrence consists of surgical intervention. In this group of patients, the highest degree of tumor control is achieved by mastectomy (Jobsen, JJ et al. 2001). If surgical treatment is again administered in the form of an organ-conserving procedure, the patient will have an increased risk of developing a new in-breast recurrence (30% after 5 years). A breast-conserving procedure can be performed again in patients with a favorable starting position, e.g. DCIS or invasive cancer with a long recurrence-free interval, no skin involvement or recurrence at a sizable distance from the site of the primary tumor. The best local control is achieved in patients with a disease-free interval of over 5 years in whom clearly negative resection margins are found during the repeat breast-conserving operation (Kurtz, JM et al. 1991). If radiotherapy has not been administered as part of the primary therapy, it should be performed postoperatively.

In patients with a recurrence who were initially treated with a breast-conserving procedure followed by radiotherapy, consideration can now be given to administering renewed external irradiation or local brachytherapy after repeat local excision in the interest of lowering the risk of recurrence and avoiding salvage mastectomy.

The survival rates recorded after local or locoregional recurrences vary greatly. The disease-free interval and the tumor mass of the recurrence, as well as the initial tumor stage and the time up to metastasis, have been shown to be independent and significant prognostic factors for survival both with and without additional therapy ((Dunst, J et al. 2001; Engel, J et al. 2003;
Feigenberg SJ et al. 2003; Moran, MS et al. 2002; Perez CA et al. 2004; Schmoor, C et al. 2000). Additional prognostic factors are: grading, resectability (R0 vs. R1 vs. R2), and the hormone receptor status and HER-2/neu oncogene status of the tumor recurrence (Borner, M et al. 1994; Dunst, J et al. 2001; Schmoor, C et al. 2000).

If the appropriate conditions are met, patients with a recurrence should be informed about the option of a repeat breast-conserving procedure. A local recurrence does not necessarily indicate that metastasis has taken place. In this situation avoidance of salvage mastectomy must not necessarily be associated with a worsening of overall survival.

Clinical studies are urgently required to confirm that repeated breast-conserving therapy and salvage mastectomy are of equal value (Kuerer, HM et al. 2004)

### C 3.2 Local recurrence after mastectomy

**Statement Rec-2**

<table>
<thead>
<tr>
<th>An isolated recurrence in the chest wall is to be removed completely by surgery (R0) if possible.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LOE 2a, Grade of Recommendation A</strong> (Schmoor, C et al. 2000)</td>
</tr>
</tbody>
</table>

The incidence of local and locoregional recurrences following mastectomy with or without adjuvant chemotherapy is 10–20%. About one-third of these recurrences are locoregional; they are found in order of decreasing frequency in the chest wall, supraclavicular region or axilla; they may also appear in a multifocal pattern (10–30% of cases) ((Perez CA et al. 2004; Taylor, ME et al. 1995)).

The aim should be complete excision of the tumor. Small recurrences in the scar can be removed by wide excision in healthy tissue: large chest-wall recurrences can be treated by chest wall resection. If larger sections of the chest wall are removed, it may be necessary to repair the resulting defects with skin flaps.

In cases where RO resection is achieved, the 5-year survival rate is 40–60%. If no radiotherapy has been performed as part of the primary therapy, radiotherapy should be performed post-operatively. In the presence of unfavorable risk factors, another course of (small-volume) radiotherapy may also be indicated after surgery for a recurrence (Aberizk, WJ et al. 1986; van Dongen, JA et al. 1992).

### C 3.3 Locoregional recurrences and isolated supraclavicular lymph node recurrences

**Statement Rec-3**

In patients with an isolated regional recurrence, the therapeutic objective should be to achieve local control of the disease via surgery and/or radiotherapy.

**Grade of Recommendation A**
In patients with an isolated locoregional recurrence, repeat resection either with or without radiotherapy is an option. In patients with locoregional lymph node recurrences (in contrast to patients with local recurrences) in whom the possibilities for surgical treatment are limited and it is not possible to administer such treatment with curative intent, local radiotherapy is the most promising local therapeutic modality for tumor control and offers the possibility of a curative outcome (Newman LA et al. 2000).

C 3.4 Pharmacotherapy

Statement Rec-4

| The benefits of postoperative systemic therapy following surgical resection of a locoregional recurrence in terms of improved overall survival have not been sufficiently substantiated. |
| There is evidence that the disease-free interval can be prolonged by systemic therapy. |
| **LOE 1b, Grade of Recommendation B** (Haffty, BG et al. 1996; Rauschecker, H et al. 2001) |

Additional systemic endocrine therapy can prolong the disease-free interval in hormone-receptor-positive postmenopausal patients; however, improvement of the survival rate has not been substantiated (Feyerabend, T et al. 2001; Sherar, M et al. 1997; van der Zee J et al. 1999; Vernon, CC et al. 1996; Waeber, M et al. 2003; Yarbro JW et al. 1999). In patients with hormone-sensitive recurrences, postoperative endocrine therapy can be instituted or the current endocrine therapy changed. This approach possibly results in improved disease-free survival and overall survival. The value of adjuvant chemotherapy after resection of a recurrence has not been substantiated. In patients with extensive chest wall recurrences, chemotherapy can improve local control.

C 3.5 Radiotherapy

Statement Rec-5

| The need for radiotherapy after surgery for a recurrence should be discussed and decided upon within an interdisciplinary team. Postoperative radiotherapy is indicated if radiotherapy was not administered previously or radical surgical excision of the local recurrence was not performed (R1–2). In patients with an inoperable local recurrence, palliative radiotherapy may be beneficial. |
| **LOE 4, Grade of Recommendation 0** (Aberizk, WJ et al. 1986) |

If radiotherapy has not been administered as part of the primary therapy, it should now be performed postoperatively. If additional unfavorable risk factors are present, a small-volume irradiation can be indicated even if adjuvant radiotherapy has already been performed as part of the primary therapy. In inoperable cases, radiotherapy is the therapeutic modality of choice.
Literature


C 4 Distant Metastases

C 4.1 General principles

In patients with distant metastases, our present knowledge indicates that long-term recovery can be achieved only in isolated cases. A relatively favorable clinical course can be predicted if the distant metastases occur as solitary lesions affecting only the bone and/or the skin. Moreover, patients with a positive hormone-receptor status, a favorable grading (G1 or G2), and a negative HER-2 status have a comparatively favorable prognosis. A recurrence-free interval of more than two years is also associated with good odds for longer survival.

In cases where the primary tumor occurs simultaneously with an isolated metastasis (M1), consideration can be given to surgical removal of the primary tumor following local excision of the distant metastasis if there is a chance of RO resection (Rapiti, E et al. 2006).

Statement Met-1

A patient with demonstrated distant metastases of breast cancer should be given an especially detailed briefing on the therapeutic options and be involved in the decision-making process. The patient’s request for information on all pertinent available measures, including supportive and complementary treatment options, should be met.

GCP

Statement Met-2

The therapy should be selected and modified to reflect the expectations, value concepts and preferences of the individual patient as well as her symptoms, age and general condition. It should also take account of any co-morbidity, the aggressiveness of the disease, the location of the metastases, the type of prior adjuvant and palliative treatment, HER-2 status, hormone-receptor status and menopausal status.

GCP
Statement Met-3

The following prognostic and predictive factors can be defined for the employment of the various palliative therapies:

– hormone-receptor status for hormonal therapy
– HER-2 status for therapy with trastuzumab or lapatinib
– bone metastases for the administration of bisphosphonates
– the previous response to a chemo-endocrine therapy for further systemic and local therapies
– the performance status for the effect of chemotherapy.

LOE 2, Grade of Recommendation B (Andersson, M et al. 1999; Cheung, KL et al. 1997; Hortobagyi, GN et al. 1996)

Treatment of distant metastases is performed with the aim of preserving the highest possible quality of life and achieving the greatest possible freedom from symptoms. A systemic therapy should be considered for all patients with metastatic breast cancer (Fossati, R et al. 1998). The patient should be briefed on the therapy and involved in the decision-making process. The patient’s request for information on all pertinent available measures, including supportive and complementary treatment options, should be satisfied. Participation of the patient in clinical studies should be aimed at. The choice of therapy should be adapted to the illness in the particular case and custom-tailored to reflect the age and symptoms of the individual patient. It should also take account of any co-morbidity, hormone-receptor status, menopausal status, HER-2 status, the pattern of metastasis, progression of the disease, and prior adjuvant and palliative therapies. Predictive factors should be taken into account when selecting a therapy.

C 4.2 Diagnostic measures in patients with distant metastases

C 4.2.1 Skeletal metastases

The following anatomical structures are affected, in descending order of frequency, by skeletal metastases: vertebrae, proximal femur, pelvis, ribs, sternum, calvarium and proximal humerus. A bone scan should be performed as the baseline examination for assessing the extent of metastasis. Suspicious lesions are then investigated with additional imaging methods (e.g. x-ray, CT, MRI) to identify locations where stability is endangered. MRI and CT are also capable of detecting spread of the tumor into the spinal canal or the paravertebral soft tissue.

C 4.2.2 Hepatic metastases

Ultrasound examination of the liver is sufficient as the baseline examination. In cases with unclear findings, CT or MRI must be performed.
C 4.2.3 Pulmonary metastases

A chest x-ray in two planes is sufficient as the baseline examination. If consideration is given to surgical treatment of the metastasis, a thin-layer spiral CT of the lung must be performed preoperatively.

C 4.3 Systemic therapy of metastatic breast cancer

C 4.3.1 Systemic endocrine therapy

Statement Met-4

Endocrine therapy is the therapy of choice for patients with a positive hormone-receptor status. In general hormonal therapy should be given preference over chemotherapy.

LOE 2b, Grade of Recommendation B (Fossati, R et al. 1998; Stockler M et al. 1997; Stockler, M et al. 2000)

Because endocrine therapy is less toxic than chemotherapy, it should always be employed as the first-line therapy. In particular, patients with a long disease-free interval, and with only bone or soft-tissue metastases, or with single visceral metastases stand to benefit from endocrine therapy. Remission is observed in 60% of patients with a positive hormone receptor status but in less than 10% with a negative hormone receptor status. Endocrine therapy should thus be carried out in patients with negative hormone receptors only in exceptional cases. In the rare cases with an indeterminate hormone-receptor status, however, patients can also be selected for endocrine therapy on the basis of the clinical course.

If the patient responds to endocrine therapy, it should be continued until progression, after which the administration of alternative endocrine substances is indicated and justified. Patients are switched to cytotoxic therapy only after all the endocrine therapeutic options have been exhausted or if they fail to respond to endocrine therapy.

Following the administration of an aromatase inhibitor alone or of tamoxifen together with an aromatase inhibitor (“switch or extended therapy”) as adjuvant therapy, there are insufficient data to justify a particular sequence of further hormonal therapy in patients at the stage of metastatic breast cancer.
Statement Met-5

Endocrine therapy is not indicated in the following cases:

– if there is a need to achieve rapid remission to prevent pronounced symptoms in the affected organ

– negative hormone-receptor status

– brain metastases (not an adequate/sufficient therapy).

**LOE 2b, Grade of Recommendation A** (Fossati, R et al. 1998; Stockler M et al. 1997; Stockler, M et al. 2000)

Statement Met-6

Combined chemo-endocrine therapy is not recommended. Although it can raise remission rates, it causes increased toxicity without prolonging either the progression-free interval or overall survival.

**LOE 1a, Grade of Recommendation B** (Sledge, GW, Jr. et al. 2000)

C 4.3.2  Endocrine therapy in postmenopausal patients

Statement Met-7

In postmenopausal patients with metastases, the first step in endocrine treatment – following adjuvant therapy with tamoxifen or no hormonal therapy – is the administration of an aromatase inhibitor.

**LOE 1a, Degree of Recommendation A** (Ellis MJ et al. 2000; Fossati, R et al. 1998; Hayes, DF et al. 1995; Mouridsen H et al. 2001; Mouridsen, H et al. 2001)

Statement Met-8

Depending on the prior anti-hormonal treatment, the further steps in the cascade of endocrine therapy used to treat postmenopausal women are the administration of anti-estrogens, estrogen receptor antagonists and high-dose progestins or the switch from a steroidal to a non-steroidal aromatase inhibitor (or vice versa).

**LOE 3b, Grade of Recommendation 0** (Fossati, R et al. 1998; Robertson, JF et al. 2003)

Third-generation aromatase inhibitors are the first-choice drugs. In the event of renewed progression of the disease, anti-estrogens, estrogen receptor antagonists and finally high-dose progestins can be administered (Gershovich, M et al. 1998; Robertson, JF et al. 2003).

Treatment with aromatase inhibitors is associated with significantly more side-effects induced by the hormone withdrawal (Goss, PE et al. 2005). During treatment with aromatase inhibitors – in comparison with tamoxifen treatment – fewer side-effects such as heat flushes, thromboembolic events and endometrial carcinoma occur. However, treatment with aromatase
inhibitors is associated with a higher rate of arthralgia and myalgia. Furthermore, greater lose of bone density and (among other sequelae) a higher rate of osteoporotic fractures are to be expected in these patients.

C 4.3.3  
*Endocrine therapy in premenopausal patients*

**Statement Met-9**

In premenopausal patients, suppression of ovarian function (e.g. with GnRH analogs, oophorectomy, ovarian ablation via radiotherapy) in combination with tamoxifen is the first-choice therapy.  

**LOE 1b, Grade of Recommendation A** *(Klijn, JG et al. 2001)*

**Statement Met-10**

In premenopausal patients, ovarian suppression can subsequently be carried out in combination with the administration of an aromatase inhibitor. Treatment with high-dose progesterins (MA/MPA) represents a further step.  

**LOE 2c, Grade of Recommendation 0** *(Taylor, CW et al. 1998; von Minckwitz G et al. 1991)*

The initial therapeutic step is to suppress ovarian function (e.g. with GnRH analogs, oophorectomy or ovarian ablation via radiotherapy) in combination with tamoxifen. In the event of cancer progression or in cases where tamoxifen is contraindicated, a third-generation aromatase inhibitor should be administered. If there is renewed progression or if the aromatase inhibitor is not tolerated, the administration of fulvestrant represents an alternative. Should further progression occur, the administration of progestins is then justified.

C 4.4  
*Chemotherapy for metastatic breast cancer*

**Statement Met-11**

Prior to the administration of chemotherapy, the patient’s general condition and compliance must be assessed.  

**GCP**
Statement Met-12

The toxicity of the therapy administered must be assessed both objectively and subjectively at regular intervals during the therapy. The doses administered, as well as the time intervals aimed at, must conform to generally accepted standard, or currently published, therapeutic regimens. After a suitable and representative measurement parameter (e.g. symptoms, tumor markers, indicator metastasis) has been selected prior to the institution of therapy, the therapeutic effect should be evaluated at least every 3 months. Cytotoxic maintenance therapy increases toxicity without improving survival. For this reason, cytotoxic therapy is recommended only in the event of increased symptomatology and/or cancer progression.

GCP

Statement Met-13

The therapy should be stopped immediately if progression or intolerable toxicity is observed.

GCP

Statement Met-14

The administration of combination chemotherapy, instead of single-agent chemotherapy, may confer a slight advantage in terms of survival. However, combination chemotherapy is often associated with higher toxicity rates.

LOE 1a, Grade of Recommendation 0 (Fossati, R et al. 1998)

In patients with mild symptoms and slow tumor growth – as well as cases where endocrine therapy is ineffective – single-agent chemotherapy is useful. However, in patients with severe symptoms and rapidly growing or aggressive tumors (i.e. in cases where there is a strong pressure to achieve remission), combination chemotherapy may be indicated.

LOE 1a, Grade of Recommendation B (Fossati, R et al. 1998)

Statement Met-15

The following substances, for example, may be used for single-agent chemotherapy: anthracyclines (including liposomal anthracyclines), anthraquinones, taxanes, vinorelbine and fluoropyrimidine. If polychemotherapy is administered, these cytotoxic agents can be combined with each other or with other substances. The highest remission rates are achieved by using a taxane in combination with an anthracycline or antimetabolite.

LOE 1b, Grade of Recommendation B (Fossati, R et al. 1998)

Statement Met-16

After the benefits of anthracycline and taxane chemotherapies have been fully exploited, patients should not be denied further chemotherapies, e.g. to stabilize the disease or to alleviate symptoms.

LOE 2b, Grade of Recommendation B (Feher, O et al. 2002; Vogel, C et al. 1999).
Owing to the heterogeneity of the metastases and the non-uniform course taken by the disease in the individual case, no uniform therapeutic strategy can be set down. This applies, in particular, to the cytotoxic treatment of metastatic breast cancer. Although single-agent therapies result in lower rates of remission than combination chemotherapies, this difference has no significant effect on survival. Since single-agent chemotherapies are tolerated better, they should be administered whenever possible. The administration of combination chemotherapy is indicated only in cases with severe symptoms, rapid tumor growth and aggressive tumor behavior.

If the patient has not yet received any anthracyclines as part of the adjuvant therapy, anthracyclines should be administered as the primary therapy since they can be expected to produce the best response rates.

Before and during the administration of chemotherapy, the patient’s general condition must be assessed. The degree of toxicity is determined regularly during the therapy. The therapeutic effect should be evaluated at least every 3 months. If progression or pronounced toxicity is observed, the therapy should be terminated. In the overall assessment of the therapy, the therapeutic index (i.e. the ratio between the benefits and the adverse effects of the therapy in the individual patient) should have a positive value.

The doses administered, as well as the planned intervals for the administration of the therapy, should be in line with general therapeutic guidelines, i.e. recognized published protocols. To date dose-intensified and high-dose therapies have not led to any improvement in effectiveness. Consequently, their use is acceptable only within the framework of studies.

**Statement Met-17**

Dose-intensified and high-dose therapies do not result in any improvement in survival.  
**LOE 1b** (Stadtmauer, EA et al. 2000)

**C 4.5 Targeted therapies**

**C 4.5.1 HER-2 inhibitors (trastuzumab, lapatinib)**

**Statement Met-18**

HER-2 status should be determined in advance of any potential therapy with HER-2 inhibitors. This status can be determined in the primary tumor or in a new biopsy.  
**LOE 1c, Grade of Recommendation A** (Schaller, G et al. 2001)
Statement Met-19

<table>
<thead>
<tr>
<th>Statement Met-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment with HER-2 inhibitors is indicated in patients with HER-2-overexpressing tumors. It can be administered in combination with chemotherapy or as a single-agent therapy in patients previously treated with taxanes and anthracyclines.</td>
</tr>
<tr>
<td><strong>LOE 1b, Grade of Recommendation B</strong> (Burstein, HJ et al. 2001; Seidman, AD et al. 2001; Slamon DJ et al. 2001)</td>
</tr>
</tbody>
</table>

In patients with metastatic breast cancer who overexpress HER-2/neu, trastuzumab, administered alone or in combination with chemotherapy, lengthens survival time. At present there are no comparable data available for lapatinib.

Trastuzumab can be used in the treatment of patients who overexpress HER-2/neu. It can be administered either as a single-agent chemotherapy (following prior treatment with anthracyclines and taxanes) or in combination with paclitaxel (first-line therapy). Combinations of trastuzumab with anthracyclines and other potentially cardiotoxic substances should be avoided since there is not yet a sufficient empirical base to support their use. Cardiac adverse reactions are observed in 14% of patients treated with trastuzumab; they occur, in particular, when this agent is administered in combination with an adriamycin-containing chemotherapy regimen (Slamon DJ et al. 2001).

Lapatinib is effective in patients with advanced local breast cancer or metastatic breast cancer who have previously been treated with trastuzumab (+ chemotherapy). Owing to lapatinib’s ability to pass the blood-brain barrier, brain metastases also appear to be treatable with lapatinib (Geyer, CE et al. 2006).

HER-2/neu oncogene status can be determined in the primary tumor. On the basis of our present knowledge, the following approach should be taken to determine the HER-2 status as a prerequisite for the administration of anti-HER-2 therapy (Wolff, AC et al. 2007):

- Standardized immunohistological determination of HER-2/neu overexpression (e.g. Hercep-Test® (DAKO) with interpretation strictly according to the manufacturer’s instructions).

In patients with a weakly positive test result (2+), FISH should be carried out additionally to explore the question of gene amplification. This study should be performed by a laboratory possessing the necessary expertise. To ensure the validity of the test method, standardized probe kits should be used (Inform®, Ventana; PathVysion®, Vysis).

Statement Met-20

<table>
<thead>
<tr>
<th>Statement Met-20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitoring of cardiac function before and during therapy with potentially cardiotoxic substances is essential.</td>
</tr>
<tr>
<td><strong>GCP</strong></td>
</tr>
</tbody>
</table>
C 4.5.2 Anti-angiogenesis: VEGF inhibitors (bevacicumab)

In patients with metastatic breast cancer, the employment of bevacicumab in combination with paclitaxel as the primary therapy, in comparison with paclitaxel alone, improves the therapeutic response (response rates) and prolongs the time to progression. There is currently no evidence that the use of bevacicumab at a later time results in a positive therapeutic outcome. During treatment with bevacicumab, blood pressure and renal function, in particular, must be monitored.

Statement Met-21

In patients with metastatic breast cancer receiving paclitaxel as the first-line cytotoxic therapy, bevacicumab can be administered to improve the therapeutic outcome.

GCP

C 4.6 Specific treatment of skeletal metastases

C 4.6.1 Indications for radiotherapy

Statement Met-22

In patients with symptomatic bone metastases or bone metastases posing a risk of fracture, radiotherapy is the local therapy of choice. The following constitute indications for radiotherapy:

– local pain symptomatology
– danger to stability (if necessary in combination with surgical stabilization)
– impairment of mobility and/or function, in particular neurological symptoms (emergency: spinal cord compression)
– pathological fractures which cannot be treated surgically
– as a postoperative therapeutic modality following the surgical treatment of bone metastases (insofar as only non-resecting methods have been used).

LOE 1a, Grade of Recommendation B (Hoskin PJ et al. 2001; Roos, DE et al. 2000; Steenland, E et al. 1999)

Administered to patients with bone metastases, radiotherapy is a very effective therapy for pain control, for the improvement of mobility and function, and for local stabilization or lessening of the danger of fracture. The single administration of 8 Gy or a brief radiotherapy, e.g. with the administration of 5×4 Gy, alleviates pain in most cases. Radiotherapy may also be necessary in patients with pathological fractures and following the surgical treatment of bone metastases. As a standard therapeutic regimen, 30 Gy broken down into 10 fractions is administered in single doses of 3 Gy at the rate of 5 radiotherapy fractions per week. In patients with solitary metastases, higher doses may also be administered to achieve long-term stabilization. Recalcification can be expected after 2–3 months in about 2/3 of the osteolytic metastases.
C 4.6.2 Operative therapy

Statement Met-23
Surgical therapy of skeletal metastases is carried out for pain management and to restore or preserve function and stability in order to improve the patient’s quality of life. The decision to operate is made as a function of the urgency and of the therapeutic objective of this surgery: If necessary the decision may be made by an interdisciplinary team including the surgeon (general surgeon, orthopedic surgeon or neurosurgeon), the radio-oncologist, the medical specialist with oncological expertise, and the pain therapist.

LOE 1c, Grade of Recommendation B (Ali, SM et al. 2003; Wunder, JS et al. 2003)

Statement Met-24
The following constitute indications for operative therapy:
– pathological fractures (especially in the lower extremities and the acetabulum)
– unstable pathological vertebral fractures
– progressive spinal or radicular compression (the option of radiotherapy should be considered)
– impending fractures of the lower extremities.


The operative therapy of bone metastases serves the purpose of restoring or maintaining function and stability. It should be carried out in patients with pathological fractures of the lower extremities or the acetabulum, unstable pathological vertebral fractures, impending fractures of the lower extremities or progressive spinal or radicular compression. The surgical principle consists of resection of the metastases and stabilization via internal fixation. If resection is performed in the proximity of a joint, a complete joint replacement procedure may be performed.

C 4.6.3 Bisphosphonates

Statement Met-25
The following constitute indications for bisphosphonate therapy: hypercalcemia, bone pain caused by metastases, osteolytic metastases, and manifest osteoporosis induced by cancer therapy.

LOE 1b, Grade of Recommendation A (Conte, PF et al. 1996; Hortobagyi, GN et al. 1998; O’Rourke, N et al. 1995; Rosen, LS et al. 2001; Theriault, RL et al. 1999)
In patients with hypercalcemia resulting from osseous metastases, bisphosphonates are the therapy of first choice. The bisphosphonate therapy should be continued after the hypercalcemic crisis has been overcome.

Bisphosphonates are indicated as a systemic therapy in addition to chemotherapy or radiotherapy in patients with bone metastases, especially patients with osteolytic metastases. This therapy can delay the occurrence of new osseous lesions and slow the progression of existing metastases. Moreover, bone pain caused by metastases can be lessened by bisphosphonates. The indication for local therapeutic measures remains unchanged.

Bisphosphonates can also be used to treat osteoporosis induced by cancer therapy. In a few cases, bisphosphonates can lead to the development of necrosis of the jaws. The pathogenetic mechanism has not yet been elucidated. Prior to the institution of bisphosphonate therapy and during the treatment, therefore, a dentist or orthodontist should be involved in the case with the aim of prevention or early detection of necrosis of the jaws. (Mignogna, MD et al. 2006). The recommendations of the German Society of Dentistry and Oral and Maxillary Medicine (DGZMK) should be followed here (http://www.zm-online.de).

C 4.6.4 Specific treatment of brain metastases

Statement Met-26

An isolated brain metastasis can be treated by surgery, by single-session stereotactic irradiation or by fractionated radiotherapy (SFRT) especially if the extracerebral disease is under control.

LOE 2a, Grade of Recommendation 0 (Alderson, PO et al. 1983; Antoniades J et al. 1993; Kundziolka D et al. 1999)

Statement Met-27

In patients with multiple brain metastases, percutaneous irradiation of the entire cranium (whole brain radiotherapy), supported by steroid medication in patients with perifocal edema, is indicated for the control of existing neurological symptoms. Substantial (including transient complete) improvement of symptoms is achieved in 50–70% of patients with headache, 30–40% with paresis, and 40–50% with cerebral dysfunction.

LOE 2a, Grade of Recommendation A (Kundziolka D et al. 1999)

An isolated brain metastasis should be treated by surgery, by single-session stereotactic irradiation (“radiosurgery” (RS)) or by fractionated radiotherapy (SFRT) especially if the extracerebral disease is under control. Surgery and radiosurgery are of equal value with respect to local effectiveness. In comparison with surgical therapy, RS has the advantage that it can be used to treat metastases that are inoperable by virtue of their location and has a lower risk of complications. Both methods improve local disease control in comparison with conventional radiotherapy techniques. Percutaneous irradiation of the entire cranium additionally improves the results achieved by the therapeutic measures aimed at local control (Kundziolka D et al. 1999).
In patients with multiple brain metastases, whole brain irradiation, accompanied by corticoid therapy if necessary, is indicated to control progressive neurological symptoms. Substantial (including transient complete) improvement of symptoms is achieved in 50–70% of patients with headache, in 30–40% with paresis, and in 40–50% with cerebral dysfunction (Lagerwaard FJ et al. 1999). In individual cases where progression is again observed, stereotactic irradiation may be indicated. In cases with meningeal involvement, intrathecal chemotherapy may be indicated.

If brain metastases develop in patients with HER2-positive tumors during treatment with trastuzumab, consideration can be given to treatment with lapatinib (in combination with capecitabine if necessary). Such treatment should be administered only to patients with a low level of clinical symptomatology and must be monitored closely (Geyer, CE et al. 2007; Lin, Nu et al. 2007).

C 4.7 Special treatment of visceral distant metastases

**Statement Met-28**

In individual cases satisfying the criteria listed below, local therapy may be indicated for patients with visceral metastases (i.e. metastases located in the liver, lungs or other organs):

- no disseminated metastases
- no local recurrence or second primary
- metastases in only one lobe of the lungs or liver (if both lobes are affected, surgery is not indicated)
- the metastases did not occur during the first year after primary treatment.

LOE 3b, Grade of Recommendation 0 (Bathe, OF et al. 1999; Vogl, TJ et al. 1999)

C 4.7.1 Hepatic metastases

If hepatic metastases occur in only one lobe of the liver, resection of the metastases can be undertaken. Alternatively, consideration can be given to radiofrequency ablation. The surgical treatment must be followed by systemic therapy. Local treatment of hepatic metastases can be performed if the following conditions are met: 1) exclusion of extrahepatic metastases, local or locoregional recurrence and second primary 2) appearance of the metastasis one year after the primary treatment at the earliest.

C 4.7.2 Pulmonary metastases

Resection of pulmonary metastases is indicated only in the following cases (after extrapulmonary metastases have been excluded): 1) occurrence of a solitary pulmonary metastatic lesion or 2) involvement of only one lobe of the lung. Systemic therapy is administered postoperatively. A 5-year survival rate of up to 35% has been reported for the curative resection of pulmonary metastases.
**C 4.7.3 Malignant pleural effusion**

**Statement Met-29**

| In cases where pleural carcinosis occurs together with symptomatic effusion, pleurodesis may be indicated. |
| LOE 2b, Grade of Recommendation 0 (Cardillo, G et al. 2002) |

If the malignant pleural effusion contributes to the patient’s symptoms, and there are no other manifestations of greater importance, pleurodesis is indicated; bleomycin or talc can be used. There is no clear-cut evidence to support the use of mitoxantrone as a therapy for pleural effusion.

**C 4.7.4 Cutaneous and soft-tissue metastases**

Circumscribed cutaneous metastases and metastases of soft-tissue may be excised with clear margins or treated with local percutaneous radiotherapy. Non-extensive lesions can be treated with a topical cytotoxic agent, e.g. miltefosine.

**Literature**


Section D
Treatment, Care and Support
Owing to the significant developments in diagnostic and therapeutic options in recent years, the terms “aftercare/follow-up care” and “support” (previously Chapter 9 in the section “Locoregional Primary Disease” as well as Chapter 3 “Rehabilitation” and Chapter 4 “Psychosocial Measures” in the section “General Guidelines”) have to be redefined and restructured. To date aftercare has been regarded as commencing directly after the completion of primary treatment (six months after operation at the latest). The definition of this period has changed following the introduction of neoadjuvant therapies, adjuvant long-term therapies with antibodies and (anti-)hormones, and modified forms of radiation therapy. This means that both the content and the time frames associated with the term “aftercare” must now be adapted to the current situation. Furthermore, the various subject areas, which play a role at different points along the chain of care for patients with breast cancer, overlap to some extent.

The new chapter “Treatment, Ongoing Care and Support” therefore also includes the psychosocial aspects and psychooncology (previously C 4) and the supporting therapies (now discussed in a separate new chapter). Both chapters dealt thematically with treatment situations that begin during primary treatment but also continue seamlessly into long-term support. The chapter “Rehabilitation” (previously C 3) covers the period occurring directly after the primary local therapy. This is generally the point at which primary treatment in the form of surgery (also after preceding neoadjuvant chemotherapy) or radiotherapy (also after preceding adjuvant chemotherapy) is completed.

After completion of the primary local therapy, in particular a completed course of radiotherapy, the newly defined aftercare (previously A 9) begins, focusing on the earliest possible detection of locoregional or intramammary recurrences and of new cancers in the contralateral breast, the targeted search for metastases if the patient has symptoms or there are grounds for suspecting the existence of metastases, and the diagnosis and treatment of side-effects and late sequelae of both the primary and long-term therapies.

The last part of this restructured section is devoted to palliative medicine, which is given more space because of its increasing importance.

The tasks of the doctors have changed because of the increasing complexity of the diagnostic and therapeutic options and the time periods involved. Some prospective randomized studies dealing with single aspects such as side effects, long-term toxicities or the use of supportive measures do exist. However, the definitions of the examinations, both in terms of the interval and the type of examinations, are specific to the individual studies. Summaries of overall data from prospective randomized studies for evidence-based recommendations for action within this altered spectrum of tasks are not available. A general recommendation for routine clinical practice can therefore only be issued after evaluation of the data and merging of individual aspects. Here it must also be borne in mind that since 2004 no new prospective randomized studies have been published on the testing of new methods or new time intervals for the diagnosis of a locoregional recurrence or distant metastases. The frequent, almost annual,
changes in the recommendations for therapy therefore render it impossible to update the recom-
recommendations on the intervals and the types of diagnostic procedures to be used. Prospective
randomized studies to explore this are currently not being initiated owing to the heterogeneous
problems. As a result, the body of data on this subject is not going to improve in the near future.
D 2  Psychosocial Aspects and Psychooncology

D 2.1  Basic principles of psychooncological care

Today psychooncology is recognized as a separate discipline devoted to scientifically studying the various psychosocial aspects of the development, treatment and course of a cancer in childhood, adolescence or adulthood, and applying the findings to the care and treatment of patients (Holland, JC 2002; Sellschopp A, et al. 2002; Weis, J et al. 2000). Psychooncology is an integral part of oncological diagnosis, treatment and aftercare of patients with breast cancer. In Germany a number of specialist societies offer further and continuing training programs in psychooncology as a basis for the necessary professional qualification. The programs are aimed at doctors, psychologists and social educators, referred to in the following as psychooncological specialists. An additional qualification in psychooncology is required for a person to be recognized as a psychooncological specialist. The psychooncological care of breast cancer patients should be interdisciplinary, including all the occupations involved in treatment. This implies that a psychooncological specialist in a given care setting (inpatient and outpatient treatment, inpatient rehabilitation, outpatient aftercare) is integrated into the treatment team and has taken part in a regular exchange with the doctor in charge of the patient’s medical treatment. This exchange should take the form of, and be structured as, case conferences or ward conferences (Koch, U et al. 1998; NHMRC 1999; NHMRC 2003).

Statement Psych-1

<table>
<thead>
<tr>
<th>Psychooncological treatment measures should be integrated into the overall plan for the cancer therapy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOE 1b, Grade of Recommendation B (Edwards, AG et al. 2004; Sheard, T et al. 1999)</td>
</tr>
<tr>
<td>All patients should receive information from doctors at an early stage concerning all the types of psychooncological assistance that are available.</td>
</tr>
<tr>
<td>GCP (Luker, KA et al. 1996; Street, RL, Jr. et al. 1995)</td>
</tr>
</tbody>
</table>

D 2.2  Psychooncological care strategies and interventions

The psychooncological care of patients with breast cancer includes patient-oriented information and counseling (Burish, TG et al. 1991; Burton MV et al. 1995; Flam, B et al. 1989; Hathaway, D 1986; Johnston, M et al. 1993; Leinster SJ et al. 1989; Meyer, TJ et al. 1995), com-
petent psychological diagnosis and assessment of needs (Hall, A et al. 1996; Jenkins, PL et al. 1991; Pinder, KL et al. 1993) as well as targeted psychooncological treatment to help the patient cope with the sequelae of both disease and treatment (Devine, EC et al. 1995; McAr- dle, JM et al. 1996). Family members should be included in the ongoing psychooncological care (Christ, GH et al. 1993; Nelson, DV et al. 1994).

Owing to the diversity and complexity of the possible forms of psychological impairment that breast cancer patients may experience during the various phases of the disease and its treatment, their psychosocial treatment requirements must be determined individually and a psychooncological specialist must be called in if necessary. This is the only way to approach the widely differing problems and stresses faced by breast cancer patients.

Psychooncological interventions in patients with breast cancer are aimed at the following areas:

– anxiety, depression, subjective distress (Devine, EC et al. 1995; Sheard, T et al. 1999)
– coping with the disease, attitude to the disease (Devine, EC et al. 1995; Sheard, T et al. 1999)
– health-related quality of life and functional state (Edwards, AG et al. 2004)
– body image (Burke, S et al. 1998; Maguire, P et al. 1980; Schover, LR et al. 1995)
– concept of self
– social relationships, communication (Dowsett, SM et al. 2000; Kissane, DW et al. 1994; Pistrang, N et al. 1995)
– sexuality (Burke, S et al. 1998; Burton, MV et al. 1995; Maguire, P et al. 1980; Schover, LR et al. 1995)
– fatigue (Graydon, JE 1994; Knobf, MT 1986; Turner, J et al. 1998)
– pain (Fields, HI 1995; Loscalzo, M 1996; Spiegel, D et al. 1983)
– compliance with treatment
– neuropsychological impairment (i.e. problems in areas such as attention, memory and ability to concentrate) (Poppelreuter, M et al. 2006)

Statement Psych-2

Psychooncological interventions should be tailored to the patient’s individual needs and made available at the earliest possible opportunity as required. In addition to clinical judgment, validated measuring instruments – e.g. psychooncological basic documentation (PO BaDo), the German version of the Hospital Anxiety and Depression Scale (HADS), the Hornheide Questionnaire and the Distress Thermometer – may be used to assess the need for psychooncological intervention.

LOE 1b, Grade of Recommendation B (Edwards, AG et al. 2004; Weis, J et al. 2006)

Psychooncological interventions in breast cancer patients include the following measures, which have differing focuses in the acute hospital setting, rehabilitation clinic and in the further course of aftercare or palliative care:

– supportive one-on-one counseling sessions (Devine, EC et al. 1995; Forester, B et al. 1985; Ley, P et al. 1992; Meyer, TJ et al. 1995; Moorey, S et al. 1994)
– crisis intervention (Burton, MV et al. 1995)
– symptom-oriented procedures (relaxation, imagination) (Bindemann, S et al. 1991; Cimprich, B 1993; Edgar, L et al. 1992)
– neuropsychological training (Poppelreuter, M et al. 2006)
– artistic therapies (visual arts, music and dance therapy) (Weiss, MC et al. 1992)
– initiation of, and making arrangements for, aftercare (NHMRC 1994)
– advice on matters related to social assistance law
– terminal care (Kellehear, A 1990)

If psychological disturbances occur, the patient should receive psychooncological and psychotherapeutic treatment from medically or psychologically qualified psychotherapists.

**Statement Psych-3**

To guarantee the continuity of the psychooncological support provided after inpatient treatment, the patient should be informed about continuing aftercare options in the outpatient and community settings (cancer counseling centers, registered psychotherapists, self-help groups, social counseling services, etc.).

**GCP**

It has been found to be helpful to include not only the classical parameters but also quality of life in the assessment and planning of diagnostic and therapeutic measures. To assess the quality of life, structured and standardized questionnaires (e.g. the EORTC QlQ C30 or FACT G) (Aaronson, NK et al. 1993; Cella, DF et al. 1993) (Albert, US et al. 2002; Coates, A et al. 1997; Koller, M et al. 2002) can be used in addition to the doctor-patient interview. Such questionnaires can be employed to evaluate the patient’s state in somatic areas (e.g. intensity and frequency of physical symptoms, functional impairment), psychological areas (e.g. anxiety, depression, cognitive impairment) and social areas (e.g. family life, work, sexuality). The quality of these questionnaires as measurement instruments – i.e. their reliability, validity and sensitivity – have been tested in extensive studies (Cella, DF et al. 1993). Randomized studies exist on the use of instruments measuring the quality of life in routine care (Velikova, G et al. 1999; Velikova, G et al. 2004).

**Statement Psych-4**

The patient’s quality of life should be assessed regularly throughout the course of the disease. Standardized questionnaires for assessing quality of life may be used.

**LOE 2, Grade of Recommendation B** (Velikova, G et al. 1999; Velikova, G et al. 2004)
Literature


Burke S., Kissane D. W. Psychosocial support for breast cancer patients provided by members of the treatment team: A summary of the literature 1976-1996. NHMRC National Breast Cancer Centre 1998. [NHMRC]


Koch U., Weis J. (Hrsg.). Krankheitsbewältigung bei Krebs und Möglichkeiten der Unterstützung. Der Förder-


NHMRC. Psychosocial practice guidelines: information, support and counselling for women with breast cancer. NHMRC National Health and Medical Research Council, 1999.


Weis J., Blettner G., Schwarz R. Psychoonkologische Versorgung in Deutschland. Qualität und Quantität. Z Psycho-
som Med Psychother 2000; 46, 1:4-17. [DKG-N]
Weis J., Domann U. Interventionen in der Rehabilitation von Mammakarzinompatientinnen. Eine methodenkritische
Weiss M. C., Fowble B. L., Solin L. J., Yeh I. T., Schultz D. J. Outcome of conservative therapy for invasive breast
543.
D 3 Supportive Therapy

D 3.1 Definition

The term supportive therapy is used to signify supporting measures that optimize the safety and tolerability of cytotoxic chemotherapies and other medications, operations or radiotherapy for treating the malignant underlying disease. Supportive measures are an essential part of the oncological treatment strategy for preventing and treating complications and side effects of cancer therapy. One major objective of supportive therapy is to maintain or improve patients’ quality of life.

D 3.2 Significance and quantification of side effects

When looking at the side effects of cytotoxic therapies, a distinction must be made between objectively measurable damage on one hand and subjective impairment on the other. These effects are often evaluated differently by doctors and patients: patients regard nausea and alopecia, for example, as serious problems, while doctors tend to concentrate more on objectively measurable and possibly life-threatening organ toxicities (e.g. myelosuppression).

To achieve better understanding and documentation, it is recommended that information about the severity of unwanted effects should be recorded according to a generally accepted classification scheme, e.g. the Common Tolerability Criteria of Adverse Events of the American National Cancer Institute (NCI-CTCAE, currently in version 3.0) or the WHO toxicity scales.

D 3.3 Basic principles of supportive therapy

As a basic principle, foreseeable problematic toxicities should be anticipated and avoided from the outset whenever possible. The patient’s individual situation and comorbidities must always be taken into account when selecting the anti-cancer medication and its dosage. For side effects that cannot be avoided, prophylaxis is better, in the vast majority of cases, than treating toxicity that has already occurred. In practice, therefore, comorbidities and risk factors concerning side effects should be systematically recorded before the start of cytostatic treatment and the treatment protocol amended accordingly.

The patients should be given comprehensive information at an early stage about any side effects that can be expected, general measures for preventing them, and treatment options; preventive medication should be prescribed if necessary. Today prophylactic medication against nausea and vomiting, and avoidance of the neutropenia associated with certain chemotherapies, are standard in cancer treatment, and should be carried out in accordance with the current guidelines given below.
During therapy the patient must be asked specifically about undesired effects, which must be documented, to permit corresponding modifications to the treatment protocol (e.g. reducing the dose) or the introduction of additional measures.

**D 3.4 Nausea and vomiting induced by chemotherapy**

Nausea and vomiting induced by chemotherapy are among the most distressing side effects of cytotoxic treatment, although in the great majority of cases modern antiemetic prophylaxis can effectively prevent vomiting. The subjective distress and discomfort caused by nausea is often more problematic.

The prevention of nausea and vomiting caused by chemotherapy or radiation therapy is an essential supportive measure in the treatment of cancer. Owing to the risk of anticipatory vomiting, the antiemetic must always be administered as a prophylactic during tumor treatment. The American Society of Clinical Oncology (ASCO) and the Multinational Association of Supportive Care in Cancer (MASCC) have developed guidelines for preventing and controlling nausea and vomiting, which are reproduced in condensed form below (Table II) (ASCO 2006; Kris, MG et al. 2006; The Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC) 2006).

The antiemetic prophylaxis should always be matched to the emetogenic potential of the cytotoxic drugs.

---

<table>
<thead>
<tr>
<th>Table I. Emetogenic potential of cytotoxic drugs used to treat breast cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High:</strong> risk of vomiting in nearly all patients (&gt; 90 %)</td>
</tr>
<tr>
<td>cisplatin</td>
</tr>
<tr>
<td><strong>Moderate:</strong> risk of vomiting in 30–90% of patients</td>
</tr>
<tr>
<td>carboplatin</td>
</tr>
<tr>
<td>cyclophosphamide (&lt; 1500 mg/m²)</td>
</tr>
<tr>
<td>cyclophosphamide, per os</td>
</tr>
<tr>
<td>daunorubicin</td>
</tr>
<tr>
<td>doxorubicin</td>
</tr>
<tr>
<td>epirubicin</td>
</tr>
<tr>
<td><strong>Low:</strong> risk of vomiting in 10–30% of patients</td>
</tr>
<tr>
<td>capecitabin</td>
</tr>
<tr>
<td>docetaxel</td>
</tr>
<tr>
<td>5-fluorouracil</td>
</tr>
<tr>
<td>gemcitabine</td>
</tr>
<tr>
<td>doxorubicin HCL liposome</td>
</tr>
<tr>
<td>methotrexate (&gt; 100 mg/m²)</td>
</tr>
<tr>
<td><strong>Minimal:</strong> &lt; 10% of patients at risk of vomiting</td>
</tr>
<tr>
<td>bevacizumab</td>
</tr>
<tr>
<td>erlotinib</td>
</tr>
<tr>
<td>gefitinib</td>
</tr>
<tr>
<td>hormones</td>
</tr>
</tbody>
</table>
Table I shows the emetogenic potential of individual chemotherapeutic agents. The cytotoxic drug with the highest emetogenic potential determines allocation to the risk group “high, moderate, low or minimal.” The addition of other cytotoxic agents, e.g. in combination chemotherapy, is not expected to have an additive effect on the emetogenic potential. Readers should note that the emetogenic potentials of the various cytotoxic drugs given in Table I have not been compiled on the basis of objective evidence, but largely on the basis of subjective experience.

Table II. Antiemetic prophylaxis in chemotherapy on day 1 (acute phase) and on days 2 to 4 (delayed phase) according to the ASCO/MASCC Guidelines.

<table>
<thead>
<tr>
<th>Emetogenic potential</th>
<th>Acute phase, up to 24 h after chemotherapy</th>
<th>Delayed phase, after 24 h up to day 5 after chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>5-HT₃ receptor antagonist: granisetron 2 mg p.o./1 mg i.v. ondansetron 16 mg p.o./8 mg i.v. tropisetron 5 mg p.o./i.v. dolasetron 200 mg p.o./100 mg i.v. + steroid: dexamethasone 12 mg p.o./i.v. + neurokinin-1-receptor antagonist: aprepitant 125 mg p.o.</td>
<td>steroid: dexamethasone 8 mg p.o./i.v. for 3 - 4 days (2 x 8 mg without aprepitant) + neurokinin-1-receptor antagonist: aprepitant 80 mg p.o. for 2 days</td>
</tr>
<tr>
<td>Moderate</td>
<td>First prophylaxis recommended for anthracycline/cyclophosphamide-based chemotherapies (also for FEC and FAC): as for highly emetogenic chemotherapy (see above)</td>
<td>First prophylaxis recommended for anthracycline/cyclophosphamide-based chemotherapies (also for FEC und FAC): as for highly emetogenic chemotherapy (see above) steroid: dexamethasone 8 mg p.o./i.v. for 2 days + neurokinin-1 receptor antagonist: aprepitant 80 mg p.o. for 2 days + steroid: dexamethasone 8 mg p.o./i.v. for 2 days</td>
</tr>
<tr>
<td>Low</td>
<td>steroid: dexamethasone 8 mg p.o./i.v.</td>
<td>no routine prophylaxis</td>
</tr>
<tr>
<td>Minimal</td>
<td>no routine prophylaxis</td>
<td>no routine prophylaxis</td>
</tr>
</tbody>
</table>

The antiemetic should always be administered prophylactically before the chemotherapy commences. There is no advantage of oral administration of antiemetics over i.v. administration or vice versa. The prophylaxis must be given on the first day of chemotherapy (acute
phase) and on days 2 to 3 or 4 (delayed phase). If the patient is refractive to therapy, or for patients who do not tolerate the 5-HT$_3$ receptor antagonists, aprepitant or dexamethasone, the use of metoclopramide 4 x 30 drops or 1 amp. (= 10 mg) i.v. / haloperidol 1–2 x 20 drops or 1/4–1/2 ampoule (1 amp. = 5 mg) as a short infusion can be effective.

The following anti-emetic medications are effective as prophylactic agents but are not sufficiently effective to be used alone:

– Benzodiazepines: lorazepam 1–2 x 1 mg; alprazolam 0.25–1.0 mg
– Diphenhydramine (depending on the manufacturer)
– Promethazine 1–2 x 20 drops (= 20 mg) or 25 mg (= 1/2 amp.) as a short i.v. infusion
– Olanzapine 2.5–5 mg p.o. 2 x daily

### D 3.5 Nausea and vomiting induced by radiation therapy

The emetogenic potential of radiation therapy applied to the breast is regarded as minimal (< 30%). Routine antiemetic prophylaxis is therefore not recommended. If nausea or vomiting occurs, dopamine-receptor antagonists (metoclopramide, alizapride) or 5-HT$_3$ serotonin receptor antagonists may be used; their continued daily administration before the start of each radiotherapy session is recommended.

### D 3.6 Neutropenia – febrile neutropenia – infections

Myelosuppression is one of the genuine cytotoxic effects of chemotherapeutic agents. Its extent in the individual case is influenced by patient- and disease-related factors as well as by the properties of the cytotoxic drugs. Prior extensive cytotoxic treatment and irradiation of major parts of the axial skeleton are regarded as independent risk factors. If elimination of the cytotoxic agents is delayed by organ damage (hepatic or renal insufficiency), it can be expected that the effects of certain cytotoxic drugs will be increased and that neutropenia will occur more frequently.

In patients with recurrences, in particular, it may be helpful to begin the therapy with a reduced dose or to increase gradually to the standard dose in the following cycles – in cases where there has been extended pretreatment or other risk factors exist – if the treatment is sufficiently well tolerated.

Afebrile neutropenia is generally not an indication for the therapeutic use of granulocyte colony-stimulating factor (G-CSF) preparations. In cases of serious prolonged neutropenia, e.g. an absolute neutrophil count (ANC) < 100/μl over > 3 days, or ANC < 500 μl over > 7 days, antibiotic prophylaxis may be considered e.g. a gyrase inhibitor. Depending on the toxicity profile, in individual cases switching to a different chemotherapeutic agent may be considered.

The most important sign of an infection in neutropenic patients is the diagnosis of febrile neutropenia (FN). According to the guidelines of the NCCN and the Infectious Diseases Working Party of the German Society of Hematology and Oncology, FN is defined by an elevated temperature (≥ 38° C) with a concomitant lowered granulocyte concentration < 500/μl or < 1000/μl in the following 48 hours.
D 3.6.1 Risk factors for febrile neutropenias

The most important determinants of the risk of FN include the type of chemotherapy and the intensity of the dose. Combination chemotherapies increase the risk in comparison to monotherapies, as does therapy with strongly myelotoxic or mucotoxic cytotoxic agents. High-dose cyclophosphamide and high-dose anthracyclines (in early breast cancer) have been described as significant predictors of severe or febrile neutropenias (Crawford, J et al. 2007).

Table III gives an overview of frequently used regimens with high (> 20 %), intermediate (10–20 %) or low (< 10 %) risk of FN.

<table>
<thead>
<tr>
<th>FN risk (%)</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 20</td>
<td>AC → docetaxel; doxorubicin/docetaxel; doxorubicin/paclitaxel; TAC</td>
</tr>
<tr>
<td>10–20</td>
<td>AC; EC; docetaxel; FE120C (q4 weeks); CEF</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>CMF</td>
</tr>
</tbody>
</table>

A dose-dense therapy should always be regarded as a higher risk > 20%.

Table IV. Risk factors for febrile neutropenia (according to the National Comprehensive Cancer Network, NCCN 2006) (Crawford, J et al. 2007; Lyman, GH 2005).

Chemotherapy-related risk factors
- Type of chemotherapy
  - Previous history of severe neutropenia during comparable chemotherapy
  - 80 % of the planned relative dose intensity
  - Pre-existing neutropenia (< 1000/μl) or lymphocytopenia
  - Previous extensive chemotherapy
  - Simultaneous or previous radiation treatment involving the bone marrow

Patient-related risk factors
- Age (> 65 years)
- Female
- Compromised general condition (ECOG ≥ 2 “Eastern Cooperative Oncology Group”)
- Poor nutritional state
- Impaired immune function

Risk factors associated with increased risk of infection
- Open wounds
- Active infections
- Comorbidity
- Chronic obstructive pulmonary disease
- Cardiovascular disease
- Diseases of the liver (raised level of bilirubin, alkaline phosphatase)
- Diabetes mellitus
- Low hemoglobin level at diagnosis
**D 3.6.2 Relative dose intensity of chemotherapy**

Many treatment protocols can only reach the required relative dose intensity, i.e. the planned required quantity of cytotoxic agents, in a defined time interval if neutropenia and febrile neutropenia are avoided or kept within a clinically acceptable range. This applies in particular to dose-dense protocols with short intervals between treatment cycles and increased dose intensity.

**D 3.6.3 When is prophylactic use of G-CSF to prevent febrile neutropenia indicated in chemotherapy?**

The current recommendations issued by the NCCN, ASCO and EORTC, i.e. to use G-CSF as soon as the risk of febrile neutropenia exceeds 20 %, are based on the results of randomized studies. These show that patients with an FN risk of between 20 % and 40 % benefit significantly from the administration of G-CSF (Green, MD et al. 2003; Holmes, FA et al. 2002; Martin, M et al. 2006; Vogel, CL et al. 2005).

If a chemotherapy is planned that induces a moderate FN risk (10–20 %), the NCCN, ASCO and EORTC recommend that before each chemotherapy cycle, the individual overall FN risk should be assessed and patient-related and tumor-related risk factors should be considered (see Table IV).

The algorithm shown in Figure 1 should be used for G-CSF prophylaxis.

---

**Figure 1.** Algorithm for estimating primary prophylaxis with G-CSF; according to the ASCO Guidelines 2006 (Smith, TJ et al. 2006).
D 3.6.4 **G-CSF: Dosages and duration of therapy**

According to the marketing authorization documentation, the following dosages are recommended (preparations are listed in alphabetical order).

- Filgrastim: 5 μg/kg/day s.c. or i.v., within 1–3 days after chemotherapy
- Lenograstim: 150 μg/m² of surface area/day s.c. or i.v. within 1–3 days after chemotherapy
- Pegylated filgrastim: approx. 24 hours after chemotherapy: one-off dose of 6 mg s.c. per cycle

D 3.6.5 **Infections in neutropenic patients**

In over 95 % of cases, fever during chemotherapy-associated neutropenia is caused by an infection. However, no pathogen can be identified in 50–70 % of patients. The immediate administration of broad-spectrum antibiotics is therefore necessary to provide prompt and effective treatment and prevent further development into a potentially life-threatening infection (Link, H et al. 1994; Link, H et al. 2003; Link, H et al. 2006; Schiel, X et al. 2006). Infections are the most frequent treatment-related cause of death in cancer patients. The risk of febrile neutropenia or life-threatening infections correlates with the severity and duration of neutropenia (Bodey, GP et al. 1966). The mortality due to infections in chemotherapy-associated neutropenia is 2.8 %, and early mortality overall comes to 5.7 % (Kuderer, NM et al. 2007). Documented infections in cases of neutropenia have a significantly worse prognosis than febrile neutropenia (Elting, LS et al. 1997; Kuderer, NM et al. 2006; Link, H et al. 1994). Multivariate analysis revealed the following risk factors for a fatal outcome of FN: gram-negative sepsis (relative risk: 4.92), invasive aspergillosis 3.48, invasive candidiasis 2.55, pulmonary disease 3.94, cerebrovascular disease 3.26, kidney disease 3.16, liver disease 2.89, pneumonia 2.23, gram-positive sepsis 2.29, hypotension 2.12, embolism of the pulmonary artery 1.94, heart disease 1.58, leukemia 1.48, lung cancer 1.18, age ≥ 65 years 1.12 (Kuderer, NM et al. 2006).

D 3.6.6 **Clinical work-up at commencement of therapy**

Before commencement of antimicrobial therapy: careful physical examination, with particular attention paid to: skin/mucous membranes, airways, abdomen, central or peripheral venous access sites, puncture sites, perianal region; if fever continues physical examination should be repeated (several times) daily.

Imaging and other examinations depending on the risk and symptoms: see Checklist C.

Initial microbiological diagnosis:

- At least 2 separate pairs of venous blood cultures from peripheral veins for microbiological culture (aerobic/anaerobic) immediately after a rise in the patient’s temperature, i.e. immediately before commencement of the antibiotic therapy; if the patient has a central venous catheter: one pair of the blood cultures (aerobic/anaerobic) from the catheter.
- Additional microbiological diagnostic procedures should only be carried out if symptoms of infection are present as listed in Checklist D.
Clinical chemical diagnosis:

- Minimal laboratory diagnostic procedures before and during the therapy, at least 2 x weekly:
  - Blood count with differential blood count, routine lab tests with CRP; if there are indications of sepsis: lactate, D-dimers quantitatively, Quick, aPTT, possibly also procalcitonin
  - If fever persists, repeat complete initial diagnostic procedure after 72–96 h.; high-resolution chest CT is obligatory in cases of persistent neutropenia!

### D 3.6.7 Treatment strategies

Empirical therapy and management

Indications for immediate antimicrobial therapy

- neutropenia and fever
- exception: fever not due to infection
- neutropenia and microbiologically documented infection
- neutropenia and clinically or radiologically documented infection
- signs of infection (even in the absence of fever) and neutrophilic granulocytes < 500/mm³ or < 1000/mm³ with expected fall below 500/mm³
- patients with symptoms or findings indicating infection or clinical diagnosis of sepsis

Treatment must be commenced empirically or based on calculation, without waiting for microbiological evidence of infection.

The therapy must commence within 2 hours; the diagnostic procedures must not delay the start of therapy!

Oral quinolone (ciprofloxacin or levofloxacin) combined with oral amoxicillin + clavulanic acid

For the treatment of all other patients: initial therapy should be as for medium risk. If, during the course of therapy, the patient is assigned to a higher risk category, the corresponding therapy strategy can be applied if necessary (see below).

Defined therapy in microbiologically or clinically documented infection

Immediate consultation of a hematologist or medical oncologist with experience in the management of patients with infections and neutropenia is necessary.
### Low risk

<table>
<thead>
<tr>
<th>Is oral treatment appropriate for this patient?</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Oral treatment: ciprofloxacin + amoxicillin / clavulanic acid or levofloxacin + amoxicillin / clavulanic acid</td>
</tr>
</tbody>
</table>

**Primary clinical deterioration during oral treatment?**

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue oral treatment</td>
<td>Treatment as for medium risk: 1) Monotherapy: piperacillin + tazobactam or ceftazidim or cefepim, or imipenem/cilastatin or meropenem 2) Combination therapy: acylaminopenicillin or cephalosporin group 3–4, with aminoglycoside in each case</td>
</tr>
</tbody>
</table>

**Fever after 72 to 96 h? ➔ diagnostic workup**

<table>
<thead>
<tr>
<th>No</th>
<th>Yes, and no documented infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinue treatment after 3 days without fever</td>
<td>No further modification, discontinue treatment after 3 days without fever</td>
</tr>
</tbody>
</table>

For documented infections always use the defined treatment

### Medium risk

1) Monotherapy: piperacillin + tazobactam or ceftazidim or cefepim, or imipenem/cilastatin or meropenem
2) Combination therapy: acylaminopenicillin or cephalosporin group 3–4, with aminoglycoside in each case

**Primary clinical deterioration?**

<table>
<thead>
<tr>
<th>Yes</th>
</tr>
</thead>
</table>

**Fever after 72 to 96 h? ➔ diagnostic workup**

<table>
<thead>
<tr>
<th>No</th>
<th>Yes, and no documented infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes, and no documented infection</td>
<td>After 1: add aminoglycoside in each case After 2: imipenem/cilastatin or meropenem; after initial imipenem/cilastatin or meropenem also quinolone + vancomycin or teicoplanin</td>
</tr>
</tbody>
</table>

**Clinically stable?**

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

**Fever after 72 to 96 h? ➔ diagnostic workup**

<table>
<thead>
<tr>
<th>Yes, and no documented infection</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add fluconazole; after another 72 h of fever switch to liposomal amphotericin B or caspofungin or itraconazole or voriconazole</td>
<td>Discontinue treatment after 3 days without fever, full therapy for at least 10 days</td>
</tr>
</tbody>
</table>

For documented infections always use the defined treatment
Checklists

A: Risk factors speaking against outpatient therapy for patients in the low-risk group (duration of neutropenia ≤ 5 days)

- ECOG Performance Status > 2
- Definitions in the ECOG Performance Status: score of 3: patient is capable of only limited self-care, confined to bed or chair more than 50% of waking hours; score of 4: completely disabled, cannot carry out any self-care, totally confined to bed or chair.
- Indications of CNS infection, severe pneumonia, venous catheter infection
- Signs of sepsis or shock
- Contraindications for oral therapy: severe abdominal symptoms (e.g. diarrhea), intravenous supportive therapy (e.g. nutrition), dehydration, recurring vomiting
- Constant or frequent monitoring is necessary (e.g. uncontrolled diabetes mellitus, hypocalcaemia)
- Oral quinolone prophylaxis and quinolone therapy within the last 4 (to 7) days;
- Medical care not guaranteed (various options); patient lives alone, patient/cohabitants have no telephone; hospital with experience in the treatment of neutropenic patients cannot be reached within 1 h; patient is not fully alert, no understanding of risks of outpatient therapy
- Compliance with oral treatment regimen cannot be expected.

B: Etiologically insignificant microbiological findings with regard to pulmonary infiltrates

*Enterococci* from blood cultures, swabs, sputum or broncho-alveolar lavage; *coagulase-negative Staphylococci* or *Corynebacterium spp.* from any materials; *Candida spp.* from smears, saliva, sputum, tracheal secretion or bronchoalveolar lavage; any microbial growth in monitoring cultures, stool or urine cultures

NB: There can, however, be a causal relationship between this microbial evidence and other infections.

Other findings, for example *Staphylococcus aureus* or *Legionella* in respiratory secretions, all require critical assessment in relation to their etiological significance (consultation with the infectious disease specialist or microbiologist is recommended) before the antimicrobial therapy is modified on this basis.

C: Further imaging and other investigative procedures may be necessary depending on the risks and symptoms

Chest X-ray (2 planes); high-resolution CT of the chest, CT or MRI of the nasal sinuses, sonography of the upper abdomen, echocardiography, examination of the fundus of the eye, etc.
D: Further microbiological diagnostic procedures

- Aspergillus galactomannan antigen in the serum
- Urine culture
- Stool culture including detection of *Clostridium difficile* enterotoxin in patients with diarrhea or suspected enteritis or colitis; if appropriate also viral diagnostic procedures for rotavirus, norovirus
- Wound swab (nasopharynx, anal region)
- Cerebrospinal fluid: culture for bacteria, fungi, if appropriate also PCR for HSV
- Aspirates (histology + culture)
- BAL: culture + microscopic examination; if appropriate CMV, HSV, RSV, *Mycobacteria, Legionella, Pneumocystis jiroveci*, other fungi
- If infection associated with a venous catheter is suspected, microbiological examination of the removed central venous catheter (CVC) should be performed

If appropriate, discuss the diagnostic method with a specialist.

Further detailed information

Further information may be obtained from the Infectious Diseases Working Party of the German Society of Hematology and Oncology: www.dgho-infektionen.de

D 3.7 Anemia in oncology

Patients with malignant disease often suffer from anemia that can cause clinical symptoms (Knight, K et al. 2004). The causes may be found both in the cancer and in the cancer treatment. Depending on the type and stage of the tumor, the probability of anemia is already approx. 50% upon diagnosis of solid tumors (Knight, K et al. 2004). Anemia occurs in 70.8% of breast cancer patients during their chemotherapy (Ludwig, H et al. 2004).

The most frequent form of anemia, after that caused by iron deficiency, is anemia triggered by activation of the immune system in chronic disease (ACD, anemia of chronic disease) (Weiss, G et al. 2005). The causes of ACD include not only acute and chronic infections, autoimmune diseases associated with chronic kidney diseases, but also in particular malignant diseases (both hematological neoplasms and solid tumors). ACD has a multifactorial pathophysiology. In the foreground are the disturbances mediated by inflammatory cytokines (tumor necrosis factor α, interleukin-1 α and β, interleukin-6, interferon-γ). They affect iron homeostasis: increased iron uptake into cells of the reticuloendothelial system (RES) and reduced release from the RES, proliferation of erythroid precursor cells, insufficient synthesis of erythropoietin (EPO) in relation to the anemia and reduced response to erythropoietin (Miller, CB et al. 1990), and reduced lifespan of the erythrocytes. The iron that is not used is stored in the RES and in parenchymatous organs. Hepcidin, a type II acute phase peptide formed in the liver, inhibits intestinal iron absorption and iron mobilization from the RES. This means that it plays a major role in the pathophysiology of ACD.
Chemotherapy and radiation therapy induce anemia by virtue of their myelosuppressive effect, and platinum-containing chemotherapies possibly also cause anemia by damaging the kidneys. Dose-intensified or dose-dense therapies are associated with a greater risk of anemia than conventional therapies are.

Anemia, defined as a drop in hemoglobin (Hb) to below 12 g/dl, should always be investigated and, if necessary, treated in accordance with the cause.

D 3.7.1 Diagnostic workup of anemia

Effective treatment of anemia requires reliable diagnosis of its causes (Table V).

Table V. Diagnostic workup of anemia.

- Exclusion of additional causes of anemia before therapy
  - iron deficiency
  - bleeding
  - cobalamin (vitamin B12) deficiency and folic acid deficiency
  - hemolysis
  - impaired renal function
  - systemic hematological disease

- Laboratory tests
  - blood count incl. MCV, MCH, reticulocyte count, differential blood count
  - routine laboratory studies with hepatic and renal function parameters: bilirubin, transaminases, albumin, Quick, creatinine, urea
  - iron status: iron, ferritin, transferrin, transferrin saturation
  - inflammation parameters: ESR, fibrinogen, CRP, haptoglobin, LDH
  - if appropriate, erythropoietin level
  - test for occult blood in stool, Coombs test, blood group typing

Laboratory results in anemia of chronic disease (ACD)

In ACD the peripheral blood contains (normochromic, normocytic or hypochromic) microcytic erythrocytes (MCV and MCH normal to low) with anisocytosis and poikilocytosis. The reticulocyte count can be normal or reduced; the reticulocytes are often hypochromic.

The following clinical chemical parameters are raised: ferritin, transferrin-iron-binding capacity, ESR, fibrinogen, CRP and haptoglobin.

Serum erythropoietin is raised, but insufficiently in relation to the anemia.

D 3.7.2 Treatment of anemia

Indication for transfusion of erythrocyte concentrates

In the event of acute blood loss in a patient with cancer or a hematological disease, the decision to order a transfusion must be made on an individual basis if Hb < 8 g/dl. In patients with chronic anemia much lower Hb values of between 6 and 8 g/dl are tolerated in some cases without symptoms, and for this reason in these cases there is no compelling indication for the transfusion of erythrocytes. In patients with coronary heart disease or an existing risk of...
impaired cerebral perfusion, red cell concentrates should already be administered if the Hb value drops to 10 g/dl.

**Treatment of causes of anemia**

The treatment of the underlying causes of anemia depends on the underlying disease or the specific causes of the anemia.

a) Iron deficiency, either nutritional or due to bleeding

   Oral replacement: Fe (II) sulfate or other bivalent iron compounds 100–300 mg/d

   Parenteral iron replacement: In patients with oral intolerance, in particular, slow parenteral administration of iron (III) sodium gluconate complex or iron (III) hydroxide saccharose is an effective alternative.

   (NB: possible adverse drug reactions, incl. local pain, headaches, heat sensation, nausea and vomiting, intolerance reactions, and even anaphylactic shock). Daily doses should not exceed 100 mg Fe (III) and, to avoid iron overloading, should be calculated exactly: the body’s iron requirement (mg) = \(15 – \text{patient-Hb (g/dl)}\) x body weight (kg) x 3. Since only half of the parenterally administered iron is available for Hb synthesis, the body’s iron requirement must be multiplied by a factor of 2 to give the total quantity of iron to be injected.

   Example: Hb of 8 g/dl, bodyweight 60 kg:

   \[(15 – 8) \times 60 \times 3 \times 2 = 7 \times 60 \times 3 \times 2 = 2520 \text{ mg}\]

   Iron is administered for around 6 months until the ferritin level has normalized.

b) Megaloblastic types of anemia

   Vitamin B12 replacement: hydroxycobalamin 1 mg i.m. (in cases of thrombocytopenia s.c. or i.v.) initially 6 injections within 2–3 weeks, then one injection every 6 months as maintenance therapy. Oral vitamin B12 replacement (1 mg daily) is also effective.

   In cases of folic acid deficiency, substitute 5 mg daily p.o. over 4 months.

c) Other causes

   Other possible causes of anemia, which are many and varied, must be diagnosed and treated in cooperation with internists (hematologists).

d) Anemia of chronic disease (ACD)

   Therapy: red cell concentrates in cases of anemia symptoms, erythropoiesis-stimulating factors (darbepoietin or erythropoietin if appropriate).

   For detailed information, refer to the guidelines of the German Cancer Society and the Working Group on Supportive Measures in Oncology concerning diagnosis and treatment of anemia in cancer patients with special attention to erythropoietin therapy (no. 032/50 in the register of the Association of the Scientific Medical Societies in Germany).
Literature


D 4 Rehabilitation

The multimodal treatment of patients with breast cancer can lead to somatic and psychosocial disorders causing functional disabilities that impair the patient’s ability to participate in everyday life. Medical rehabilitation measures undertaken to reduce or eliminate functional disorders are available under the German Code of Social Law (Sozialgesetzbuch, SGB) IX if the patient requires rehabilitation, is able to take part in rehabilitation, and has a positive rehabilitation prognosis. The International Classification of Functioning, Disability and Health (ICF) is used to evaluate the functional disorders.

Pursuant to Section 4 SGB IX, the services aimed at promoting participation in everyday life include social services (i.e. in this context medical rehabilitation services in particular) with the following aims (independent of the cause of the disability):

– averting or eliminating the disability, preventing it from becoming worse, or mitigating its consequences
– preventing a situation in which the patient’s ability to work is restricted and he/she requires nursing care
– ensuring that the patient can participate in working life commensurate with his/her inclinations and abilities
– encouraging the patient’s personal development in a holistic manner, and enabling and facilitating his/her independent participation in society.

The costs of the rehabilitation measures are borne largely by the health insurance schemes, statutory pension organizations and providers of social services. According to Section 19 SGB IX, rehabilitation can be provided in either inpatient or outpatient form depending on the personal circumstances of the patient. According to Section 26 SGB IX, the services of medical rehabilitation include treatment by doctors and nurses, pharmacological treatment, physiotherapy and the use of aids, functional ergotherapy and psychosocial programs.

The Deutsche Rentenversicherung Bund (German Pension Insurance Federation) has drawn up separate guidelines for the medical rehabilitation of patients with breast cancer. Evidence-based treatment modules are summarized in these guidelines (Cf. http://www.deutsche-rentenversicherung-bund.de).

Two of the most important sections on the provision of rehabilitation to patients with breast cancer deal with educative and psychosocial approaches which aim to improve the patients’ quality of life by helping them to cope with their disease and by reducing anxiety and depression (Chlebowski, RT et al. 2002; Djuric, Z et al. 2002; Edwards, AG et al. 2004; Fawzy, FI et al. 1995; Hebert, JR et al. 2001; Kissane, DW et al. 1998; Rehse, B et al. 2003).

Sport therapy interventions are aimed at the restoration of physical performance capability as well as the reduction of fatigue and psychosocial stresses (Courneya, KS 2003; Friedenreich, CM et al. 1996; Pinto, BM et al. 1999; Stricker, CT et al. 2004). Physiotherapy is employed to counteract the restricted mobility of the shoulder and arm following breast surgery (Box, RC et al. 2002; Wingate, L et al. 1989). Manual lymph drainage can help to reduce lym-
phedema and infection in the arms caused by lymph congestion (Andersen, L et al. 2000; Badger, C et al. 2004; Harris, SR et al. 2001; McNeely, ML et al. 2004).

The rehabilitation of patients following breast cancer requires an interdisciplinary approach supported by somatic and psychosocial elements (Cf. also section D 2.2 “Psychooncological care strategies and interventions”).

A patient’s application for medical rehabilitation is submitted to the relevant pension insurance scheme if the patient is in employment where social security insurance contributions are paid; otherwise it is submitted to the patient’s health insurance company. Directly after completion of the primary treatment the application is submitted either via the social services of the hospital that most recently treated the patient or via the doctor treating the patient. Repeat medical rehabilitation is possible if serious functional disorders persist as a consequence of the disease itself or of the cancer treatment.

Statement Reha-1

The use of surgery, radiotherapy and systemic therapy to treat a patient with breast cancer can result in therapeutic sequelae of varying severity that require targeted somatic and psychosocial rehabilitation. The patients should be informed at an early date about the options for outpatient and inpatient rehabilitation and about additional claims arising under German social law. The patient’s preferences should be taken into consideration when establishing the necessity for, and recommending, a particular type of rehabilitation.

GCP

Literature


D 5 Follow-up Care Including Diagnostic Workup of Recurrences and Metastases and Support During Therapy

D 5.1 Objectives

Follow-up care in the narrower sense comprises the structured examinations performed to detect locoregional or intramammary recurrences and contralateral breast cancer, examinations performed to detect remote metastases, and support provided during long-term therapies. The latter includes the diagnosis and treatment of sequelae and side-effects. Because of the wide variation of therapeutic regimens, follow-up care starts after completion of primary treatment (Khatcheressian, JL et al. 2006).

Follow-up care is provided for many different types of patients including, for example, those receiving neoadjuvant or adjuvant chemotherapy, antibody treatment, long-term antihormonal therapy or complementary and alternative treatments (CAM), as well as those being treated within the framework of studies.

What is required is individualized and risk-adapted follow-up care. Whereas treatment decisions are taken based on risk classifications (e.g. TNM stage, steroid hormone receptors, growth factor receptors, age, etc.), there are no large-scale valid studies that have examined individualized risk-adjusted follow-up. Comparisons of survival rate by stage show that the survival rate is a function of the stage of the disease, and that therefore risk stratification adjusted to the stage of the disease could be carried out. There are no criteria for modifying the structured procedures established for follow-up care to date. This means that during structured follow-up care identical support and treatment are given to patients with a high risk of local recurrence and systemic metastases and to those with a distinctly low risk of recurrence.

At the same time, it has been shown that the practice of limiting follow-up to a period of five years is not adequate in view of the different risk constellations in individual patients. Even in the absence of empirical data to support this, the time frame for follow-up should be extended, therefore, from the current five years to a period of ten years (Saphner, T et al. 1996).

There are no new prospective randomized studies taking account of the various risk constellations, adapted follow-up regimens, or the integration of newer diagnostic methods. The current strategy for follow-up care, which is supported by the data from prospective randomized studies, should be viewed as a starting point; however, it should be adapted to the woman’s individual situation in a way that takes account of her risk constellation and symptomatology.
Statement FU-1

Follow-up care for breast cancer begins after the completion of local primary treatment. It consists of history-taking, a physical examination, and guidance, support and continuing care provided by physicians.

**LOE 1c, Grade of Recommendation A**

Follow-up care should be symptom-oriented, if required.


In contrast to the situation of women with metastatic breast cancer, patients with an intramammary or locoregional recurrence have a chance of curative treatment.

There are no large-scale prospective randomized studies showing that the early detection and treatment of distant metastases confers a significant survival benefit. An additional distinction must be made here between patients who developed metastases during ongoing long-term treatment and those who developed them after an interval without treatment (Palli, D et al. 1999; Rosselli, DT et al. 1994).

Follow-up care is based on empathic concern for the patient and verbal communication between doctor and patient. Its principal aim is to reduce anxiety and improve the patient’s quality of life. This is complemented by a physical examination, during which special attention is paid to the local findings and the contralateral breast. The patient should also be encouraged to take part in the statutory screening programs for the early detection of cancer including, in particular, examinations to detect genital malignancies (Khatcheressian, JL et al. 2006).

Statement FU-2

As part of her follow-up care the breast cancer patient requires intensive interdisciplinary support and continuing care. Doctors specializing in oncology and also other healthcare professionals (e.g. psychooncologists, physiotherapists, oncological nursing staff, etc.) should be involved as needed. The patient should be given information appropriate to her individual needs about the options for further treatment and support.

**LOE 2a, Grade of Recommendation B** (Selby, P et al. 1996)

D 5.2 Examinations to detect locoregional and intramammary recurrences and contralateral breast cancer

Local and locoregional recurrences following mastectomy and/or axillary dissection can best be diagnosed by clinical examination. Palpation of the chest wall and the lymph drainage areas is therefore a central element of the follow-up examinations (Dalberg, K et al. 1998). The majority of local and locoregional or intramammary recurrences after breast-conserving surgery can be treated with curative therapy. For this reason they should be diagnosed as early as
possible. The follow-up care should therefore include mammography of the ipsilateral breast at least annually.

**Statement FU-3**

In asymptomatic women who have undergone breast-conserving therapy, imaging studies (e.g. mammography and ultrasound) of the ipsilateral breast are indispensable.

**GCP** (Grunfeld, E et al. 2002; Khatcheressian, JL et al. 2006; Loprinzi, CL 2004)

The time at which mammography is commenced as part of follow-up care depends on many factors including the type of radiotherapy (e.g. intraoperative irradiation, postoperative brachytherapy, etc.) and the local findings in the breast.

Since the scar region frequently undergoes changes during the postoperative period and it is difficult to differentiate between scar tissue changes and a recurrence, mammography and sonography of the ipsilateral breast are recommended every six months in the first three years after the operation (Haffty, BG et al. 1991). In the case of results that are difficult to evaluate (e.g. scar, DD recurrence) an MRI examination is necessary for further diagnostic exploration (Muuller, RD et al. 1998; Viehweg, P et al. 1998). Breast cancer patients should therefore not be integrated into the mammography screening programs with their two-year interval between examinations.

Previous breast cancer is a major risk factor for contralateral breast cancer. The contralateral breast should be palpated at every follow-up visit and regular mammography and sonography should be performed (Kollias, J et al. 2000).

**Statement FU-4**

All patients should receive annual follow-up mammograms of the contralateral breast.


### D 5.3 Examination to detect metastases

The three most common sites of metastases in breast cancer patients are the lungs, the liver and the bones. The spread of the disease is investigated during primary therapy depending on the stage of the disease. The prospective randomized studies available at this time have shown that, in patients without symptoms, intensified follow-up surveillance at fixed intervals with x-ray examination of the lung, bone scan, upper abdominal sonography, tumor marker assays or CT diagnostic methods does not confer any survival benefit (Palli, D et al. 1999; Rosselli, DT et al. 1994). There are currently no prospective randomized studies with a risk-adjusted diagnostic follow-up program or the integration of procedures such as PET, SPECT/CT, monitoring of tumor markers at short intervals, testing for circulating tumor cells, risk assessment using gene chips or tissue microarrays, etc. Furthermore, it is possible for metastases to be detected in breast cancer patients between the visits for follow-up care. For this reason it is all
the more important to instruct patients concerning self-observation of persistent symptoms and self-examination of the operation site.

**Statement FU-5**

<table>
<thead>
<tr>
<th>Laboratory tests and apparative diagnostic methods should be employed in cases where the history or clinical findings yield grounds for suspecting a recurrence and/or metastases.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A routine search for remote metastases is not indicated in asymptomatic women, owing to the uncertainty of the methods used and of the intervals between examinations. Patients with persistent symptoms should undergo a targeted diagnostic workup.</td>
</tr>
</tbody>
</table>

**GCP**

**D 5.4 Diagnostic workup and treatment of side-effects and sequelae of primary and long-term treatments**

Follow-up examinations should, among other things, check and document the success of the primary treatment. The most important priority is to relieve patients’ fear of recurrences and metastases. For patients with favorable tumor staging (pT1 N0 M0), the probability of ten-year survival is over 90%.

Treatment sequelae and toxicities of local treatments such as surgery and radiation and of systemic treatments such as chemotherapy, antibody treatment, antihormonal treatment or complementary and alternative methods (CAM) can be recognized and treated if appropriate. Because an increasing number of breast cancer patients receive curative treatment, but the necessary treatments are given over a longer period of time, continuing care for patients on long-term treatment and the treatment of side-effects or late sequelae are also gaining in importance. It is important to distinguish between early and late sequelae, between local and systemic side-effects, and between long-term side-effects of completed treatments and acute side-effects of current treatments (GIVIO Investigators 1994).

The patients should be informed about treatment-specific short-term and long-term side-effects and later sequelae. Targeted diagnostic and therapeutic measures should be recommended and carried out as required.

The principal local side-effects of treatment are edema, disturbances of sensation, pain in the chest wall or breast (in the case of breast-conserving treatment), restricted movement, and lymphedema (Brennan, MJ 1992).

Side-effects (acute and late toxicity) of systemic medication include myelotoxicity, hepatotoxicity, alopecia, nephrotoxicity, ototoxicity, pulmonary toxicity, cardiotoxicity, infections, thromboembolic events, osteoporosis, sterility, climacteric syndrome, occurrence of second cancers, cognitive disturbances, etc. (Hayes, DF 2007).
As it is not possible to provide an exhaustive list of all the possible problem areas, only the most frequently encountered will be dealt with below:

1. **Lymphedema**

Secondary lymphedema of the arm is a common problem in breast cancer patients, with an incidence of 20–30% (Khatcheressian, JL et al. 2006; Saphner, T et al. 1996). The associated morbidity involves functional restrictions, increased arm circumference, and associated reduction of quality of life.

**Statement FU-6**

| All patients who have undergone axillary lymph node dissection must be informed of the options for detection, prophylaxis and treatment of lymphedema. |

The main influencing factors are:

– the extent of the surgical intervention in the axilla; the number of lymph nodes removed correlates significantly with the occurrence of lymphedema ($p < 0.001$) (Grunfeld, E et al. 2005; Gulliford, T et al. 1997) RR 1.11 (95% CI 1.05–1.18) (Selby, P et al. 1996)

– irradiation of the axillary lymph drainage areas (RR 1.35; 95% CI 1.00–1.83)

The results of three randomized studies confirm the individual benefit of reduced morbidity in the case of less radical surgery through sentinel lymph node biopsy (SLN): absolute risk reduction for loss of sensation 8% (5% SLN versus 11% ALND), for symptoms of lymphedema in the arm 20% (11% SLN versus 31% ALND) (Clark, B et al. 2005; Kokke, MC et al. 2005; Mansel, RE et al. 2006; Purushotham, AD et al. 2005).

**Statement FU-7**

| For breast cancer patients sentinel lymph node biopsy without more extensive axillary lymph node dissection constitutes primary prophylaxis of lymphedema in the arm. These patients should be informed after surgery about normal use of the arm and should contact the medical specialist treating them if functional disturbances or signs of lymphedema occur. |
| LOE 1b, Grade of Recommendation A (Francis, WP et al. 2006; Golshan, M et al. 2003; Sanjuan, A et al. 2005; Torrenga, H et al. 2004) |
2. **Cardiotoxicity**

The possibility of cardiotoxicity should be considered when anthracyclines and trastuzumab are administered (Bonneterre, J et al. 2004). Combination of these two drug classes increases the risk significantly and is not recommended. Factors predisposing to cardiotoxicity include age, obesity, pre-existing congestive heart failure, arterial hypertension, diabetes mellitus, status post myocarditis or infarction, and irradiation of the left side. If the patient develops acute and chronic myopathic disorders together with congestive heart failure, a distinction is made between the acute and subacute dose-independent early-onset form, the chronic form (within one year) and the late-onset form. The extent ranges from reduction of the left ventricular ejection fraction (LVEF) to clinically relevant congestive heart failure. In patients experiencing a general reduction in physical performance or exercise capacity, diagnostic exploration is urgently necessary. Early diagnosis of cardiac damage is necessary for instituting appropriate supportive measures such as the targeted treatment of congestive heart failure, etc., which improve the patient’s quality of life and prevent a worsening of the survival prognosis (Jensen, BV 2006; Perez, EA et al. 2004; Tan-Chiu, E et al. 2005).

3. **Leukemia**

Leukemia is the most common second cancer induced by treatment. The highest risk of secondary leukemia exists during the first ten years. The most common type of leukemia is acute myeloid leukemia associated with the use of anthracyclines (Le Deley, MC et al. 2007; Smith, RE 2003).

4. **Climacteric syndrome**

The climacteric syndrome comprises symptoms originating in the autonomic nervous system (e.g. hot flushes, sweating, dizziness, headaches, tachycardia, etc.), psychological symptoms (e.g. insomnia, depression, fear of abandonment, neurotic behavior, irritability, nervousness, apathy, difficulty concentrating, etc.), and organic menopausal symptoms (e.g. organ involution, metabolic changes, etc.) (Stearns, V et al. 2002). These physiological changes can be intensified by the treatments or the treatment-specific side-effects. The latter include vaginal bleeding, thromboembolic events, muscle and joint pain, dryness of the mucous membranes, etc. Chemotherapy and antihormonal therapy can induce the climacteric syndrome in premenopausal or perimenopausal patients, and trigger or aggravate it in postmenopausal patients (Mom, CH et al. 2006).

Patients’ subjective experiencing of their symptoms varies, depending on things such as the onset and duration of amenorrhea and the duration of the treatment, especially antihormonal therapy. Treatment of the symptoms of the climacteric syndrome is symptom-oriented. Hormonal therapy after breast cancer should be approached with the greatest reservation and only considered in cases where there is a serious reduction of the patient’s quality of life and following a weighing of the risks and benefits expected in the individual case. In patients with hormone-receptor-positive breast cancer hormonal therapy is contraindicated by current empirical data (S2 Guidelines on Hormonal Therapy 2008, under revision) (Pritchard, KI et al. 2002).
5. *Thromboembolic events*

Thromboembolic events can occur as a paraneoplastic syndrome during primary treatment. They often indicate the presence of more extensive cancer or metastases (Caine, GJ et al. 2003). In the case of antihormonal therapies, thromboembolic events are possible particularly in patients receiving long-term treatment (Gail, MH et al. 1999). The diagnostic workup and treatment of thrombosis or pulmonary embolism and their prophylaxis are set forth in the interdisciplinary S2 and S3 Guidelines of other professional associations (AWMF 065/002).

6. *Osteoporosis*

Estrogens constitute one of the main factors in the regulation of bone metabolism. The reduction of bone mass that takes place as the menopause commences is a normal physiological occurrence. Breast cancer treatment – i.e. chemotherapy or antihormonal therapy inducing premature menopause in premenopausal patients or administration of anti-estrogens to postmenopausal patients – can foster this effect. In patients with factors predisposing to osteoporosis in the history or known osteoporosis, appropriate medication should be recommended. Patients without osteoporosis should receive information on behavioral measures such as physical exercise, dietary modifications and replacement of Vitamin D and calcium (Hayes, DF 2007; Hillner, BE et al. 2003; Winer, EP et al. 2005).

7. *Fatigue*

Patients with a chronic fatigue syndrome after the treatment of breast cancer should be informed about physical training strategies and possibilities for psychosocial assistance (Servaes, P et al. 2002).

**D 5.5 Frequency of follow-up examinations**

Follow-up examinations should take place every three months during the first three years, every six months during the fourth and fifth year, and annually during the 6th and subsequent years.

In view of the tumor biology of breast cancer, a phase of follow-up-care lasting for at least ten years should be considered (Donnelly, J et al. 2001; Khatcheressian, JL et al. 2006).

**Statement FU-8**

Follow-up visits should be scheduled four times a year during the first three years after the local primary therapy and twice a year during the fourth and fifth year; starting in the sixth year, the visits should be scheduled annually and include the normal gynecological checkups for early cancer detection.

**LOE 2a, Grade of Recommendation A** (Khatcheressian, JL et al. 2006)
Table I. Follow-up care schedule for breast cancer patients.

<table>
<thead>
<tr>
<th>Years after primary treatment</th>
<th>Follow-up care</th>
<th>Early detection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st-3rd year</td>
<td>4th + 5th year</td>
</tr>
<tr>
<td>History-taking</td>
<td>Every 3 mos.</td>
<td>Every 6 mos.</td>
</tr>
<tr>
<td>Physical examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient briefing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imaging studies (apart from mammography)</td>
<td>Only if the history and physical examination produce a suspicion of a recurrence and/or metastasis.</td>
<td></td>
</tr>
</tbody>
</table>

Table II. Follow-up schedule for breast cancer patients – mammograms

<table>
<thead>
<tr>
<th>Years after primary treatment</th>
<th>1st-3rd year</th>
<th>From 4th year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast-conserving surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ipsilateral breast</td>
<td>At least once annually</td>
<td>Once annually</td>
</tr>
<tr>
<td>- contralateral breast</td>
<td>Once annually</td>
<td></td>
</tr>
<tr>
<td>Mastectomy – contralateral breast</td>
<td>Once annually</td>
<td></td>
</tr>
</tbody>
</table>

*Recommended every six months, especially in patients with scarring that is difficult to evaluate*

**Literature**


The approach to be taken in the palliative situation should be elaborated in an interdisciplinary setting, e.g., at a tumor conference. Patients should be given detailed information about the treatment options according to their individual needs and should be included in the decision-making process.

Tumor-specific treatment options (Cf. Section C of these Guidelines), supportive measures, needs-based psychosocial and psychooncological care (Cf. Sections D1 to D3), measures taken to ensure appropriate pain therapy, and nutrition are all integral parts of the palliative treatment strategy.

Patients should be given the information they request concerning all the relevant measures available and possibilities for obtaining assistance and support (e.g., cancer counseling centers, self-help groups, hospices). Complementary/unconventional treatment methods should be discussed frankly with the patients – also with an eye to avoiding unwanted interactions with other therapeutic agents.

The reader is referred to the following sources for specific guidelines on the various aspects of palliative medical care:

- S3 Guidelines of the German Society of Nutritional Medicine (Deutsche Gesellschaft für Ernährungsmedizin e.V.) and the ESPEN Guidelines on Enteral Nutrition: www.awmf-leitlinien.de, index nos. 073/006e and 073/005e
- Guidelines for Pharmacological Pain Therapy of the German Cancer Society (DKG): www.awmf-leitlinien.de, index no. 032/039, currently under revision in cooperation with the umbrella organization German Interdisciplinary Collaboration for Pain Therapy (Deutsche Interdisziplinäre Vereinigung für Schmerztherapie)
Section E
Quality Management and
Coordination of Patient Care
A multidisciplinary concept is required for the diagnosis and treatment of breast cancer and the provision of follow-up care. It is not only the experience of the individual physician treating the patient that is important but also the smooth coordination between the various therapeutic disciplines involved.

Quality-assured early detection, professional diagnostic imaging, histopathological confirmation of the diagnosis by core biopsy, excellent surgical procedures, consistent radiotherapy and pharmacological therapy— including sophisticated therapeutic methods and professional follow-up care – must all be viewed as part of a comprehensive strategy which can be implemented only via cross-disciplinary collaboration.

Optimizing quality at all points along this medical care chain is the only viable strategy for lowering breast cancer mortality. All measures taken to improve the care of women with breast cancer must thus be directed not only at single aspects of treatment but always at the entire medical care chain.

The cornerstones of the coordination of the care of breast cancer patients are:

– the establishment of early detection and screening programs
– the certification of interdisciplinary breast centers
– observance of the S3 Guidelines for the Diagnosis, Treatment and Follow-up Care of Breast Cancer
– improvement of communication in the medical care chain in the interest of providing cross-sectoral care for patients, especially in the sector of follow-up care (e.g. DMP)
– the integration of self-help activities into the care strategies

All measures must take place in a quality-assured and transparent manner. Structural, process and outcome quality must be continually monitored and the relevant data reported to the clinical cancer registries (Cf. Annex 8).

Annual audits and recertification at three-year intervals with demonstration of patient and referring-physician satisfaction, observance of quality objectives, implementation of quality indicators and presentation of outcome quality are prerequisites for adequate quality management.

All persons bearing responsibility in our healthcare system are called upon to set aside individual interests and to make every effort to work toward – and to achieve – optimal treatment conditions and therapeutic results in the interest of our patients.

Institutions whose work is not supported by quality assurance programs should be excluded from the care of patients with breast cancer.
Appendix
Appendix 1: Diagnostic Chain for the Early Detection of Breast Cancer: Clinical Algorithm

(Re Chapter B 2.1)


![Diagram of Diagnostic Chain for the Early Detection of Breast Cancer: Clinical Algorithm]

* Basic diagnostic workup (clinical examination/mammography/ultrasound): in women younger than 40 years primary ultrasound examination

** Accepted reasons for declining minimally invasive biopsy: patient’s wish, primary surgical procedure preferable for medical reasons (coagulation disorder or medically indicated anticoagulation, patient’s age), location of lesion unfavorable for an interventional procedure, suspicion of intra-cystic proliferation.

Definition of the standard elements: Clinical state → Decision → Action → Logical consequence
Appendix 2: Breast Reconstruction Options/Indications

(Re Chapter B 4.4, Plastic reconstructive procedures)
Appendix 3: Pathomorphological Examination

(Re Chapter B5: Pathomorphological examination)

This appendix contains extracts from established classifications and grading systems referred to in the Guidelines as well as proposed standard forms for the “Pathology Request Form” and the “Pathology Reporting Form.” It also goes into the current nomenclature for benign breast lesions and contains supplementary information on interpretation of the hormone receptor and HER2 tests. Special aspects of reporting after neoadjuvant systemic therapy are also addressed.

3.1 Histological classification

The nomenclature and grouping of the breast lesions is based on the WHO classification of breast tumors (WHO 2003) supplemented by the European Guidelines for Quality Assurance in Breast Cancer Screening (Amendoeira, I 2006a; Amendoeira, I 2006b).

The European Guidelines also contain an index for screening offices for systematic categorization of the lesions, which is helpful for documentation of the pathology reporting on forms.

In the following only selected points are addressed which are of particular differential diagnostic importance with regard to pathological-radiological correlation or of particular clinical importance. In addition individual newly introduced terms from the WHO classification are explained and commented on.

3.1.1 Normal findings and benign lesions (various)

“Normal tissue” includes minimal age-appropriate alterations such as fibrosis, lobular involution, microscopic dilatation of acini and ducts and minor microcystic adenosis. These minimal changes are not usually sufficient to explain an abnormal clinical or radiological finding.

The term fibrocystic change is used for alterations involving numerous macroscopically visible cysts, apocrine metaplasia and fibrosis.

This is distinct from a solitary cyst, which is usually larger than 1 cm and lined with attenuated or apocrine epithelium.
Periductal mastitis (duct ectasia, plasma cell mastitis) involves larger and intermediate size ducts, usually in subareolar location. The chronic inflammatory reaction around the ducts, often containing numerous plasma cells, may also contain large numbers of histiocytes and have a granulomatous appearance. It can be accompanied by pronounced periductal fibrosis. Calcification may be present.

3.1.2 Benign epithelial proliferation

In the early phase sclerosing adenosis tends to be more cellular. Lesions become more sclerotic with increasing time. It is recommended that sclerosing adenosis should only be entered on the screening form if it is a prominent finding (Amendoeira, I 2006b). Calcification may be present.

The differential diagnosis of sclerosing adenosis includes tubular carcinoma, microglandular adenosis and radial scars.

If adjacent lobules are affected a mass can form which is detectable by mammography or palpation. The term adenosis tumor is used to describe such lesions.

Adenosis with marked apocrine metaplasia which takes up at least 50% of the adenosis is documented as apocrine adenosis.

Microglandular adenosis, in contrast to sclerosing adenosis, lacks the lobular organoid growth pattern of the latter. The round, glandular structures are lined with a layer of single cells without atypia. There is no myoepithelium but an intact basement membrane is present.

The radial scar consists of a central, fibroelastotic zone from which tubular structures radiate out. The lesion is rarely larger than 1 cm. The epithelium is two-layered or exhibits ductal hyperplasia. Tubules can be entrapped within the central zone of hyalinized fibrosis, distorted and canted.

The complex sclerosing lesion mimics invasion. It exhibits all the characteristics of the radial scar but is larger than 1 cm and more irregularly structured, often with nodular masses around the periphery. The lesion can be accompanied by changes such as papilloma, apocrine metaplasia or sclerosing adenosis. The most important differential diagnosis for both radial sclerosing lesions is tubular carcinoma, which lacks the myoepithelium and intact basement membrane around the tubules of the sclerosing lesions.

A diagnosis of radial scar or complex sclerosing lesion in the core biopsy or vacuum-assisted biopsy usually means that the alteration must be classified as B3 (Amendoeira, I 2006a) and constitutes an indication for surgical excision. An exception are small radial scars which have been completely removed by vacuum-assisted biopsy and are an incidental histological finding (without mammographic correlate). These do not require excision and can be classified as B2 according to the European guidelines for mammography screening. The reason for classification as B3 is that atypical ductal hyperplasia and carcinomas (in situ and invasive) are relatively often found in the periphery of mammographically detected radial scars and complex sclerosing lesions, particularly in the case of lesions measuring > 0.6 cm and in women > 50 years (WHO 2003). Some 4-32% of the excision specimens following diagnosis of a radial scar in the core biopsy contain DCIS or invasive carcinoma, particularly if ADH was already documented in the core biopsy.
The lesions termed ductal adenoma have a variable appearance. They are characterized by well circumscribed benign glandular proliferation which extends at least partially intraductally. There are overlaps with other benign changes such as papilloma or complex sclerosing lesion which is why such lesions are also termed sclerosing papillomas.

3.1.3 Papilloma

Papillomas may be solitary or multiple. Solitary papillomas usually occur centrally (central papilloma), in subareolar ducts, while multiple papillomas are more likely to be peripheral in the region of the terminal duct lobular units (TDLUs) (peripheral papillomas). Peripheral papillomas are frequently associated not only with usual ductal hyperplasia (UDH) but also with atypical ductal hyperplasia (ADH), DCIS or invasive carcinoma. Therefore the presence of this change requires extensive tissue embedding.

The term “papillomatosis” should be avoided as it has previously been used both for UDH and for multiple papillomas.

The diagnosis of atypical papilloma according to the WHO guidelines requires the presence of focal intraductal epithelial proliferation corresponding to ADH or small, low-grade DCIS, i.e. focal atypical proliferation of uniform cells with low-grade nuclei (WHO 2003). There is no defined cut-off for the maximum extent of the atypical epithelial proliferation. Atypical apocrine proliferation can be disregarded unless it is very extensive, dominant or highly atypical (Putti, TC et al. 2005).

The quantitative criteria for distinguishing between atypical papilloma in terms of papilloma with ADH and papilloma with DCIS are controversial. Some authors regard atypical epithelial proliferation with an extent of less than 3 mm as ADH (O’Malley, BA et al. 2006), others atypical epithelial proliferation which accounts for less than 30% of the cross section of the papilloma (Tavassoli, FA 2000). Lesions larger than this correspond to papilloma with DCIS.

The B classification of papillary lesions depends on the epithelial component. As the epithelial changes within the papillary lesions can be heterogeneous and the core biopsy does not usually contain the lesion in its entirety, most papillary lesions must be classed as B3 (of uncertain biological potential). This does not include small papillomas which have been extensively sampled and can be assumed to have been completely removed by the core/vacuum-assisted biopsy. These can be classified as B2. A higher B category is appropriate if the epithelial proliferation shows atypia which justifies either a suspicion of malignancy (B4) or an unequivocal diagnosis of papilloma with DCIS or of intraductal papillary carcinoma (B5).

3.1.4 Myoepithelial lesions

While myoepitheliosis is a usually multifocal, microscopic process, adenomyoepitheliomas appear as circumscribed masses which can be multilobular. They are characterized by their biphasic cellular differentiation. The myoepithelial component, composed partly of clear cells, usually surrounds the tubular component with luminal epithelial lining. There are three main morphological variants: lobulated, tubular and spindle-cell/myoid. The differential diagnosis includes papilloma and adenosis (fluid transitions in each case) as well as tubular ade-
noma (sharply circumscribed in contrast to the tubular variant of the adenomyoepithelioma) and invasive carcinoma (lacks the biphasic cellular architecture).

The majority of adenomyoepitheliomas are benign. However, they are considered to have a small degree of malignant potential and should therefore be classed as B3 if diagnosed in the core or vacuum-assisted biopsy and complete excision should be recommended.

Malignant adenomyoepitheliomas, with malignant degeneration of the epithelial and/or myoepithelial component, are considerably less common than the benign forms.

### 3.1.5 Fibroepithelial tumors

**Fibroadenomas** are benign biphasic tumors which are usually diagnosed in women of reproductive age. Epithelial (ductal) hyperplasia is not uncommon in fibroadenomas. The presence of ADH or DCIS in a fibroadenoma should always be recorded separately. The diagnosis of these changes in the core biopsy increases the B category from B2 to B3, B4 or B5 depending on the degree and extent of the atypia.

Fibroadenomas must be distinguished from **phyllodes tumors**, which have a more cellular stroma. To determine whether the lesion is malignant or benign a sufficient number of tissue sections is necessary (rule of thumb: 1 tissue block per cm tumor diameter), in order to obtain a representative picture of the characteristic stroma features (cellularity, pleomorphism, mitotic activity, pattern of distribution) and the relationship to the surrounding tissue.

Fibroepithelial tumors which suggest the presence of a phyllodes tumor (PT) in the core or vacuum-assisted biopsy on account of their cellular stroma, the predominance of the stroma component or increased mitotic activity of the stroma cells should always be classified as B3.

### 3.1.6 Intraductal proliferative lesions

In the updated WHO classification (WHO 2003) this group encompasses various types of intraductal proliferation which have a common point of origin, namely the terminal duct lobular unit (TDLU). They are associated with an increased risk for the development of invasive breast cancer, although the extent of this risk varies considerably.

**Usual ductal hyperplasia** (UDH) includes all cases of intraluminal epithelial proliferation which display no atypia. The cell composition is usually mixed and fluid. If secondary lumina are present these are slit-like, ovoid and irregular in shape with tangential orientation of the nuclei in the peripheral epithelial cells. One of the most important indicators of UDH is the presence of a mixture of at least 2 cell types (luminal and basal/myoepithelial and/or metaplastic apocrine cells). It is associated with an only very slightly increased risk (1.5-fold) for the development of breast cancer. It is usually accompanied by diffuse or mosaic-like expression of the basal cytokeratins (incl. CK5, CK14) (Otterbach, F et al. 2000).

The term **flat epithelial atypia** (FEA) was introduced for the first time in the current WHO classification (WHO 2003). This is a descriptive term rather than a specific pathologic diagnosis and encompasses lesions which are probably neoplastic and are also termed clinging carcinoma (monomorphic type), atypical cystic lobules, atypical lobules type A, columnar cell metaplasia with atypia or columnar cell hyperplasia with atypia. It is characterized by replace-
ment of the original epithelium by a single layer of cells showing low-grade atypia and often displaying apical snouts, or by 3-5 layers of a monotonous atypical cell population consisting of prismatic cells or columnar cells. Micropapillae or more complex structures such as arcades are absent or very rare. The affected dilated lobules often contain secretions and microlcalci-

The biological significance and thus the clinical relevance of FEA is not currently clear. On the one hand more extensive changes such as lobular neoplasia, ADH, low-grade DCIS or a well-differentiated invasive carcinoma are often found in the neighborhood of FEA. On the other hand the few observational studies available to date indicate that there is only a very low risk of progression (for overview cf. Pinder, SE et al. 2007; Schnitt, SJ 2003). Thus FEA is currently considered primarily a marker lesion rather than a precursor lesion, although molecular pathological studies suggest that in some cases it might be the earliest morphological manifestation of low-grade DCIS (Simpson, PT et al. 2005). If FEA is diagnosed in the core or vacuum-assisted biopsy this change should be classified as B3. There is no consensus at present as to whether diagnosis of FEA in the core/vacuum-assisted biopsy should always be followed by excision of the surrounding tissue. While most authors recommend general excision on account of the more frequent association with DCIS and invasive carcinomas, others consider it only necessary if the microcalcifications which were usually the reason for the histological examination were not completely removed by the intervention (overviews in Pinder, SE et al. 2007; Schnitt, SJ 2003). Further studies are therefore needed to give us a better understanding of the biological nature and clinical significance of these changes.

As already described above, FEA is usually a columnar cell change with or without hyperplasia which shows low- to moderate-grade cytological atypia. This must be distinguished from columnar cell hyperplasia with architectural atypia, in which chiefly micropapillae but also epithelial bridges are present, although there is only low-grade cytological atypia (Amenodeira, I 2006b). These changes are now classified as ADH or low-grade DCIS depending on the nature and extent of the cytological and structural atypia (Pinder, SE et al. 2007).

It should also be mentioned that columnar cell proliferations are homogeneously ER positive and CK5 negative. The immunohistochemical determination of basal cytokeratins is not helpful in the differential diagnostic distinction between columnar cell hyperplasia with and without atypia as the characteristic mosaic-like reaction pattern of UDH is absent in columnar cell hyperplasia without atypia.

Atypical ductal hyperplasia (ADH) is now regarded as neoplastic intraductal epithelial proliferation. It is characterized by intraductal proliferation of evenly distributed, uniform cells which can exhibit micropapillae, arches, and solid or cribriform architectural patterns (WHO 2003). Roundish, rigid-appearing secondary lumina occur alongside others that are irregularly shaped. Cytologically the cells of ADH thus correspond to low-grade DCIS. However, in ADH the characteristic cells only partly involve the TDLUs and/or occur alongside usual ductal hyperplasia (UDH).

In individual cases differentiation between ADH and low-grade DCIS can be difficult. The immunohistochemical demonstration of basal cytokeratins does not help with the differential diagnosis as they are not expressed by the proliferating epithelia in either lesion.
In the context of second pathologist review there is therefore known to be discordance, even between experts, in the evaluation of intraductal proliferative lesions on the borderline between ADH and low-grade DCIS (Collins, LC et al. 2004; Nahrig, J. et al. 2006; Rosai, J 1991; Sloane, JP et al. 1994; Sloane, JP et al. 1999; Verkooijen, HM et al. 2003). This can only to some extent be eliminated by defining uniform evaluation criteria so that further supplementation and objectification of these is necessary.

Nevertheless, on account of the clinical consequences, the need for diagnostic distinction between ADH and DCIS remains. The current WHO classification (WHO 2003) takes this into account by retaining the traditional terminology of intraductal proliferative lesions, with the distinction between usual ductal hyperplasia (UDH) and atypical ductal hyperplasia (ADH) and DCIS, and not replacing it by the term ductal intraepithelial neoplasia (DIN). However, the DIN classification may be reported optionally in addition to the conventional terminology (DIN 1A: flat epithelial atypia; DIN 1B: ADH; DIN 1C: low-grade DCIS; DIN 2: intermediate-grade DCIS; DIN 3: high-grade DCIS).

Although there is no international consensus as to whether quantitative criteria should be used for diagnostic differentiation in addition to the qualitative characteristics (WHO 2003), ADH is nevertheless usually a small lesion – except when it coexists with other lesions such as a papilloma or a radial scar.

For some authors the lower limit for DCIS is the presence of characteristic epithelial proliferation which fills at least 2 duct structures (Page, DL et al. 1992) whereas others define the involvement of one or more duct structures having a total diameter of not more than 2-3 mm as the upper limit for ADH (NHSBSP 2005; Tavassoli, FA et al. 1990).

Altogether, this means that ADH exhibits morphological features which are such that low-grade DCIS must be considered a possibility, while the architecture, cytology and quantitative criteria are not sufficient for an unequivocal diagnosis of DCIS.

ADH is associated with a moderate risk for the development of invasive carcinoma (WHO 2003). The relative risk after diagnosis of ADH is increased in both breasts (and not just in the breast where ADH was diagnosed) by a factor of 4-5 for the next 10-15 years (O’Malley, BA et al. 2006; WHO 2003). The presence of ADH in an excision biopsy is not usually an indication for further surgery. The procedure of choice is regular mammographic monitoring.

The detection of atypical intraductal epithelial proliferation in the core or vacuum-assisted biopsy results in classification of the lesion as B3 or B4 depending on the degree and extent of the atypia. Open biopsy is indicated. The purpose of this is to exclude or diagnose higher-grade changes (DCIS or invasive carcinoma).
3.1.7 Lobular neoplasia (LN)

According to the current WHO classification (WHO 2003) the term lobular neoplasia (LN) encompasses the entire spectrum of atypical epithelial proliferations which arise from TDLUs and are characterized by the proliferation of usually small cells with poor cell cohesion and with or without pagetoid involvement of the terminal ducts. Thus the changes atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS) are now grouped together as lobular neoplasia (LN).

A special feature of LN is its frequent multicentricity (46-85%) and bilateral occurrence (30-67%). In principle, as we understand it today, LN is an indicator lesion for an increased risk of carcinoma. The relative risk of a patient with a diagnosis of LN is increased bilaterally by the factor 6.9 to 12. According to the WHO guidelines, a pleomorphic variant and a signet ring cell variant of the classical form of LN are recognized, as well as a necrotic subtype with massive dilatation of the acini. This differentiation is relevant with a view to the therapeutic consequences. While in the case of classical LN, life-long follow-up with or without tamoxifen is recommended, according to the WHO classification re-excision should be considered if massive acinus dilatation or the pleomorphic, signet-ring or necrotic variant are demonstrated at or close to the resection margin. This recommendation in effect reflects the difficulty of distinguishing LN from genuine low-grade DCIS in individual cases. Although the immunohistochemical detection of E-cadherin can be helpful (LN: E-cadherin negative; DCIS: E-cadherin positive), lesions occasionally occur which exhibit the criteria of both LN and DCIS. These problematic cases often have the cytological features of classical LN but exhibit a solid, cohesive architectural pattern, with or without central necroses, or form microacinar structures. It can be assumed that the in situ lesions with E-cadherin expression are most likely to represent genuine DCIS, while the E-cadherin-negative cases should be regarded as LN. However, the natural history of these lesions is unclear. The same applies to histologically doubtful cases with E-cadherin-positive and –negative tumor cells which are currently classed as a combination of DCIS and LN (O’Malley, BA et al. 2006).

According to the WHO classification, grading of LN is not generally recommended (WHO 2003).

If classical LN is diagnosed in the core or vacuum biopsy in the context of mammographic screening this corresponds to category B3. Usually the LN is an incidental finding which coexists with another mammographically detected lesion. It should be discussed at an interdisciplinary conference whether the mammographically detected lesion is included in the core or vacuum-assisted biopsy. If this is not the case further histological examination, including diagnostic excision, is necessary (Amendoeira, I 2006c). Apart from this, according to the present level of knowledge surgery is not necessary unless indicated on account of other changes.

If it is not possible to decide on the basis of the core or vacuum-assisted biopsy material whether small-cell epithelial proliferation in TDLUs and/or ducts should be classified as LN or DCIS a higher B category is recommended, i.e. B4 or B5. The pleomorphic variant of LN can also be classified as B5 (Amendoeira, I 2006a).
3.1.8 **Ductal carcinoma in situ (DCIS)**

In the current WHO classification ductal carcinoma in situ (DCIS) is defined as a neoplastic intraductal lesion which is characterized by increased epithelial proliferation, subtle to pronounced cellular atypia and inherent but not necessarily obligatory tendency to progression to invasive carcinoma (WHO 2003). Small, low-grade or non-high-grade DCIS must be distinguished from ADH.

Artifacts at the specimen margin, retrograde extension of DCIS into terminal duct lobular units (so-called lobular cancerization) or ductal sclerosis with the inclusion of atypical epithelial complexes must not be misinterpreted as microinvasion (pseudoinvasion). Preparation of step sections and the use of immunohistochemistry to identify the epithelium-stroma border often permit clarification of the diagnosis. Markers to demonstrate myoepithelia (particularly p63) and basement membrane components (e.g. type IV collagen) have proved particularly helpful.

**Grading and classification**

For correlation with imaging and further treatment planning grading of DCIS should be undertaken not only on the excision specimen but on the core or vacuum-assisted biopsy material. However, the grading can vary between the core/vacuum-assisted biopsy and the final surgical specimen on account of intratumoral heterogeneity.

The following parameters should be included in the grading:


– comedo-type necrosis present/not present

**Table 1. Nuclear Grading of DCIS (The Consensus Conference Committee 1997).**

<table>
<thead>
<tr>
<th>Nuclear grade</th>
<th>Nuclear shape</th>
<th>Nuclear size</th>
<th>Chromatin</th>
<th>Nucleoli</th>
<th>Mitoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Low</td>
<td>Monotonous and isomorphic</td>
<td>1.5-2 times the diameter of an erythrocyte or ductal epithelial cell nucleus</td>
<td>Usually diffuse, finely granular</td>
<td>Only occasionally</td>
<td>Rare</td>
</tr>
<tr>
<td>2 Intermediate</td>
<td>Neither nuclear grade 1 nor 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 High</td>
<td>Markedly pleomorphic</td>
<td>Usually &gt; 2.5 times the diameter of an erythrocyte or ductal epithelial cell nucleus</td>
<td>Usually vesicular or irregular</td>
<td>Prominent, often multiple</td>
<td>Possibly abnormal</td>
</tr>
</tbody>
</table>
The grading can currently be based on either the WHO grading system (WHO 2003) or on the Van Nuys Classification (Silverstein, MJ et al. 1995). The available data base is not currently sufficient to permit a decision in favor of one or the other of the two grading systems. On the one hand there are no published data to date on the prognostic relevance of the WHO grading system while, on the other hand, the prognostic relevance of the Van Nuys Classification has only been analyzed retrospectively (Bijker, N et al. 2001; Silverstein, MJ et al. 1995).

Based on the recommendations of the Consensus Conference on the Classification of DCIS (Philadelphia, 1997) (The Consensus Conference Committee 1997), the WHO grading system takes into account mainly cytology/nuclear grade and the absence or presence of necroses (cf. Table II). In this respect it resembles the Van Nuys Classification (cf. Table III), but it differs from the latter in the subdivision of the non-high-grade lesions. The presence of nuclear grade 2 without comedo necroses is classed as intermediate-grade DCIS according to the WHO system but as group 1 (non-high-grade without comedo necroses) according to the Van Nuys Classification.

**Table II. WHO Grading of DCIS (WHO 2003)**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Cytology/nuclear grade (NG)</th>
<th>Necroses</th>
<th>Calcification</th>
<th>Architecture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade</td>
<td>Small, monomorphic cells with uniform nuclei (NG 1)</td>
<td>–</td>
<td>Lamellar</td>
<td>Arches, cribriform, solid and/or micropapillary</td>
</tr>
<tr>
<td>Intermediate grade</td>
<td>Cytology similar to low grade (NG 1) or intermediate nuclear grade (NG 2)</td>
<td>+</td>
<td>Lamellar or amorphous</td>
<td>Solid, cribriform, micropapillary</td>
</tr>
<tr>
<td>High grade</td>
<td>High grade cell atypia with pleomorphic nuclei (NG 3)</td>
<td>–/+</td>
<td>Amorphous</td>
<td>One cell layer, micropapillary, cribriform or solid</td>
</tr>
</tbody>
</table>

**Table III. Van Nuys Classification of DCIS (Silverstein, MJ et al. 1995)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Nuclear grade</th>
<th>Comedo necroses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Nuys Group I</td>
<td>Non high grade</td>
<td>–</td>
</tr>
<tr>
<td>Van Nuys Group II</td>
<td>Non high grade</td>
<td>+</td>
</tr>
<tr>
<td>Van Nuys Group III</td>
<td>High grade</td>
<td>–/+</td>
</tr>
</tbody>
</table>

If different grades are present within a DCIS the highest category determines the final classification in the respective grading system used.

In addition to nuclear grade and necroses, the current WHO classification also recommends documentation of the architecture of the DCIS (WHO 2003). This recommendation is supported by the fact that certain architectural patterns of DCIS (solid and cribriform) were associated with a significantly increased risk of local recurrence in the multivariate analysis of the
European Organization for Research and Treatment of Cancer (EORTC) Trials 10853 (excision with and without radiation therapy) (Bijker, N et al. 2001).

Five main forms are distinguished on the basis of their architecture: comedo type (multi-layer neoplastic epithelium surrounding a central necrotic zone), cribriform type (sieve-like proliferation pattern with evenly distributed, rounded secondary lumina), papillary type (epithelial proliferation with fibrovascular core) solid type (duct structures filled with atypical epithelium), micropapillary type (pseudopapillary cell proliferation without fibrovascular core).

However, there is often intratumoral heterogeneity with different architectural patterns existing alongside each other.

**Determination of hormone receptor expression**

In addition to the above pathomorphological factors, determination and documentation of the hormone receptor status of DCIS is recommended (Amendoeira, I 2006b; Carlson, RW et al. 2006a). The evaluation and interpretation of the immunohistochemistry is based on the procedure for invasive breast cancer (cf. Appendix 3: Chapter 3.2).

**University of Southern California/Van Nuys Prognostic Index (USC/VNPI)**

In 1996 Silverstein and coworkers introduced the Van Nuys Prognostic Index (VNPI) in order to help with the therapeutic decision (Silverstein, MJ et al. 1996). The original version included size, resection margin status and pathological classification on account of their predictive value. The VNPI has since been extended by addition of the parameter patient age and is now called the USC/VNPI (cf. Table IV) (Silverstein, MJ 2003). This modification was the result of a multivariate analysis of the data of 706 patients with DCIS who had received breast conserving surgery. For the three USC/VNPI groups the recurrence free survival after 10 years was 97% (USC/VNPI 4-6), 73% (USC/VNPI 7-9) and 34% (USC/VNPI 10-12). Patients with USC/VNPI scores of 7-9, unlike those with scores of 4-6, showed a significant improvement in recurrence free survival by 12-15% (p<0.05) after radiation therapy. Statistically speaking, patients with a score of 10-12 benefited most from radiotherapy but with unacceptably high 5-year-recurrence rates of almost 50%. The treatment recommendations which Silverstein and coworkers (Silverstein, MJ 2003) derived from these results are also shown in Table IV.

With regard to the use of the USC/VNPI in routine treatment planning it is important to remember that its value is controversial. A major criticism is that these treatment recommendations are based only on retrospectively collected data and not on the results of a prospective randomized study. General use of the USC/VNPI is therefore not recommended. Its reporting is optional.
Table IV. University of Southern California/Van Nuys Prognostic Index (USC/VNPI) (Silverstein, MJ 2003)

<table>
<thead>
<tr>
<th>Score</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size (mm)</strong></td>
<td>≤ 15</td>
<td>16–40</td>
<td>≥ 41</td>
</tr>
<tr>
<td><strong>Distance to resection margin (mm)</strong></td>
<td>≥ 10</td>
<td>1–9</td>
<td>&lt; 1</td>
</tr>
<tr>
<td><strong>Pathomorphological classification</strong></td>
<td>Non high grade without necroses</td>
<td>Non high grade with necroses</td>
<td>High grade without/with necroses</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>&gt; 60</td>
<td>40–60</td>
<td>&lt; 40</td>
</tr>
</tbody>
</table>

VNPI = score (size + resection margin + pathological classification + age)

<table>
<thead>
<tr>
<th>VNPI (total score)</th>
<th>Risk of recurrence</th>
<th>Treatment recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>4–6</td>
<td>Low</td>
<td>Excision</td>
</tr>
<tr>
<td>7–9</td>
<td>Intermediate</td>
<td>Excision and radiation</td>
</tr>
<tr>
<td>10–12</td>
<td>High</td>
<td>Mastectomy</td>
</tr>
</tbody>
</table>

**3.1.9 Invasive breast cancer**

**Histological typing**

(cf. also Statement Patho-2).

Histological typing according to the current WHO classification should be undertaken for all invasive breast carcinomas (cf. Table V (WHO 2003)). In the case of pre-operative diagnosis this should already be performed on the material from the core or vacuum-assisted biopsy. This is useful on the one hand for correlation with the imaging findings and on the other hand for the purpose of treatment planning. However, at the interdisciplinary conference it is important to address the fact that heterogeneity within the tumor can result in discrepancies between the core/vacuum-assisted biopsy and the surgical specimen. The final classification of the histological type is therefore made on the basis of the surgical specimen. However, the rate of agreement is relatively high.

Some specific histological types have been shown to have a more favorable course (Ellis, IO et al. 1992; Rosen, PP et al. 1993). These include tubular, invasive cribriform, mucinous and adenoid cystic carcinomas. Some authors also include tubulo-lobular and papillary carcinoma in this group (Fisher, ER et al. 1993).
According to the EU guidelines and the WHO classification (Amendoeira, I 2006b; WHO 2003) a rule of thumb that can be applied for the prognostically relevant differentiation of carcinomas of a “pure” specific type from mixed types is to classify a carcinoma as “pure” type if at least 90% of the tumor exhibits the respective characteristic pattern (e.g. tubular carcinoma). If the share of a second component is greater than 10% the carcinoma can be classed as mixed type (e.g. mixed ductal (NOS) and mucinous carcinoma), although according to WHO 2003 in mixed types the invasive ductal pattern (NOS) makes up 10-49% of the tumor. In the following only certain histological types will be discussed which are either particularly common or in which strict observance of diagnostic criteria is relevant for correct typing as it determines the assessment of the prognosis.

<table>
<thead>
<tr>
<th>Table V. WHO Classification of Invasive Breast Carcinomas (WHO 2003)</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Invasive ductal carcinoma, not otherwise specified (NOS)</td>
</tr>
<tr>
<td>– Mixed type</td>
</tr>
<tr>
<td>– Pleomorphic carcinoma</td>
</tr>
<tr>
<td>– Carcinoma with osteoclastic giant cells</td>
</tr>
<tr>
<td>– Carcinoma with choriocarcinomatous features</td>
</tr>
<tr>
<td>– Carcinoma with melanotic features</td>
</tr>
<tr>
<td>– Invasive lobular carcinoma</td>
</tr>
<tr>
<td>– Tubular carcinoma</td>
</tr>
<tr>
<td>– Invasive cribriform carcinoma</td>
</tr>
<tr>
<td>– Medullary carcinoma</td>
</tr>
<tr>
<td>– Mucinous carcinoma and other tumors with abundant mucin</td>
</tr>
<tr>
<td>– Mucinous carcinoma</td>
</tr>
<tr>
<td>– Cystadenocarcinoma and columnar cell mucinous carcinoma</td>
</tr>
<tr>
<td>– Signet ring cell carcinoma</td>
</tr>
<tr>
<td>– Neuroendocrine tumors</td>
</tr>
<tr>
<td>– Solid neuroendocrine carcinoma</td>
</tr>
<tr>
<td>– Atypical carcinoid tumor</td>
</tr>
<tr>
<td>– Small cell carcinoma</td>
</tr>
<tr>
<td>– Large cell neuroendocrine carcinoma</td>
</tr>
<tr>
<td>– Invasive papillary carcinoma</td>
</tr>
<tr>
<td>– Invasive micropapillary carcinoma</td>
</tr>
<tr>
<td>– Apocrine carcinoma</td>
</tr>
<tr>
<td>– Metaplastic carcinomas</td>
</tr>
<tr>
<td>– Pure epithelial metaplastic carcinomas</td>
</tr>
<tr>
<td>– Squamous cell carcinoma</td>
</tr>
<tr>
<td>– Adenocarcinoma with spindle cell metaplasia</td>
</tr>
<tr>
<td>– Adenosquamous carcinoma</td>
</tr>
<tr>
<td>– Mucoepidermoid carcinoma</td>
</tr>
<tr>
<td>– Mixed epithelial/mesenchymal metaplastic carcinoma</td>
</tr>
<tr>
<td>– Lipid-rich carcinoma</td>
</tr>
<tr>
<td>– Secretory carcinoma</td>
</tr>
<tr>
<td>– Oncocytic carcinoma</td>
</tr>
<tr>
<td>– Adenoid cystic carcinoma</td>
</tr>
<tr>
<td>– Acinic cell carcinoma</td>
</tr>
<tr>
<td>– Glycogen-rich clear cell carcinoma</td>
</tr>
<tr>
<td>– Sebaceous carcinoma</td>
</tr>
<tr>
<td>– Inflammatory carcinoma</td>
</tr>
</tbody>
</table>
The invasive ductal carcinoma (not otherwise specified, NOS) is by far the most frequent tumor type, accounting for 40-75%. It encompasses a heterogeneous group of tumors which do not exhibit sufficient features which allow them to be classified as a specific histological type (e.g. lobular or tubular carcinoma). In order to be classed as invasive ductal carcinoma a tumor must, after careful examination of representative sections, exhibit a non-specialized pattern in more than 50% of its mass (with regard to differentiation of “pure” invasive ductal carcinoma from mixed types see also above).

Invasive lobular carcinomas account for about 5-15% of invasive breast carcinomas. The classical appearance of invasive lobular carcinoma is characterized mainly by its small cells, its dissociated infiltrating growth and accompanying desmoplasia. Various morphological variants of the classical type are distinguished (solid, alveolar, pleomorphic and tubulo-lobular variants and mixed types). Their prognostic relevance is unclear. The classical form of invasive lobular carcinoma is associated with lobular neoplasia in at least 90% of cases.

The classical tubular carcinoma is characterized by the presence of neoplastic round-oval tubules lined with a single layer of cubic epithelium in dense collagenic connective tissue. The tubules can be angulated or canted with a droplet-like shape. The epithelium often shows apical snouting. The cell nuclei are minimally hyperchromatic and should only contain small inconspicuous nucleoli. Mitoses are rare. For diagnosis of a (pure) tubular carcinoma >90% of the tumor must consist of tubular structures with the described structural and cytological criteria. Although the classical tubular carcinoma only accounts for fewer than 2% of breast carcinomas it appears to be found more often with subtle radiological diagnosis. It accounts for at least 8% of tumors with a diameter of less than 1 cm, in pure screening populations for as many as 9-19% (WHO 2003).

Strict observation of the described criteria is important for estimating the prognosis. Pure tubular carcinoma has an excellent prognosis. Even in the rare cases where there are axillary lymph node metastases (6-19%) the prognosis is only minimally worse.

In mucinous carcinomas there are islands of relatively uniform cells in lakes of extracellular mucin. According to the current WHO classification (WHO 2003), classification as (pure) mucinous carcinoma is justified if the tumor shows complete mucinous differentiation. This applies to a maximum of 2% of invasive breast carcinomas. Here, too, strict observation of the diagnostic criteria has the aim of identifying tumors with a favorable prognosis, which occur particularly in older patients. The 10-year survival rate is 80-100% (O’Malley, BA et al. 2006; WHO 2003).
For a diagnosis of **medullary carcinoma** the entire tumor must fulfill the following criteria:
- syncytial growth pattern (>75% of the tumor area)
- no glandular differentiation
- diffuse lymphoplasmacellular infiltration (moderate to pronounced)
- moderate to marked nuclear pleomorphism (numerous mitoses)
- well defined circular borders (overview magnification)

The special feature of the medullary carcinoma is that with this tumor type established prognostic factors such as tumor grading and negative receptor status are evidently not significant determinants for the prognosis; i.e. the prognosis is better than is suggested by these factors. The 10-year survival rate is up to 84% (node-negative) and is thus better than that of poorly differentiated invasive ductal breast carcinomas. This is accompanied by a substantially lower rate of lymph node metastases (10-25%) (Bässler, R 1997; O’Malley, BA et al. 2006; WHO 2003).

Identification of this prognostically relatively favorable tumor depends on strict observation of the diagnostic criteria. When evaluating core and vacuum-assisted biopsies it is important to remember that the material obtained is only to a limited degree representative. The final diagnosis can therefore only be made from the resected tumor.

So-called **atypical medullary carcinomas** which exhibit 2 or 3 further features of typical medullary carcinoma in addition to having a mainly syncytial architecture, do not have any prognostic advantage. For this reason the recommendation is now to avoid this term and classify these carcinomas as invasive ductal carcinomas NOS (WHO 2003). Like the typical medullary carcinomas they are usually ER-, PgR and HER2 negative (triple negative). Some of these stand out pathogenetically from the rest. **Poorly differentiated invasive ductal carcinomas, NOS, which resemble the medullary carcinoma and are triple negative** are found more often in the group of BRCA1 associated breast carcinomas. Thus if these histological and immunohistological characteristics are found the possibility of a familial background should be pointed out in the report.

**Histological grading**
(cf. also Statement Patho-3).

Histological grading of all invasive breast carcinomas should be performed (WHO 2003). In the case of pre-operative diagnosis this should already be performed on the material from the core or vacuum-assisted biopsy. However, there can occasionally be discrepancies between the core/vacuum-assisted biopsy and the surgical specimen. The final histological grade is therefore determined on the basis of the surgical specimen. However, the rate of agreement is relatively high (approx. 75%). Grading discrepancies are not likely to exceed one level. For example, in the case of invasive carcinomas the mitosis rate determined in the core biopsy or vacuum-assisted biopsy material can be lower (Amendoeira, I 2006a).
**Table VI. Criteria for Grading of Breast Carcinoma (Elston, CW et al. 1991).**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Criterion</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubule formation</td>
<td>&gt; 75 %</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>10–75 %</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&lt; 10</td>
<td>3</td>
</tr>
<tr>
<td>Nuclear polymorphism</td>
<td>Low</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Marked</td>
<td>3</td>
</tr>
<tr>
<td>Mitotic count(a)</td>
<td>0–5/10 HPF</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>6-11/10 HPF</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&gt; 12/10 HPF</td>
<td>3</td>
</tr>
<tr>
<td>Total score:</td>
<td></td>
<td>3–9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total score</th>
<th>Degree of malignancy</th>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>3, 4, 5</td>
<td>Low</td>
<td>G1</td>
<td>Well differentiated</td>
</tr>
<tr>
<td>6, 7</td>
<td>Moderate</td>
<td>G2</td>
<td>Moderately differentiated</td>
</tr>
<tr>
<td>8, 9</td>
<td>High</td>
<td>G3</td>
<td>Poorly differentiated</td>
</tr>
</tbody>
</table>

\(a\) HPF = high power field; the assignment of the scores according to Elston and Ellis (Elston, CW et al. 1991) must be adjusted to take into account the size of field used in the individual case. The criteria given here are for a field diameter of 0.45 mm, corresponding to a simple light microscope with a field number of 18 without a widefield eyepiece.

The histological grading is performed according to a modification of the grading system of Bloom and Richardson described by Elston and Ellis (Elston, CW et al. 1991). The histological grading should usually be performed on material after primary fixation and embedding in paraffin. The histological and cytological criteria, which are evaluated semiquantitatively, are tubule formation, nuclear pleomorphism and frequency of mitoses (cf. Table VI).

When quantifying the mitosis rate the individual field size must be taken into account in order to avoid inaccuracies (cf. Table VII). The mitosis rate is determined in 10 consecutive high power fields (= 400x magnification in the microscope) in the area of the tumor with the highest mitotic activity. Only definite mitotic figures are counted.
Table VII. Assignment of Scores for Mitotic Count as a Function of Field Diameter (Elston, CW et al. 1991).

<table>
<thead>
<tr>
<th>Field diameter (mm)</th>
<th>Mitotic count</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Score 1</td>
</tr>
<tr>
<td>0.40–0.41</td>
<td>≤ 4</td>
</tr>
<tr>
<td>0.42–0.43</td>
<td>≤ 5</td>
</tr>
<tr>
<td>0.44–0.45</td>
<td>≤ 5</td>
</tr>
<tr>
<td>0.46–0.47</td>
<td>≤ 6</td>
</tr>
<tr>
<td>0.48–0.49</td>
<td>≤ 6</td>
</tr>
<tr>
<td>0.50–0.51</td>
<td>≤ 7</td>
</tr>
<tr>
<td>0.52</td>
<td>≤ 7</td>
</tr>
<tr>
<td>0.53–0.54</td>
<td>≤ 8</td>
</tr>
<tr>
<td>0.55–0.56</td>
<td>≤ 8</td>
</tr>
<tr>
<td>0.57</td>
<td>≤ 9</td>
</tr>
<tr>
<td>0.58–0.59</td>
<td>≤ 9</td>
</tr>
<tr>
<td>0.60</td>
<td>≤ 10</td>
</tr>
<tr>
<td>0.61</td>
<td>≤ 10</td>
</tr>
<tr>
<td>0.62–0.63</td>
<td>≤ 11</td>
</tr>
<tr>
<td>0.64</td>
<td>≤ 11</td>
</tr>
<tr>
<td>0.65–0.66</td>
<td>≤ 12</td>
</tr>
<tr>
<td>0.67</td>
<td>≤ 12</td>
</tr>
<tr>
<td>0.68</td>
<td>≤ 13</td>
</tr>
<tr>
<td>0.69</td>
<td>≤ 13</td>
</tr>
</tbody>
</table>

* in 10 high power fields

If the tumor area contained in the core and vacuum-assisted biopsies is less than 10 HPFs, the mitotic rate can be approximated by counting the total number of mitoses in the available HPFs. The number obtained is then divided by the number of HPFs assessed and multiplied by the factor 10.

An overview of the evaluation criteria with some sample illustrations of breast cancers with different grades of nuclear pleomorphism and a table for assignment of mitosis scores on the basis of the individual field diameter can be found in a poster of the NHS Cancer Screening Programme, UK, at: http://www.cancerscreening.nhs.uk/breastscreen/publications/nhsbsp58-poster.pdf

**Nottingham Prognostic Index**

Mention should also be made of the **Nottingham Prognostic Index** (cf. Table VIII) for invasive carcinomas which includes tumor size, grading and lymph node status and is considered to be of very good prognostic value. Its recording is optional.
Table VIII. Nottingham Prognostic Index (NPI) (Galea, MH et al. 1992; Page, DL et al. 1998).

<table>
<thead>
<tr>
<th>Item</th>
<th>Criterion</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor grade (Elston, CW et al. 1991)</td>
<td>G1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>G2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>G3</td>
<td>3</td>
</tr>
<tr>
<td>Lymph node status</td>
<td>pN0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1-3 positive nodes</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>≥ 4 positive nodes</td>
<td>3</td>
</tr>
</tbody>
</table>

\[ \text{NPI} = \text{tumor size (in cm)} \times 0.2 + \text{histological grade} + \text{lymph node score} \]

<table>
<thead>
<tr>
<th>NPI</th>
<th>Prognosis</th>
<th>15-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 3.4</td>
<td>Good</td>
<td>80 %</td>
</tr>
<tr>
<td>3.41–5.40</td>
<td>Intermediate</td>
<td>42 %</td>
</tr>
<tr>
<td>&gt; 5.40</td>
<td>Poor</td>
<td>13 %</td>
</tr>
</tbody>
</table>

3.2 **Special supplemental investigations**

(cf. also Statement Patho-4 with text).

In patients with invasive breast carcinoma the hormone receptor status and the HER2 status should also be determined as part of the primary diagnostic workup. Determination of the hormone receptor status is also recommended in the case of DCIS (Carlson, RW et al. 2006b; ICSI 2005; NCRI 2005; NHMRC 2001; Wolff, AC et al. 2007).

The reliability of the assay method used must be confirmed (Carlson, RW et al. 2006b; Wolff, AC et al. 2007).

Methods expressly recommended for confirming the reliability of the hormone receptor and HER2 assays are internal test validation, the use of standardized protocols and internal controls and the regular successful participation in external quality assurance measures (at least once a year); e.g. proficiency surveys of the Deutscher Pathologen e.V. (ER, PgR, HER2) or peer review.

3.2.1 **Hormone receptor status**

The estrogen and progesterone receptor status should be determined by immunohistochemistry assay, in the case of pre-operative diagnosis of an invasive carcinoma the determination should preferably be undertaken in the core biopsy already.

The respective percentages of tumor cell nuclei positive for estrogen and progesterone receptors should be stated.

The definition of cut-off values is currently under discussion. According to the 2005 St. Gallen Consensus a distinction is made between hormone-sensitive and non-hormone-sensitive breast carcinomas (Goldhirsch, A et al. 2005). However, it is not clear at present what exact cut-off value should be used to distinguish between these two categories. Tumors with a low percent-
age of positive tumor cell nuclei (upwards of about 1% of the tumor cells) can show some response to endocrine therapy (Harvey, JM et al. 1999). On the basis of empirical considerations the following classification is therefore recommended for ER and/or PgR (Goldhirsch, A et al. 2005):

- no response to endocrine therapy (ER-/PgR negative): 0 positive tumor cell nuclei
- uncertain response to endocrine therapy: 1–9% positive tumor cell nuclei
- response to endocrine therapy (ER-/PgR positive): ≥ 10% positive tumor cell nuclei

In addition to the percentage of positive tumor cells the internationally accepted Allred Score (Harvey, JM et al. 1999) or the immunoreactive score (IRS) of Remmele and Stegner (Remmele W et al. 1987) may also be given (cf. Table IX). Both immunohistochemical scores include the staining intensity in the calculations. If a threshold value of at least 10% positive tumor cell nuclei is used as a basis this gives a cut-off of ≥ 4 for the Allred Score and of ≥ 2 or ≥ 4 for the IRS of Remmele and Stegner depending on the staining intensity of the cells.

Table IX. Immunohistochemical Scores for Hormone Receptor Evaluation.

<table>
<thead>
<tr>
<th>Percentage of positive cell nuclei</th>
<th>Staining intensity</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunoreactive score (Remmele W et al. 1987)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No positive nuclei</td>
<td>0 points</td>
<td>No staining</td>
</tr>
<tr>
<td>&lt;10% positive nuclei</td>
<td>1 point</td>
<td>Weak staining</td>
</tr>
<tr>
<td>10-50% positive nuclei</td>
<td>2 points</td>
<td>Moderate staining</td>
</tr>
<tr>
<td>51-80% positive nuclei</td>
<td>3 points</td>
<td>Strong staining</td>
</tr>
<tr>
<td>&gt;80% positive nuclei</td>
<td>4 points</td>
<td></td>
</tr>
<tr>
<td>Allred Score (Harvey, JM et al. 1999)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No positive nuclei</td>
<td>0 points</td>
<td>No staining</td>
</tr>
<tr>
<td>&lt;1% positive nuclei</td>
<td>1 point</td>
<td>Weak staining</td>
</tr>
<tr>
<td>1-10% positive nuclei</td>
<td>2 points</td>
<td>Moderate staining</td>
</tr>
<tr>
<td>11-33% positive nuclei</td>
<td>3 points</td>
<td>Strong staining</td>
</tr>
<tr>
<td>34-66% positive nuclei</td>
<td>4 points</td>
<td></td>
</tr>
<tr>
<td>&gt;66% positive nuclei</td>
<td>5 points</td>
<td></td>
</tr>
</tbody>
</table>

3.2.2 HER-2/neu testing

Immunohistochemistry, FISH and CISH can be used for HER2 testing provided that the reliability of the assay method is confirmed.

The diagnostic equivalence of immunohistochemical HER2 determination in the core biopsy and the excised tumor has not yet been confirmed. For this reason use of the immunohistochemical HER2 status determined in the core biopsy as a decision base for trastuzumab therapy can only be recommended if it has been demonstrated for the institution concerned that there is a reliable agreement between core biopsy and excision specimen with respect to negative and positive results (Kappa > 0.81 or concordance > 95%). It must also be ensured that tissue artifacts (edge, retraction or crush artifacts) are excluded from the evaluation (Carlson, RW et al. 2006b; Wolff, AC et al. 2007).
It is easier to ensure the validity and reproducibility of the HER2 determination if standardized test kits are used; use of such test kits is therefore recommended. In this case the manufacturer’s instructions must be exactly followed.

HER2 positivity as precondition for trastuzumab therapy is defined as protein overexpression with a score of 3+ demonstrated by immunohistochemistry assay or gene amplification demonstrated by fluorescence in situ hybridization (FISH) or chromogenic in situ hybridization (CISH) (Carlson, RW et al. 2006b; Crump, M 2005; NCRI 2005; Wolff, AC et al. 2007).

**Figure 1.** Currently recommended HER2 testing algorithm (adapted from the Guidelines of the American Society of Clinical Oncology (ASCO), of the College of American Pathologists (CAP) and of the National Comprehensive Cancer Network (NCCN), USA (Carlson, RW et al. 2006b; Wolff, AC et al. 2007)).

**Evaluation criteria**

Positive HER2 status:
- IHC score 3+ (uniform intense circular membrane staining of more than 30 % of the invasive tumor cells)
- or FISH/CISH positive:
  - HER2/CEP17 ratio ≥ 2.0
  - or average HER2 gene copy numbers > 6 per nucleus
Equivocal HER2 status:
– IHC score 2+ (irregular or weak circular membrane staining of more than 10% of the invasive tumor cells or intense circular membrane staining of ≤30% of the invasive tumor cells)
– or FISH/CISH borderline:
  – HER2/CEP17 ratio 1.8-2.2
  – or average HER2 gene copy numbers 4-6 per nucleus
– In the case of an equivocal test result further diagnostic measures are necessary to determine the HER2 status (e.g. FISH or CISH in the case of an IHC score of 2+; cf. Fig. 1)

Negative HER2 status:
– IHC score 0/1+ (no membrane staining or weak incomplete membrane staining)
– or FISH/CISH negative:
  – HER2/CEP17 ratio <1.8
  – or average HER2 gene copy numbers <4 per nucleus

3.2.3 Further special investigations

Fresh material for additional molecular studies (e.g. determination of proteinases/proteinase inhibitors by ELISA) or for tissue banking can only be taken if it has been ensured that sufficient and representative material is available for adequate histopathological examination. When fresh material for such investigations is taken from surgical specimens, this should always be supervised by the pathologist.

So-called “newer prognostic factors” which can be determined by immunohistochemistry or analyzed by molecular biological methods (e.g. p53 and others) should only be examined if there is a specific reason and/or therapeutic consequence. According to current knowledge, routine analysis of such parameters is not necessary. If evidence of the therapeutic and prognostic relevance of such factors is shown in the future there would be a specific indication for their determination.

3.3 Processing and reporting of surgical specimens after primary (neoadjuvant) chemotherapy

The pathomorphological examination of the surgical specimens after neoadjuvant chemotherapy provides objective information about the effect of the treatment and the prognosis. Patients with pathological complete remission (pCR) after neoadjuvant chemotherapy have a significantly better survival chance than patients in whom pCR was not achieved (Fisher, B et al. 1998; Kuerer, HM et al. 1999; van der Hage, JA et al. 2001; Wolmark, N et al. 2001).

Determination of the residual tumor size, tumor morphology and lymphatic invasion permit the identification of patients with an increased risk of locoregional recurrence (Chen, AM et al. 2004). Consequently the careful pathomorphological examination of the surgical specimens forms the decisive framework for assessing the prognosis and planning the further therapy.

The pathologist should always be informed if the operation was preceded by neoadjuvant therapy.
The aim of the pathomorphological assessment is to detect foci of residual carcinoma and determine their location, extent and relationship to the resection margins.

There are currently no internationally uniform standards for the processing of resection specimens after neoadjuvant chemotherapy. In principle it has proved useful to follow the procedure used for primary operative treatment (cf. sections B.5.4-B.5.6).

If no macroscopically identifiable focus is present, extensive examination of the tissue is necessary (cf. Fig. 2).

*Figure 2. Tissue sampling in the absence of a focal finding after neoadjuvant chemotherapy (tissue blocks outlined in black).*

In this case it is recommended that at least one block should be taken systematically per 2 cm of the largest diameter of the specimen. Additional samples should be taken from the region of the resection margins (at least one block per dimension cranially, caudally, dorsally, ventrally, medially and laterally; alternatively orientation on the basis of the mamilla). Oriented tissue sampling is also necessary in the case of mastectomy specimens (e.g. with drawing of a sketch) in order to be able to determine the size of the lesion on the basis of the affected histological sections.

Effects of neoadjuvant chemotherapy/radiotherapy manifest themselves in the form of tumor cell necroses, cytopathic degenerative changes with vacuolization and resorptive inflammatory reactions and fibrosis (Langer, F et al. 2004). Additional immunohistochemical examination with pankeratin antibodies is occasionally useful to identify residual tumor cells. If there are marked regressive changes determination of the greatest tumor diameter can be problematic. In these cases the chemotherapy leads to considerable reduction of the tumor cellularity with cluster-like aggregates of tumor cells and tumor-free areas of fibrosis at the former tumor site. This can give a false impression of multifocality. However, immunohistological examination can often demonstrate partly degeneratively altered tumor cells in the areas of fibrosis. It is therefore expedient to base the evaluation of the tumor size on the total histological extent
of the tumor and not, for example, on the histological size of the largest individual lesion. Systematic and oriented tissue workup is therefore a prerequisite for exact determination of the histological extent of the tumor.

The \( pT \) category should only be based on the largest lesion in the case of unequivocally macroscopically identifiable multifocality and histologically tumor-free zones between the tumor islands.

The \( pTNM \) classification should be preceded by the prefix \( y \) to make it clear that the resection was performed after primary chemotherapy.

If no residual tumor cells are found in the initial tissue embedding a more extensive examination should be performed before confirming \( pCR \) with complete absence of residual tumor. The reliable diagnosis of \( pCR \) includes detection of a so-called “tumor bed” with characteristic changes such as groups of foam cells, foci of lymph cells, fibrosis and absence of glandular tissue.

There are now various classification systems available for pathomorphological grading of tumor regression which differ at least in part with regard to their definition of \( pCR \) (Kaufmann, M et al. 2006). This makes comparison of the published studies difficult. While some authors require the complete absence of residual tumor cells in the breast and the examined lymph nodes as a precondition for \( pCR \) (Chevallier, B et al. 1993; van der Hage, JA et al. 2001), others have modified this definition by including cases of non-invasive residual tumor (Kuerer, HM et al. 1999) or applying the term to the findings in the breast only (Fisher, B et al. 1998; Ogston, KN et al. 2003; Sinn, HP et al. 1994).

In spite of these different definitions, various studies have shown a significant correlation between \( pCR \) and patient survival. There is still no consensus as to the best way to define \( pCR \). However, numerous experts are of the opinion that standardization of the definition would be desirable so as to facilitate comparison of the different studies with regard to their treatment effect. It has therefore been recommended that the term \( pCR \) should only be used if no residual tumor cells are detectable either in the tissue excised from the breast or in the removed lymph nodes (Kaufmann, M et al. 2006).

Inclusion of a regression grade in the documentation, e.g. acc. to Sinn et al. (Sinn, HP et al. 1994) (cf. Table X), is optional.

---

**Table X. Regression Grade acc. to Sinn et al. (Sinn, HP et al. 1994).**

<table>
<thead>
<tr>
<th>Regression grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No effect</td>
</tr>
<tr>
<td>1</td>
<td>Increased tumor sclerosis with focal resorptive inflammation and/or marked cytopathic effects</td>
</tr>
<tr>
<td>2</td>
<td>Extensive tumor sclerosis with only focal, possibly multifocal, evidence of minimally invasive residual tumor (( \leq 0.5 ) cm); frequently extensive intraductal tumor spread</td>
</tr>
<tr>
<td>3</td>
<td>No invasive residual tumor</td>
</tr>
<tr>
<td>4</td>
<td>No residual tumor</td>
</tr>
</tbody>
</table>
Literature


NCRI. UK Clinical Guidelines for the use of adjuvant Trastuzumab (Herceptin®) with or following chemotherapy in HER2-positive Early breast Cancer. NCRI Breast Clinical Studies Group, 2005.


Remmele W, Stegner HE. Recommendation for uniform definition of an immunoreactive score (IRS) for immunohistochemical estrogen receptor detection (ER-ICA) in breast cancer tissue. Pathologe 1987; 8:138-140.


Form 1: Pathology Request Form.

<table>
<thead>
<tr>
<th>Patient details</th>
<th>Requesting surgeon/clinic:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last name:</td>
<td></td>
</tr>
<tr>
<td>First name:</td>
<td></td>
</tr>
<tr>
<td>Date of birth:</td>
<td></td>
</tr>
<tr>
<td>Specimen No. (Pathology Dept.)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site (laterality/location in breast)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core/excision biopsy: indicate sampling site; mastectomy: indicate tumor location</td>
</tr>
<tr>
<td>[] right</td>
</tr>
<tr>
<td>[] left</td>
</tr>
<tr>
<td>lateral</td>
</tr>
<tr>
<td>medial</td>
</tr>
<tr>
<td>caudal</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Topographic markings</th>
<th>Removed in one piece?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: ___________________</td>
<td>[] yes [ ] no</td>
</tr>
<tr>
<td>2: ___________________</td>
<td>in no: number of re-excisions: ________</td>
</tr>
<tr>
<td>3: ___________________</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical and radiological findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpable lesion [ ] yes [ ] no</td>
</tr>
<tr>
<td>Microcalcifications [ ] yes [ ] no; specimen radiograph attached: [ ] yes [ ] no</td>
</tr>
<tr>
<td>Other information (e.g. skin findings; neoadjuvant chemotherapy planned/performe, previous biopsy results):</td>
</tr>
<tr>
<td>Specimen type</td>
</tr>
<tr>
<td>[] High-speed core biopsy</td>
</tr>
<tr>
<td>[] Vacuum-assisted core biopsy; no. of cores: ____</td>
</tr>
<tr>
<td>Image-guided by: [ ] mammography [ ] ultrasound [ ] MRI</td>
</tr>
<tr>
<td>[] Diagnostic excision/open biopsy</td>
</tr>
<tr>
<td>Wire localization [ ] yes [ ] no</td>
</tr>
<tr>
<td>Image-guided by: [ ] mammography [ ] ultrasound [ ] MRI</td>
</tr>
<tr>
<td>[] Segmental excision/lumpectomy specimen</td>
</tr>
<tr>
<td>[] Mastectomy specimen</td>
</tr>
<tr>
<td>[] Lymph nodes [ ] Sentinel node [ ] Axillary dissection specimen; level ____</td>
</tr>
<tr>
<td>Lokalisation [ ] right [ ] left</td>
</tr>
<tr>
<td>[ ] Other; please specify: ___________________________</td>
</tr>
<tr>
<td>[ ] Other; please specify: ___________________________</td>
</tr>
</tbody>
</table>

| Date: ___________________ | Signature: ___________________ |
**Form 2A: Pathology Report Form on Core or Vacuum-Assisted Biopsy.**

<table>
<thead>
<tr>
<th>Requesting surgeon/clinic</th>
<th>Patient details:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Procedure performed, macroscopic description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core biopsy</td>
</tr>
<tr>
<td>Vacuum-assisted biopsy</td>
</tr>
</tbody>
</table>

| No. of cores: ______ | Specimen radiograph seen? | yes | no |
| No of incisions: ______ | Calcifications > 100 μm | yes | no |
| If yes, specify type: lamellar | amorphous |

<table>
<thead>
<tr>
<th>Histopathological diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-assessable</td>
</tr>
<tr>
<td>Normal tissue</td>
</tr>
<tr>
<td>Benign lesions</td>
</tr>
<tr>
<td>Fibrocystic change</td>
</tr>
<tr>
<td>Solitary cyst</td>
</tr>
<tr>
<td>Periductal mastitis/ductal ectasia</td>
</tr>
<tr>
<td>Adenosis</td>
</tr>
<tr>
<td>Sclerosing adenosis/apocrine adenosis</td>
</tr>
<tr>
<td>Other:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Benign lesions with uncertain biological potential or suspicious for malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex sclerosing lesion/radial scar</td>
</tr>
<tr>
<td>Intraductal papillary lesion</td>
</tr>
<tr>
<td>Flat epithelial atypia</td>
</tr>
<tr>
<td>Atypical ductal hyperplasia (ADH)</td>
</tr>
<tr>
<td>Lobular neoplasia</td>
</tr>
<tr>
<td>Other:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Malignant lesion, non-invasive (DCIS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear grade: low</td>
</tr>
<tr>
<td>Comedo necroses: present</td>
</tr>
<tr>
<td>WHO grade: low</td>
</tr>
<tr>
<td>Van Nuys group: II</td>
</tr>
<tr>
<td>Growth pattern: cribriform</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Malignant lesion, invasive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive ductal M8500/3</td>
</tr>
<tr>
<td>Intraductal component: yes</td>
</tr>
<tr>
<td>Invasive lobular M8520/3</td>
</tr>
<tr>
<td>Tubular M8211/3</td>
</tr>
<tr>
<td>Medullary M8510/3</td>
</tr>
<tr>
<td>Mucinous M8480/3</td>
</tr>
<tr>
<td>Grade: G1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other malignant neoplasia:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Unclear lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>not clear whether invasive or non-invasive</td>
</tr>
<tr>
<td>not clear whether lobular neoplasia or DCIS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1a: non-assessable</td>
</tr>
<tr>
<td>B1b: exclusively normal tissue</td>
</tr>
<tr>
<td>w/o breast parenchyma</td>
</tr>
<tr>
<td>with breast parenchyma</td>
</tr>
<tr>
<td>B2: benign</td>
</tr>
<tr>
<td>B3: benign</td>
</tr>
<tr>
<td>B4: suspicious of malignancy</td>
</tr>
<tr>
<td>B5: malignant</td>
</tr>
<tr>
<td>a. in situ</td>
</tr>
<tr>
<td>b. invasive</td>
</tr>
<tr>
<td>c. unclear whether in situ or invasive</td>
</tr>
<tr>
<td>d. other</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If evidence of microcalcifications: Are the microcalcifications associated with the lesion diagnosed?</th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
</tr>
<tr>
<td>yes, with: invasive cancer</td>
</tr>
<tr>
<td>uncertain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hormone receptors:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER: ___ % positive tumor cells</td>
</tr>
<tr>
<td>PgR: ___ % positive tumor cells</td>
</tr>
<tr>
<td>IHC score: Remmele and Stegner</td>
</tr>
<tr>
<td>Alfred</td>
</tr>
<tr>
<td>HER2: ICH score:</td>
</tr>
<tr>
<td>FISH/CISH: amplified</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Commentary/additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date: __________________________</td>
</tr>
<tr>
<td>Signature: ______________________</td>
</tr>
</tbody>
</table>

---

**Right left**
<table>
<thead>
<tr>
<th>Requesting surgeon/clinic</th>
<th>Patient details:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Last name:</td>
</tr>
<tr>
<td></td>
<td>First name:</td>
</tr>
<tr>
<td></td>
<td>Date of birth:</td>
</tr>
<tr>
<td></td>
<td>Specimen no.</td>
</tr>
<tr>
<td></td>
<td>Date of report:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Side:</th>
<th>right</th>
<th>left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topographic marking of specimen performed</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Specimen cut open before submission</td>
<td>yes</td>
<td>no</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specimen type:</th>
<th>Diagnostic excision/open biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tumorectomy/segmental excision/lumpectomy</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>sentinel</td>
</tr>
<tr>
<td>Lymph nodes:</td>
<td>axillary dissection specimen;</td>
</tr>
<tr>
<td></td>
<td>other; please specify:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specimen weight:</th>
<th>g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specimen size:</td>
<td>mm x mm x mm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specimen radiograph seen?</th>
<th>yes</th>
<th>no</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammographic abnormality in specimen?</td>
<td>yes</td>
<td>no</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histological calcification in specimen?</th>
<th>yes, in benign changes</th>
<th>yes, in malignancy</th>
<th>uncertain</th>
</tr>
</thead>
</table>

### Histopathological diagnosis

- **Benign lesions (including benign lesions seen together with malignancy)**
  - Fibrocystic change
  - Solitary cyst
  - Periductal mastitis/ductal ectasia
  - Sclerosing adenosis
  - Other: __________

- **Intraductal epithelial proliferation**
  - Usual ductal hyperplasia (UDH)
  - Flat epithelial atypia (ADH)
  - Atypical ductal hyperplasia (ADH)
  - Other: __________

- **Lobular neoplasia**
  - Classical type
  - With massive acinar dilation
  - Pleomorphic variant
  - With central necroses
  - Signet ring variant

- **Malignant lesions, non-invasive**
  - DCIS
    - Nuclear grade:
      - Comedo necroses
      - WHO grade:
      - Van Nuys group
      - Paget's disease
    - Size: _______ mm
      - 1
      - 2
      - 3

- Combination of DCIS and lobular neoplasia

**ICD O Code**

8520/2

---

*Form 2B: Pathology Report Form on Surgical Specimen.*
<table>
<thead>
<tr>
<th>Patient: ______________________________</th>
<th>Specimen no. ________</th>
</tr>
</thead>
</table>

**Invasive carcinoma**

- □ present
- □ not present

**Histological type**

- □ Invasive ductal, NOS
- □ Invasive lobular
- □ Medullary
- □ Mucinous
- □ Other primary breast carcinoma

<table>
<thead>
<tr>
<th>Invasive ductal, NOS</th>
<th>Invasive lobular</th>
<th>Medullary</th>
<th>Mucinous</th>
</tr>
</thead>
<tbody>
<tr>
<td>8500/3</td>
<td>8520/3</td>
<td>8510/3</td>
<td>8480/3</td>
</tr>
</tbody>
</table>

**Histological grade**

- □ G1
- □ G3
- □ non-assessable

**Tumor size**

- Maximum diameter of invasive carcinoma: ___________mm
- Size of associated DCIS (for extensive intraductal tumor component): ___________mm

**Peritumoral vascular invasion**

- □ present
- □ not seen

**Multifocality**

- □ present
- □ not present

**Multicentricity (acc. to Faverly et al., 1994)**

- □ present
- □ not present

**Resections margins**

- DCIS reaches margin
  - □ yes
  - □ no
- If yes, specify where: ______________________
- Invasive carcinoma reaches margin
  - □ yes
  - □ no
- If yes, specify where: ______________________
- If no; closest margin:______________________
  - Specify where: ______________________
  - DCIS
  - invasive carcinoma
  - Safety distance: __________

- □ Not assessable

**Axillary lymph nodes (LN)**

- No. of lymph nodes examined: __________
- No. of positive lymph nodes: __________
  - □ macrometastasis
  - □ micrometastasis
  - □ isolated tumor cells

**Other lymph nodes**

- Location: __________
- No. of lymph nodes examined: __________
- No. of positive lymph nodes: __________

**pTNM classification**

- □ pT □ pN □ ( ______/_______ ) □ pM

**Hormone receptors**

- ER: _____ % pos. tumor cells
- PgR: _____ % pos. tumor cells

<table>
<thead>
<tr>
<th>IHC score</th>
<th>Remmele and Stegner</th>
<th>Allred</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER: ______</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PgR: ______</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**HER2**

- ICH score: ______
- FISH/CISH:
  - □ amplified
  - □ non-amplified
  - □ uncertain

**Commentary/additional information**

- Date: __________
- Signature: __________
Appendix 4: Recommendations on Adjuvant Systemic Treatment of Breast Cancer

(Re B 7 Systemic Adjuvant Therapy)

Table I. Risk Categories According to St. Gallen 2007.

<table>
<thead>
<tr>
<th>pN status</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>All the following features:</td>
<td>At least 1 of the following features:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>pT ≤ 2 cm and G1 and V0 and ER+ or PgR+ and HER-2– and ≥ 35 years</td>
<td>pT &gt; 2 cm or G2–3 or V1 or ER- and PgR- or HER-2+ or aged &lt; 35 years</td>
<td></td>
</tr>
<tr>
<td>N+ (1–3 LN)</td>
<td>ER+ and/or PgR+ and HER-2–</td>
<td>ER- and PgR- or HER-2+</td>
<td></td>
</tr>
<tr>
<td>N+ (≥ 4 LN)</td>
<td></td>
<td>Always</td>
<td></td>
</tr>
</tbody>
</table>

Table II. Treatment Selection According to St. Gallen 2007.

<table>
<thead>
<tr>
<th>Risk</th>
<th>Endocrine responsive</th>
<th>Endocrine response uncertain</th>
<th>Endocrine non-responsive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>ET</td>
<td>ET</td>
<td>–</td>
</tr>
<tr>
<td>Medium</td>
<td>ET alone, or CT → ET (CT + ET)</td>
<td>CT → ET (CT + ET)</td>
<td>CT</td>
</tr>
<tr>
<td>HER-2+</td>
<td>Trastuzumab</td>
<td>Trastuzumab</td>
<td>Trastuzumab</td>
</tr>
<tr>
<td>High</td>
<td>CT → ET (CT + ET)</td>
<td>CT → ET (CT + ET)</td>
<td>CT</td>
</tr>
<tr>
<td>HER-2+</td>
<td>Trastuzumab</td>
<td>Trastuzumab</td>
<td>Trastuzumab</td>
</tr>
</tbody>
</table>

(CT = chemotherapy, ET = endocrine therapy)
Irrespective of the axillary lymph node status the following are considered standard regimens for adjuvant chemotherapy with appropriate anthracycline dosage and in appropriate combinations (based on a dose intensity of 20 mg/m²/week for doxorubicin and a minimum dose intensity of 30 mg/m²/week for epirubicin).

Table III. Standard Chemotherapy.

<table>
<thead>
<tr>
<th>Generally accepted regimens for adjuvant chemotherapy:</th>
</tr>
</thead>
<tbody>
<tr>
<td>French FEC</td>
</tr>
<tr>
<td>FE&lt;sub&gt;100&lt;/sub&gt;C d1, q3w x 6</td>
</tr>
<tr>
<td>American FAC</td>
</tr>
<tr>
<td>FA&lt;sub&gt;60&lt;/sub&gt;C d1, q3w x 6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>The following are accepted regimens for node-positive patients:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian FEC</td>
</tr>
<tr>
<td>C&lt;sub&gt;p,o&lt;/sub&gt;E&lt;sub&gt;60&lt;/sub&gt;F d1+8, q4w x 6</td>
</tr>
<tr>
<td>CALGB #9344</td>
</tr>
<tr>
<td>A&lt;sub&gt;p,o&lt;/sub&gt;C&lt;sub&gt;60&lt;/sub&gt;F d1 q3w x 4 → Paclitaxel&lt;sub&gt;175&lt;/sub&gt;d1 q3w x 4</td>
</tr>
<tr>
<td>NSABP-B-28</td>
</tr>
<tr>
<td>A&lt;sub&gt;60&lt;/sub&gt;C d1 q3w x 4 → Paclitaxel&lt;sub&gt;225&lt;/sub&gt;d1 q3w x 4</td>
</tr>
<tr>
<td>BCIRG #001</td>
</tr>
<tr>
<td>Docetaxel&lt;sub&gt;100&lt;/sub&gt;C d1 q3w x 4</td>
</tr>
<tr>
<td>PACS-01</td>
</tr>
<tr>
<td>FE&lt;sub&gt;100&lt;/sub&gt;C d1 q3w x 3 → Docetaxel&lt;sub&gt;100&lt;/sub&gt;d1 q3w x 3</td>
</tr>
<tr>
<td>ECOG-E1199</td>
</tr>
<tr>
<td>A&lt;sub&gt;60&lt;/sub&gt;C d1 q3w x 4 → Docetaxel&lt;sub&gt;100&lt;/sub&gt;d1 q3w x 4</td>
</tr>
<tr>
<td>Jones</td>
</tr>
<tr>
<td>Docetaxel&lt;sub&gt;175&lt;/sub&gt;C d1 q3w x 4</td>
</tr>
</tbody>
</table>

x n = number of cycles
### Table IV. Dosage Regimens.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Cyclophosphamide</th>
<th>Doxorubicin (A)</th>
<th>5-Fluorouracil (E)</th>
<th>Paclitaxel (P)</th>
<th>Docetaxel (D)</th>
<th>Methotrexate</th>
<th>Repeat (cycle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEC</td>
<td>500–600 mg/m²</td>
<td>100 mg/m²</td>
<td>500–600 mg/m²</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Every 3 weeks</td>
</tr>
<tr>
<td></td>
<td>i.v. d1</td>
<td>i.v. d1 (E)</td>
<td>i.v. d1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAC/CAF</td>
<td>500–600 mg/m²</td>
<td>60 mg/m²</td>
<td>500–600 mg/m²</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Every 3 weeks</td>
</tr>
<tr>
<td></td>
<td>i.v. d1</td>
<td>i.v. d1 (A)</td>
<td>i.v. d1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEF</td>
<td>75 mg/m²</td>
<td>60 mg/m²</td>
<td>500 mg/m²</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Every 4 weeks</td>
</tr>
<tr>
<td></td>
<td>p.o. d1–14</td>
<td>i.v. d1+8 (E)</td>
<td>i.v. d1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AC-T</td>
<td>600 mg/m²</td>
<td>60 mg/m²</td>
<td>175 mg/m²</td>
<td>—</td>
<td>d1 (P)</td>
<td>—</td>
<td>Every 3 weeks</td>
</tr>
<tr>
<td></td>
<td>i.v. d1</td>
<td>i.v. d1 (A)</td>
<td>d1 (P)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AC-D</td>
<td>600 mg/m²</td>
<td>60 mg/m²</td>
<td>100 mg/m²</td>
<td>—</td>
<td>d1 (D)</td>
<td>—</td>
<td>Every 3 weeks</td>
</tr>
<tr>
<td></td>
<td>i.v. d1</td>
<td>i.v. d1 (A)</td>
<td>d1 (D)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAC</td>
<td>500 mg/m²</td>
<td>50 mg/m²</td>
<td>75 mg/m²</td>
<td>—</td>
<td>d1 (D)</td>
<td>—</td>
<td>Every 3 weeks</td>
</tr>
<tr>
<td></td>
<td>i.v. d1</td>
<td>i.v. d1 (A)</td>
<td>d1 (D)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Important**

Dose intensity: 20 mg/m²/week for doxorubicin, *at least* 30 mg/m²/week for epirubicin. The planned dose intensity of the chemotherapy should be adhered to.

Adjuvant Endocrine Therapy (Following Chemotherapy) in Patients with Positive Hormone Receptor Status (ER-pos and/or PgR-pos)

**Premenopausal:** Tamoxifen for 5 years or goserelin for 2 to 3 years and tamoxifen for 5 years

**Postmenopausal:** Tamoxifen for 5 years (only in low-risk patients)

Aromatase inhibitor (e.g. anastrozole, letrozole) for 5 years

Or: switch to an aromatase inhibitor (e.g. exemestan, anastrozole) after 2 to 3 years of tamoxifen

Or: extended endocrine adjuvant therapy: tamoxifen for 5 years followed by a further 2 to 5 years of an aromatase inhibitor (e.g. letrozole)

The side-effects of treatment with aromatase inhibitors include fewer hot flushes, thromboembolic events and endometrial carcinomas as compared to tamoxifen, but arthralgia and myalgia are more frequent. Furthermore, greater loss of bone density can be expected and in some cases more frequent osteoporotic fractures.
Figure 1. Prevention of osteoporosis during treatment with aromatase inhibitors

- **General Scheme for Osteoporosis Prevention + Calcium + Vit. D**
- **Normal T-Score > –1**
  - BMD screening
- **Osteopenia T-Score -2.5 < –1**
  - Individualized drug therapy
- **Osteoporosis T-Score < –2.5**
  - Bisphosphonates

*Do not use tamoxifen + raloxifen in combination with AI (loss of action)*
Appendix 5: Algorithm for Systemic Treatment of Metastatic Breast Cancer

(Re C 4.3, Systemic therapy of metastatic breast cancer)

Algorithm for systemic treatment of metastatic breast cancer (cont./1)

Strategy for Chemotherapy

- Slow progression, Mild symptoms
- Single-agent chemotherapy
- Poor general condition
- Rapid progression, severe symptoms
- Combination chemotherapy
Algorithm for systemic treatment of metastatic breast cancer (cont'd. 2)

**Slow progression, few symptoms**

- **Previous anthracycline treatment?**
  - *HER-2/neu positive?*
    - no
    - **Anthracyclines**
  - yes
    - no
    - **Taxane + trastuzumab**
    - yes
    - **Taxanes**

- **HER-2/neu positive?**
  - no
  - **Taxanes**
  - yes
    - **Capecitabine/lapatinib**

- **I**
  - Anthracyclines
  - **II**
    - Taxanes
      - **III**
        - Capecitabine/lapatinib
        - **IV**
          - Vinorelbine, gemcitabine, liposomal doxorubicin or experimental treatment

**Rapid progression with symptoms**

- **Previous anthracycline treatment?**
  - *HER-2/neu positive?*
    - no
    - **Anthracycline + taxane**
    - yes
    - **Taxane + trastuzumab**
  - yes
    - no
    - **Taxane (D)/capecitabine or: taxane/(D)/gemcitabine or: taxane (T)/Avastin [bevacizumab]**
    - yes
    - **Taxane + trastuzumab**

- **I**
  - Anthracycline + taxane
  - **II**
    - Taxane + trastuzumab
    - **III**
      - **IV**
        - Capecitabine/lapatinib
        - **V**
          - Single-agent therapy with substances not previously used or experimental therapy
Appendix 6: Dosage Recommendations for Palliative Chemotherapy

(Re C 4.4 Chemotherapy for metastatic breast cancer)

Table I. Single-Agent Therapy.

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug</th>
<th>Dosage</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td>Adriamycin</td>
<td>60 mg/m²</td>
<td>q 3w</td>
</tr>
<tr>
<td></td>
<td>Epirubicin</td>
<td>30 mg/m²</td>
<td>q 1w</td>
</tr>
<tr>
<td></td>
<td>Epirubicin</td>
<td>90–100 mg/m²</td>
<td>q 3w</td>
</tr>
<tr>
<td>Taxanes</td>
<td>Docetaxel</td>
<td>100 mg/m²</td>
<td>q 3w</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>80–100 mg/m²</td>
<td>q 1w</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>175 mg/m²</td>
<td>q 3w</td>
</tr>
<tr>
<td>Vinca alkaloids, antimetabolites</td>
<td>Capecitabine</td>
<td>100–1250 mg/m² bid d1–14</td>
<td>q 3w</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine</td>
<td>1250 mg/m² d1+8+15</td>
<td>q 4w</td>
</tr>
<tr>
<td></td>
<td>Vinorelbine</td>
<td>30 mg/m² d1</td>
<td>q 1w</td>
</tr>
<tr>
<td></td>
<td>Vinorelbine</td>
<td>60–80 mg/m² p.o.</td>
<td>q 1w</td>
</tr>
<tr>
<td>liposomal Doxorubicin</td>
<td>Myocet</td>
<td>75 mg/m²</td>
<td>q 3w</td>
</tr>
<tr>
<td></td>
<td>Caelyx</td>
<td>40–50 mg/m²</td>
<td>q 4w</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Herceptin</td>
<td>2 mg/m²</td>
<td>q 1w</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Herceptin</td>
<td>6 mg/m²</td>
<td>q 3w</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Tykerb/Tyverb</td>
<td>1250 mg p.o.</td>
<td>daily</td>
</tr>
</tbody>
</table>

Table II. Combination Therapy.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Agent I</th>
<th>Dosage</th>
<th>Agent II</th>
<th>Dosage</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT</td>
<td>Adriamycin</td>
<td>60 mg/m² d1</td>
<td>Paclitaxel</td>
<td>175 mg/m² d1</td>
<td>q 3w</td>
</tr>
<tr>
<td>AD</td>
<td>Adriamycin</td>
<td>60 mg/m² d1</td>
<td>Docetaxel</td>
<td>75 mg/m² d1</td>
<td>q 3w</td>
</tr>
<tr>
<td>CT</td>
<td>Capecitabine</td>
<td>1000 mg/m² bid d1–14</td>
<td>Paclitaxel</td>
<td>175 mg/m² d1</td>
<td>q 3w</td>
</tr>
<tr>
<td>CD</td>
<td>Capecitabine</td>
<td>1250 mg/m² bid d1–14</td>
<td>Docetaxel</td>
<td>75 mg/m² d1</td>
<td>q 3w</td>
</tr>
<tr>
<td>ET</td>
<td>Epirubicin</td>
<td>60 mg/m² d1</td>
<td>Paclitaxel</td>
<td>175 mg/m² d1</td>
<td>q 3w</td>
</tr>
<tr>
<td>GT</td>
<td>Gemcitabine</td>
<td>1250 mg/m² d1+8</td>
<td>Paclitaxel</td>
<td>175 mg/m² d1</td>
<td>q 3w</td>
</tr>
<tr>
<td>GD</td>
<td>Gemcitabine</td>
<td>1000 mg/m² d1+8</td>
<td>Docetaxel</td>
<td>75 mg/m² d1</td>
<td>q 3w</td>
</tr>
<tr>
<td>AvT</td>
<td>Avastin</td>
<td>10 mg/kg d1+15</td>
<td>Paclitaxel</td>
<td>90 mg/m² d1+8+15</td>
<td>q 3w</td>
</tr>
<tr>
<td>Avatin</td>
<td>Avastin</td>
<td>15 mg/kg d1</td>
<td>Paclitaxel</td>
<td>175 mg/m² d1</td>
<td>q 3w</td>
</tr>
<tr>
<td>NG</td>
<td>Navelbine</td>
<td>30 mg/m² d1+14</td>
<td>Gemcitabine</td>
<td>1200 mg/m² d1+8</td>
<td>q 3w</td>
</tr>
<tr>
<td>NCap</td>
<td>Navelbine</td>
<td>60 mg/m² d1+8</td>
<td>Capecitabine 1000 mg/m² bid d1–14</td>
<td>q 3w</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lapatinib (Tyverb)</td>
<td>1250 mg/d</td>
<td>Capecitabine 1000 mg/m² bid d1–14</td>
<td>q 3w</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trastuzumab (Herceptin)</td>
<td>2 mg/m²</td>
<td>CT</td>
<td>q 1w</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trastuzumab (Herceptin)</td>
<td>6 mg/m²</td>
<td>CT</td>
<td>q 3w</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 7:  TNM and pTNM Classification and UICC Staging¹

Primary Tumor (T) Classification

<table>
<thead>
<tr>
<th>TX</th>
<th>Primary tumor cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>Tis (DCIS)</td>
<td>Ductal carcinoma in situ</td>
</tr>
<tr>
<td>Tis (LCIS)</td>
<td>Lobular carcinoma in situ</td>
</tr>
<tr>
<td>Tis (Paget)</td>
<td>Paget’s disease of the nipple with no evidence of tumor (Paget’s disease combined with evidence of tumor is classified according to the size of the tumor)</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T1a</td>
<td>More than 0.1 mm but not &gt; 0.5 mm in greatest dimension</td>
</tr>
<tr>
<td>T1b</td>
<td>More than 0.5 mm but not &gt; 1 cm in greatest dimension</td>
</tr>
<tr>
<td>T1c</td>
<td>More than 1 cm but not &gt; 2 cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt; 2 cm but not &gt; 5 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt; 5 cm in greatest dimension</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size with extension to chest wall or skin, as described in T4a to T4d</td>
</tr>
<tr>
<td>T4a</td>
<td>Extension to chest wall (ribs, intercostal muscles, serratus anterior muscle, but not the pectoral muscles)</td>
</tr>
<tr>
<td>T4b</td>
<td>Edema (including “peau d’orange”), ulceration of the skin or satellite skin nodules</td>
</tr>
<tr>
<td>T4c</td>
<td>Both T4a and T4b</td>
</tr>
<tr>
<td>T4d</td>
<td>Inflammatory carcinoma</td>
</tr>
</tbody>
</table>

pT Classification

pT1 mic: microinvasion is extension of cancer cells beyond the basement membrane into adjacent tissues with no focus more than 0.1 cm in greatest dimension. When there are multiple foci of microinvasion, the size of the largest focus only is used to classify the microinvasion: do not use the sum of all the individual foci. The presence of multiple foci should be noted, as with multiple larger carcinomas. Use the sizes in the T classification.

Regional Lymph Node (N) Classification

NX Regional lymph nodes have not been assessed. Only “clinically apparent” lymph node involvement as determined by clinical examination or imaging (except lymph scanning) is taken into account here. Sentinel node biopsy findings are always classified as pN and not taken into account in the clinical N classification.

Definition of regional lymph nodes (cf. Table 7.1)
Ipsilateral axillary (including intramammary and interpectoral “Rotter’s lymph nodes”), infraclavicular, supraclavicular lymph nodes and lymph nodes at the A. mammaria interna. All other lymph nodes are classified as distant metastases.

Table 7.1. N: Regional Lymph Nodes.

| N3a: Clinically apparent involvement of ipsilateral infraclavicular lymph nodes |
| N3c: Clinically apparent involvement of ipsilateral supraclavicular lymph nodes |

**pN Classification (cf. Table 7.2)**

* pN classification requires resection and histological examination at least of the lower axillary lymph nodes (Level I). At least 10 lymph nodes should be given histological examination. The number of lymph nodes examined should be recorded. One or more sentinel lymph nodes can be examined for the pathological classification. This can be described in the format pN1 (sn).

* pN1mi: exclusively micrometastases ≤ 2 mm in size

**Table 7.2. pN: Lymph Node Metastases > 2 mm (Axillary and/or Internal Mammary) Dependent on Localization.**

<table>
<thead>
<tr>
<th>Internal mammary lymph nodes</th>
<th>Axillary lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor-free or not examined</td>
<td>Tumor-free 1–3 LN involved 4–9 LN involved ≥ 10 LN involved</td>
</tr>
<tr>
<td>Only detected histologically</td>
<td>pN0 pN1a pN2a pN3a</td>
</tr>
<tr>
<td>Clinical or macroscopic</td>
<td>pN1b pN1c pN3b pN3b</td>
</tr>
<tr>
<td>involvement</td>
<td>pN2b pN3b pN3b pN3b</td>
</tr>
</tbody>
</table>

**M Distant Metastases**

* MX: Distant metastases have not been assessed

* M0: No distant metastases

* M1: Distant metastases

**UICC Staging (cf. Table 7.3)**

**Table 7.3. UICC Stages I–IV.**

<table>
<thead>
<tr>
<th>Stage 0</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis</td>
<td>T1mic, T1</td>
<td>T1mic, T1</td>
<td>T0, T1mic, T1</td>
<td>T0, T1mic, T1</td>
</tr>
<tr>
<td>N0</td>
<td>N0</td>
<td>N1</td>
<td>N1</td>
<td>N2</td>
</tr>
<tr>
<td>M0</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 8: Standards for a Quality Management System for Breast Cancer

8.1 Quality indicators relating to the S3 Guidelines

8.1.1 Updating and reaching of a consensus on the quality indicators

The first German S3 Guidelines for the Diagnosis and Treatment of Breast Cancer already contained recommendations for quality indicators drawn up by a panel of experts on the basis of an analysis of the literature. Now, during the revision of the Guidelines, even higher standards have been applied for the methodological quality of the quality indicators.

For this purpose the quality indicators which were already included in the first version – some of which were rewritten to bring them into line with the revised Guideline Statements – were subjected to methodological assessment by means of a consensus process. With the recent introduction of the QUALIFY instrument by BQS [German organization for quality assurance in the health care sector] (cf. www.bqs-online.de), it is now possible to carry out a complete methodological quality assessment. For this purpose, however, comprehensive data must be available on patient care; so far such data are available only for those quality indicators that are already subject to the BQS process. Since data of this kind do not exist for most of the indicators, the authors of the Guidelines have limited themselves to a methodological assessment by means of the consensus process, a method which has gained widespread acceptance worldwide. As part of this “RAND-UCLA method” expert panels assess the validity and feasibility of the quality indicators during a two-staged Delphi process. The indicators are rated on a scale of 1 to 9; the highest score – 9 – is given to indicators which are “extremely valid or feasible” while the lowest score – 1 – is given to indicators which are “not valid or feasible at all” (Kerr, E. at al. 2000).

These two criteria are subject to the following definitions in this context:

Validity (according to RAND-UCLA)
– The QI is supported by sufficient scientific evidence or a sufficient professional consensus.
– Patients treated as specified by the QI derive noticeable health benefits.
– It can be established, on the basis of the professional experience of the evaluators, that service providers who follow the QIs significantly more often are deemed to be “of high quality.”
– The majority of factors determining the rating of the QI is within the control of (or can be influenced by) the service provider.

Feasibility (according to RAND-UCLA)
– The information which is required to measure a QI can be found, with a high degree of probability, in a typical patient’s file.
– Estimates of a QI on the basis of data from the patient’s file are, with a high degree of probability, reliable and non-distorted.
– The absence of documentation of relevant data on a QI is in itself a sign of poor quality.

The Guideline authors were asked to rate each of the quality indicators on a scale of 1 to 9 on the basis of these definitions. The evaluation results (scores) and any comments made were reported back to everyone participating in the consensus process. On this basis the participants then carried out a second – and final – round of evaluation.

In the RAND-UCLA process all indicators are accepted for further use which received a median score of 7 or higher for the criterion of “validity” and for which there was no dissent (dissent = at least one-third of the panel members gave the QI a score of 1–3 while at the same time at least one-third gave the QI a score of 7–9 for validity) and which, in addition, were given a median score of at least 4 for feasibility.

The following list contains the quality indicators included in the assessment and their validity and feasibility assessments (scores).

For the further development culminating in a set of valid and consensus-approved quality indicators suitable for assessing the quality of care in Germany with respect to the diagnosis, treatment and follow-up care of breast cancer, it will be urgently important, during a pilot phase, to generate data on the QIs rated as suitable for this purpose so that we can then subject them to a complete methodological quality assessment with the QUALIFY instrument. On this basis specific recommendations could then be made for the various – and possibly different – areas of application (e.g. internal quality management or external comparisons, documentation on the level of the patient’s file or in databases) for the indicators. Furthermore, the entire set of indicators should be assessed to determine whether all core processes in the diagnosis, treatment and follow-up care of breast cancer in Germany have been included and whether, in addition, a sufficient number of outcome indicators is available by means of which the degree of implementation of the Guidelines can be measured over the long term.

In this respect the present list developed as part of the revision of the Guidelines, represents solely a first – but nevertheless important – step in the direction of an acceptable set of indicators. The further work on such a set should be completed, under the aegis of the professional societies involved, by the next revision of the Guidelines.

Those measures or indicators of outcome quality which are documented in cancer registries or are required for the recertification of breast centers are listed separately in Appendix 8.1.3.

**Literature**

## 8.1.2 Quality indicators and assessment results

<table>
<thead>
<tr>
<th>Quality Indicator (QI)</th>
<th>Reference Range</th>
<th>Validity (Median)</th>
<th>Feasibility (Median)</th>
<th>Assessment: QI accepted/not accepted</th>
</tr>
</thead>
<tbody>
<tr>
<td>QI 1: Percentage of all patients with breast cancer treated within the framework of clinical studies - during primary therapy</td>
<td>≥ 10 %</td>
<td>7</td>
<td>9</td>
<td>Accepted</td>
</tr>
<tr>
<td>QI 2: Percentage of all patients with breast cancer treated within the framework of clinical studies - at stage of metastasis</td>
<td>≥ 10 %</td>
<td>8</td>
<td>9</td>
<td>Accepted</td>
</tr>
<tr>
<td>QI 3: Percentage of all symptomatic patients with primary disease in whom the breasts and lymphatic drainage areas were examined by palpation before treatment</td>
<td>≥ 95 %</td>
<td>8,5</td>
<td>9</td>
<td>Accepted</td>
</tr>
<tr>
<td>QI 4: Percentage of all symptomatic patients with primary disease who undergo mammography using standard radiographic techniques (cc and mlo views) before treatment</td>
<td>≥ 95 %</td>
<td>9</td>
<td>9</td>
<td>Accepted</td>
</tr>
<tr>
<td>QI 5: Percentage of all symptomatic patients with primary disease who undergo high-frequency ultrasound examination before treatment</td>
<td>≥ 95 %</td>
<td>8,5</td>
<td>9</td>
<td>Accepted</td>
</tr>
<tr>
<td>QI 6: Percentage of all symptomatic patients treated for breast cancer in whom the diagnosis of breast cancer is confirmed histologically before the beginning of treatment</td>
<td>≥ 95 %</td>
<td>8,5</td>
<td>7,5</td>
<td>Accepted</td>
</tr>
<tr>
<td>QI 7: Percentage of all symptomatic patients treated for breast cancer in whom the diagnosis of breast cancer is confirmed via minimally invasive histological techniques before the beginning of treatment</td>
<td>≥ 70 %</td>
<td>9</td>
<td>9</td>
<td>Accepted</td>
</tr>
<tr>
<td>QI 8: Percentage of all symptomatic patients with locally advanced breast cancer or clinical suspicion of metastasis who undergo chest x-ray, ultrasound examination and bone scan before treatment</td>
<td>≥ 90 %</td>
<td>8,5</td>
<td>8,5</td>
<td>Accepted</td>
</tr>
<tr>
<td>QI 9: Percentage of patients with breast cancer suspected upon mammography or confirmed by core biopsy or vacuum-assisted biopsy who are treated according to an interdisciplinary treatment plan</td>
<td>≥ 95 %</td>
<td>8,5</td>
<td>7,5</td>
<td>Accepted</td>
</tr>
<tr>
<td>QI 10: Percentage of all patients undergoing breast-conserving surgery for DCIS who receive postoperative adjuvant radiotherapy</td>
<td>≥ 70 %</td>
<td>9</td>
<td>8</td>
<td>Accepted</td>
</tr>
<tr>
<td>Quality Indicator (QI)</td>
<td>Reference Range</td>
<td>Validity (Median)</td>
<td>Feasibility (Median)</td>
<td>Assessment: QI accepted/not accepted</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------------</td>
<td>------------------</td>
<td>---------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>QI 11: Percentage of all patients undergoing local surgery for non-advanced breast cancer in whom the tumor is excised with clear resection</td>
<td>≥ 95 %</td>
<td>9</td>
<td>9</td>
<td>Accepted</td>
</tr>
<tr>
<td>QI 12: Percentage of all patients undergoing local surgery for invasive breast cancer in whom the tumor is excised with a microscopically measured safety distance of 1 mm or more between the resection margin and the carcinoma</td>
<td>≥ 95 %</td>
<td>8</td>
<td>8</td>
<td>Accepted</td>
</tr>
<tr>
<td>QI 13: Percentage of all patients undergoing local surgical treatment of DCIS in whom a safety distance of 5 mm or more is measured microscopically between the resection margin and the tumor</td>
<td>≥ 95 %</td>
<td>8</td>
<td>7,5</td>
<td>Accepted</td>
</tr>
<tr>
<td>QI 14: Percentage of all patients undergoing surgery for invasive breast cancer classified as pT1 without an indication for MRM who receive breast-conserving therapy</td>
<td>≥ 60 %</td>
<td>9</td>
<td>9</td>
<td>Not accepted</td>
</tr>
<tr>
<td>QI 15: Percentage of all patients treated with mastectomy without an indication (1-7) for mastectomy</td>
<td>≤ 10 %</td>
<td>8,5</td>
<td>7</td>
<td>Not accepted</td>
</tr>
<tr>
<td>QI 16a: Percentage of all patients with invasive breast cancer in whom sentinel node biopsy (SNB) is possible and is actually performed to determine the histological nodal status</td>
<td>≥ 60 %</td>
<td>9</td>
<td>9</td>
<td>Accepted</td>
</tr>
<tr>
<td>QI 16b: Percentage of all patients with invasive breast cancer in whom axillary dissection is performed with removal of at least 10 lymph nodes at Levels I and II (in cases where SNB is not possible or has yielded positive results)</td>
<td>≤ 40 %</td>
<td>9</td>
<td>9</td>
<td>Accepted</td>
</tr>
<tr>
<td>QI 17: Percentage of all invasive carcinomas which are classified histologically</td>
<td>≥ 95 %</td>
<td>9</td>
<td>9</td>
<td>Accepted</td>
</tr>
<tr>
<td>QI 18: Percentage of all invasive carcinomas which are graded according to the WHO system (Elston and Ellis modification of the classification system of Bloom and Richardson)</td>
<td>≥ 95 %</td>
<td>9</td>
<td>9</td>
<td>Accepted</td>
</tr>
<tr>
<td>QI 19: Percentage of all invasive carcinomas in which hormone receptor status and HER-2 status are determined during the primary diagnostic workup</td>
<td>≥ 95 %</td>
<td>9</td>
<td>9</td>
<td>Accepted</td>
</tr>
<tr>
<td>Quality Indicator (QI)</td>
<td>Reference Range</td>
<td>Validity (Median)</td>
<td>Feasibility (Median)</td>
<td>Assessment: QI accepted/not accepted</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------------------</td>
<td>-----------------</td>
<td>-------------------</td>
<td>----------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>QI 20: Percentage of patients in whom documentation of pTNM, menopausal status, safety</td>
<td>≥ 95 %</td>
<td>9</td>
<td>9</td>
<td>Accepted</td>
</tr>
<tr>
<td>distance, grading, estrogen and progesterone receptors and HER-2/neu status is performed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QI 21: Percentage of all patients who exhibit a lesion &gt; 10 mm that can be palpated intraoperatively and in whom an intraoperative frozen section is performed to determine the malignancy of the lesion</td>
<td>&lt; 15 %</td>
<td>9</td>
<td>8</td>
<td>Accepted</td>
</tr>
<tr>
<td>QI 22: Percentage of all patients undergoing lymph node dissection in whom lymph nodes status is described on the basis of the histological examination of all lymph nodes removed including specification of the number of lymph nodes removed, the number of positive lymph nodes, whether or not there was capsule penetration, and the pN category</td>
<td>≥ 95 %</td>
<td>9</td>
<td>9</td>
<td>Accepted</td>
</tr>
<tr>
<td>QI 23: Percentage of all patients with invasive carcinoma treated with breast-conserving surgery in whom postoperative adjuvant irradiation of the remaining breast and chest wall is performed</td>
<td>≥ 95 %</td>
<td>9</td>
<td>9</td>
<td>Accepted</td>
</tr>
<tr>
<td>QI 24: Percentage of all patients with invasive carcinoma receiving adjuvant radiotherapy after breast-conserving surgery who receive a local boost</td>
<td>No data available</td>
<td>6</td>
<td>8</td>
<td>Not accepted</td>
</tr>
<tr>
<td>QI 25: Percentage of all patients with insufficient resection with clear margins (R1-R2), axillary lymph node involvement (≥ 4 positive lymph nodes), pt3/T4 carcinoma or status post mastectomy who receive postoperative adjuvant radiotherapy</td>
<td>No data available</td>
<td>8</td>
<td>9</td>
<td>Not accepted</td>
</tr>
<tr>
<td>QI 26: Percentage of all patients with inoperable locally advanced or inflammatory breast cancer who receive radiotherapy</td>
<td>≥ 95 %</td>
<td>8</td>
<td>7</td>
<td>Not accepted</td>
</tr>
<tr>
<td>QI 27: Percentage of all premenopausal patients with receptor-positive breast cancer treated with GnRH analogs for at least 2 years</td>
<td>No data available</td>
<td>8.5</td>
<td>7</td>
<td>Not accepted</td>
</tr>
<tr>
<td>QI 28: Percentage of all postmenopausal patients with receptor-positive breast cancer who are treated with 3rd generation aromatase inhibitors primarily for five years, or for 2-3 years after 2-3 years of tamoxifen treatment, or for 5 years after 5 years of tamoxifen treatment</td>
<td>≥ 90 %</td>
<td>8</td>
<td>6</td>
<td>Not accepted</td>
</tr>
<tr>
<td>QI 29: Percentage of all patients treated with adjuvant combination chemotherapy who receive anthracyclines</td>
<td>≥ 80 %</td>
<td>8</td>
<td>8</td>
<td>Accepted</td>
</tr>
<tr>
<td>Quality Indicator (QI)</td>
<td>Reference Range</td>
<td>Validity (Median)</td>
<td>Feasibility (Median)</td>
<td>Assessment: QI accepted/not accepted</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------------</td>
<td>-----------------</td>
<td>------------------</td>
<td>----------------------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>QI 30: Percentage of all patients with locally advanced, primarily inoperable or inflammatory breast cancer who receive primary (preoperative) systemic therapy</td>
<td>No data available</td>
<td>9</td>
<td>8</td>
<td>Not accepted</td>
</tr>
<tr>
<td>QI 31: Percentage of all patients with HER-2 positive breast cancer (immunohistochemical score 3+ and/or FISH/CISH positive) treated with trastuzumab for more than one year</td>
<td>≥ 80 %</td>
<td>9</td>
<td>8</td>
<td>Accepted</td>
</tr>
<tr>
<td>QI 32: Percentage of all patients with an invasive in-breast recurrence who undergo secondary mastectomy</td>
<td>No data available</td>
<td>4</td>
<td>3</td>
<td>Not accepted</td>
</tr>
<tr>
<td>QI 33: Percentage of all patients with a recurrence in the chest wall following mastectomy who undergo complete excision (RO) of this recurrence</td>
<td>≥ 90 %</td>
<td>6,5</td>
<td>5</td>
<td>Not accepted</td>
</tr>
<tr>
<td>QI 34: Percentage of all patients with an isolated regional recurrence treated with surgery/radiotherapy</td>
<td>≥ 90 %</td>
<td>6,5</td>
<td>7</td>
<td>Not accepted</td>
</tr>
<tr>
<td>QI 35: Percentage of all patients with distant metastases (at the time of primary therapy) and positive hormone receptor status who receive anti-oestrogen therapy</td>
<td>≥ 90 %</td>
<td>6,5</td>
<td>7</td>
<td>Not accepted</td>
</tr>
<tr>
<td>QI 36: Percentage of all patients with distant metastases and positive hormone receptor status who receive combined chemo-endocrine therapy</td>
<td>&lt; 10 %</td>
<td>5</td>
<td>5</td>
<td>Not accepted</td>
</tr>
<tr>
<td>QI 37: Percentage of all postmenopausal patients with distant metastases and positive hormone receptor status who are treated with aromatase inhibitors after adjuvant therapy with tamoxifen or without prior hormonal therapy</td>
<td>≥ 95 %</td>
<td>8</td>
<td>7</td>
<td>Not accepted</td>
</tr>
<tr>
<td>QI 38: Percentage of all premenopausal patients with distant metastases and positive hormone receptor status who undergo suppression of ovarian function (via GnRH analogs, oophorectomy or irradiation of the ovaries) in combination with tamoxifen</td>
<td>≥ 95 %</td>
<td>6,5</td>
<td>7</td>
<td>Not accepted</td>
</tr>
<tr>
<td>QI 39: Percentage of all patients with distant metastases and ongoing chemotherapy in whom the effect of therapy is evaluated at least every 3 months according to a suitable and representative parameter (e.g. symptoms, tumor markers, indicator metastasis)</td>
<td>≥ 90 %</td>
<td>9</td>
<td>8</td>
<td>Accepted</td>
</tr>
<tr>
<td>QI 40: Percentage of all patients with metastatic breast cancer treated with single-agent chemotherapy or polychemotherapy (primary therapy)</td>
<td>No data available</td>
<td>7</td>
<td>7,5</td>
<td>Not accepted</td>
</tr>
<tr>
<td>Quality Indicator (QI)</td>
<td>Reference Range</td>
<td>Validity (Median)</td>
<td>Feasibility (Median)</td>
<td>Assessment: QI accepted/not accepted</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------------</td>
<td>-----------------</td>
<td>------------------</td>
<td>----------------------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>QI 41: Percentage of all patients with distant metastases being treated with trastuzumab in whom HER-2 status is determined (in the primary tumor or in a new biopsy specimen)</td>
<td>≥ 90 %</td>
<td>9</td>
<td>9</td>
<td>Accepted</td>
</tr>
<tr>
<td>QI 42: Percentage of all patients with bone metastases undergoing radiotherapy for these metastases</td>
<td>No data available</td>
<td>3,5</td>
<td>6</td>
<td>Not accepted</td>
</tr>
<tr>
<td>QI 43: Percentage of all patients with bone metastases undergoing surgical treatment for these metastases</td>
<td>No data available</td>
<td>3,5</td>
<td>6</td>
<td>Not accepted</td>
</tr>
<tr>
<td>QI 44: Percentage of all patients with bone metastases receiving biphosphonates</td>
<td>No data available</td>
<td>8</td>
<td>8</td>
<td>Accepted</td>
</tr>
<tr>
<td>QI 45: Percentage of all patients with multiple brain metastases undergoing irradiation of the entire neurocranium (whole-brain irradiation)</td>
<td>No data available</td>
<td>8</td>
<td>7,5</td>
<td>Not accepted</td>
</tr>
<tr>
<td>QI 46: Percentage of all patients receiving follow-up care for breast cancer who are given information on possibilities for obtaining further support (provided, for example, by medical specialists with training in oncology, psychooncologists, physiotherapists, oncological nurses, etc.)</td>
<td>≥ 95 %</td>
<td>7</td>
<td>2</td>
<td>Not accepted</td>
</tr>
<tr>
<td>QI 47: Percentage of all asymptomatic patients who have completed breast-conserving treatment of breast cancer who undergo an apporative diagnostic workup (e.g. mammography, ultrasound and if necessary MRI) of the ipsilateral breast</td>
<td>≥ 95 %</td>
<td>8,5</td>
<td>3</td>
<td>Not accepted</td>
</tr>
<tr>
<td>QI 48: Percentage of all patients receiving follow-up care for breast cancer who have regular annual mammograms of the contralateral breast</td>
<td>≥ 95%</td>
<td>9</td>
<td>5</td>
<td>Not accepted</td>
</tr>
<tr>
<td>QI 49: Percentage of all patients with breast cancer who have undergone axillary lymph node dissection or axillary irradiation who are informed of the possibilities for detecting, preventing and treating lymphedema</td>
<td>≥ 95%</td>
<td>9</td>
<td>7</td>
<td>Not accepted</td>
</tr>
<tr>
<td>QI 50: Percentage of all patients receiving follow-up care for breast cancer who have follow-up examinations every three months during the first three years after their primary surgery, every six months during the fourth and fifth years, and once annually in the sixth and all later years (including regular examinations for the early detection of cancer)</td>
<td>≥ 95 %</td>
<td>9</td>
<td>7</td>
<td>Not accepted</td>
</tr>
</tbody>
</table>
8.1.3 **Indicators of outcome quality used in the S3 Guidelines**

The following measures or indicators of outcome quality are documented by cancer registries or are required for the recertification of breast centers (DKG/DGS):

**Tables**

For all annual cohorts since the beginning of documentation

– No. of new illnesses per year
– Distribution of the pT category (total = 100 %) (pT1-pT4, no information on pT because:
  – the patient received neoadjuvant treatment
  – the patient did not undergo surgery – no information is available for other reasons)
– No. of patients treated with breast-conserving surgery

**Tables (Outcome)**

For all annual cohorts since the beginning of documentation

– No. of patients with a known local recurrence
– No. of patients with a known lymph-node recurrence
– No. of patients with known metastases
– No. of deaths per year

**Quality indicator: Lost to follow-up with respect to life status < 20 %**

**Kaplan-Meier Estimator (Outcome)**

For all patients since the beginning of documentation

– Total patient cohort: overall survival
– Total patient cohort: overall survival stratified on the basis of pT category (pT1, pT2, pT3, pT4)
– Survival time w/o local recurrence
– Survival time w/o metastases
– Survival time w/o metastases stratified on the basis of pT category (pT1, pT2, pT3, pT4)
– Overall survival after the onset of metastases

**Comparisons with other institutions**

For all patients since the beginning of documentation

**With respect to:** age, distribution of pT categories (see above), breast-conserving treatments according to pT category, percentage of patients who received radiotherapy after breast-conserving surgery

Overall survival according to pT category (consecutive calendar months)
8.2 Sequential procedure for the management of women with breast cancer

The following list contains criteria for good quality which are intended to serve as the basis for establishing a quality-assured patient management path:

Reasonable suspicion of breast cancer
- Organization of the pre-therapeutic phase by the gynecologist or referring practitioner (“coordinator”)
- History-taking
- If not already done: confirmation of diagnosis according to the S3 Guidelines for Early Detection of Breast Cancer (e.g. at a certified breast center)
- Completion of diagnostic workup for staging (e.g. at a certified breast center)
- Planning of treatment together with the patient (including crucial decision about the first treatment step (operation or systemic therapy) and choice of institutions where the treatment will be performed
- Involvement of self-help groups, psychooncological counseling if necessary.
- Enrolment in a DMP (Disease Management-Program for Breast Cancer) if appropriate

Operation for breast cancer
- Should be performed at a specialized hospital (e.g. at a certified breast center)
- Inform patient about treatment and any alternative options, about the possibility of participating in a clinical trial and about the availability of psychological support.
- Confirm and, if necessary, correct the treatment plan together with the patient.
- Give the patient the opportunity to obtain a second opinion.
- Surgical treatment according to national guidelines.
- Concluding talk with patient when histology, prognostic factors and all other patient-relevant information are available
- Plan further treatment (systemic therapy and radiotherapy.
- Measurement of satisfaction
- Coordination of further treatment by the gynecologist

Systemic treatment of breast cancer
- Primary or adjuvant systemic chemotherapy, hormone therapy and/or immunotherapy are performed as an outpatient procedure either in a hospital or in a gynecologist’s or oncologist’s office.
- Inform patient about the procedure, side effects and benefit-to-risk analysis, participation in clinical trials.
- Planning and performance of treatment according to the Guidelines
- Careful monitoring of toxicity in collaboration with an oncological specialist
- Concluding examination and information about procedure for follow-up care
Radiation therapy for breast cancer

- Radiation therapy is usually performed as an outpatient procedure in a radiotherapy department.
- Inform patient about the procedure, side effects and benefit-to-risk analysis, participation in clinical trials.
- Planning and performance of treatment according to the *Guidelines*
- Careful monitoring of toxicities
- Concluding examination and information about follow-up care

Follow-up care

- Follow-up care is organized and performed on an outpatient basis by the primary care practitioner in cooperation with an oncological specialist.
- General counseling (genetics, hormone replacement therapy, counseling centers, self-help groups, psychological support)
- Creation of interfaces to family practitioner and to rehabilitation specialists, psychooncologists, physiotherapists, oncological nursing facilities, nutritionists or self-help groups as needed
- The aim of the follow-up care is the patient’s full rehabilitation.
- Teach the patient the technique of breast self-examination.
- Inform the patient on a regular basis as to which procedures are necessary and which are not
- Measurement of patient satisfaction
- In the case of long-term treatments: monitor treatment compliance and toxicities/late toxicities.
- Initiation of further diagnostic and therapeutic measures if new symptoms occur
- Pass on information about the patient’s health status to the hospital providing the primary treatment and/or clinical and epidemiological cancer registries.

Local recurrence of breast cancer

- Procedure equivalent to that for primary disease
Distant metastasis of breast cancer

- The procedure is coordinated on an outpatient basis by the primary care practitioner or the oncological specialist.
- Individual treatment steps or stages of the disease may require the patient’s hospitalization.
- The patient should be given ongoing information about the prognosis, basic treatment objectives and treatment options.
- Treatment decisions made by the oncologically experienced gynecologist or an oncologist experienced in the treatment of breast cancer, in interdisciplinary conferences if appropriate.
- Pharmacotherapy performed as an outpatient procedure in a hospital or in the gynecologist’s or oncologist’s office
- Radiation therapy performed in hospital radiotherapy departments and palliative surgical procedures in a hospital with appropriate specialization
- Ensure provision of adequate supportive measures by the appropriate disciplines.
- In the terminal phase, consider referral to a palliative specialist.

At all stages psychooncological counseling and treatment (if appropriate) should be offered.

8.3 Variable set for breast cancer documentation

In the middle of 2007 the conference “Concerted Action for the Harmonization of the Variable Set for Breast Cancer Documentation” was held in Frankfurt/Main, Germany (Beckmann, commissioned by the German Cancer Society). The aim of the conference was to make the depiction of the quality of care of breast cancer simpler, more reliable and easier to compare by simplifying the contents of the documentation. In the wake of this conference a List of Variables was drawn up and presented; this list is intended for use in a documentation sheet or in a documentation program. At present this List of Variables is being compared with the basic data set of the Working Group of German Cancer Centers (ADT), the data set of the Federal Office for Quality Assurance (BQS), and the data standards of the Working Group on Epidemiological Cancer Registries. Once the final and consensus-approved version drawn by the Collaboration on Quality Assurance by Means of Clinical Cancer Registries (KoQK) is available, it will be published within the framework of the Internet versions of these Guidelines (awmf.org, dggg.de, krebsgesellschaft.de, senologie.org)
# Appendix 9: Members of the Guidelines Group

## Guidelines Steering Group

Guidelines coordination:  
*Prof. Dr. Rolf Kreienberg*, Ulm  
*Dipl. math. oec. Thomas Zemmler*, Ulm

Project management:  
*Dipl.-Ing. Anita Prescher*, ISTO/DKG, Frankfurt

Methodological support:  
*PD. Dr. Ina Kopp*, AWMF, Marburg  
*PD Dr. Ute-Susann Albert*, Marburg  
*Prof. Dr. Klaus-Dieter Schulz*, Marburg †

Expert panel:  
*Prof. Dr. Matthias W. Beckmann*, Erlangen  
*Prof. Dr. Max Geraedts*, Düsseldorf  
*Prof. Dr. Christian Jackisch*, Offenbach  
*Prof. Dr. Thorsten Kühn*, Esslingen  
*PD Dr. Annette Lebeau*, Hamburg  
*Prof. Dr. Uwe Wagner*, Marburg

## Working Party or Professional Society

<table>
<thead>
<tr>
<th>Working Party or Professional Society</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Working Group on Psychooncology (PSO)</td>
<td><em>Prof. Dr. Joachim Weis</em></td>
</tr>
<tr>
<td>Working Group on Rehabilitation, Follow-up Care and Social Medicine (ARNS)</td>
<td><em>Prof. Dr. Hans Helge Bartsch</em></td>
</tr>
</tbody>
</table>
| Working Group on Gynecological Oncology (AGO) | *Prof. Dr. Hans-Joachim Lück*  
*Prof. Dr. Gunter von Minckwitz*  
*Prof. Dr. Christoph Thomssen*  
*Prof. Dr. Michael Untch* |
| Working Group on Medical Oncology (AIO) | *Dr. Norbert Marschner*  
*Prof. Dr. Kurt Possinger* |
| Working Group on Radiological Oncology (ARO) | *Prof. Dr. Wilfried Budach*  
*Prof. Dr. Jürgen Dunst*  
*Prof. Dr. Rainer Souchon* |
| Working Group on Supportive Measures in Oncology (ASO) | *Prof. Dr. Andreas du Bois*  
*Prof. Dr. Hartmut Link* |
<p>| Professional Association of Gynecologists | <em>Dr. Klaus König</em> |</p>
<table>
<thead>
<tr>
<th>Working Party or Professional Society</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>German Professional Association of Pathologists</td>
<td>Prof. Dr. Werner Schlake</td>
</tr>
<tr>
<td>Federal Office for Quality Assurance (BQS)</td>
<td>Dr. Anne Reiter</td>
</tr>
<tr>
<td>German Federal Self-Help Organization for Women after Cancer</td>
<td>Hilde Schulte</td>
</tr>
<tr>
<td>Working Group on Surgical Oncology (CAO)</td>
<td>PD. Dr. Steffen Leinung</td>
</tr>
<tr>
<td>German Society of Plastic, Reconstructive and Esthetic Surgeons</td>
<td>Dr. Gernot Maiwald</td>
</tr>
<tr>
<td></td>
<td>Dr. Mario Marx</td>
</tr>
<tr>
<td>German Society for General and Family Medicine (DEGAM)</td>
<td>Dr. Brigitte Ernst</td>
</tr>
<tr>
<td>German Society of Gynecology and Obstetrics (DGGG)</td>
<td>Prof. Dr. Dietrich Berg</td>
</tr>
<tr>
<td>German Association for Medical Informatics, Biometry and Epidemiology (GMDS)</td>
<td>PD Dr. W. Sauerbrei</td>
</tr>
<tr>
<td>German Society of Pathology</td>
<td>Prof. Dr. Hans Kreipe</td>
</tr>
<tr>
<td>German Society of Senology (DGS)</td>
<td>PD Dr. Ute-Susann Albert</td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. Ingrid Schreer</td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. K.-D. Schulz †</td>
</tr>
<tr>
<td>German Society for Ultrasound in Medicine (DEGUM)</td>
<td>Prof. Dr. H. Madjar</td>
</tr>
<tr>
<td>German Radiological Society</td>
<td>Prof. Dr. Ulrich Bick</td>
</tr>
<tr>
<td>Clinical Epidemiology, Munich Cancer Register (TRM)</td>
<td>PD Dr. Jutta Engel</td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. Dieter Hölzель</td>
</tr>
<tr>
<td>Conference on Oncological Nursing and Pediatric Nursing (KOK)</td>
<td>Andrea Maiwald</td>
</tr>
<tr>
<td>Coordinator of the Centers for Hereditary Breast and Ovarian Cancer</td>
<td>Prof. Dr. Rita Schmutzler</td>
</tr>
<tr>
<td>Women’s Health Coalition e.V. (WHC)</td>
<td>Irmgard Nass-Griegoleit</td>
</tr>
<tr>
<td>Central Association of Physiotherapists (ZVK)</td>
<td>Ulla Henschel</td>
</tr>
</tbody>
</table>

**Acknowledgements**

Special mention should be made of the preliminary work done by the Breast Commission of the Working Group on Gynecological Oncology (AGO), whose annually updated “Recommendations for the Diagnosis and Treatment of Breast Cancer” served as a working basis during the discussions for the preparation of the S3 Guidelines (www.ago-online.de).
## Working Groups for the Revision of the S3 Guidelines 2007

<table>
<thead>
<tr>
<th>Chapter/Subject Area</th>
<th>Chairperson and Members of the Working Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Section A  General</strong></td>
<td></td>
</tr>
<tr>
<td>A 1 Introduction</td>
<td>Kreienberg, Engel, Hölzel</td>
</tr>
<tr>
<td>A 2 Patient Information</td>
<td>Kreienberg, Albert, Ernst, König, Nass-Griegoleit, Schulte, Schulz</td>
</tr>
<tr>
<td>A 3 Early Detection, Mammographic Screening</td>
<td>Albert, Schulz, Guidelines Group for Early Breast Cancer Detection 2007</td>
</tr>
<tr>
<td>A 4 Women at Increased Risk of Developing Breast Cancer</td>
<td>Schmutzler, Kreipe, Schreer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Section B  Locoregional Primary Disease</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>B 1 General Diagnostic and Therapeutic Concepts</td>
<td>Kühn, Berg, duBois, Engel, Kreienberg, Kreipe, Lebeau, Madjar, Nass-Griegoleit, Schlake, Schreer, Schulz, Souchon</td>
</tr>
<tr>
<td>B 3 Preinvasive Lesions</td>
<td>Beckmann, Kühn, Lebeau, Marx, Schreer, Souchon, Possinger, Wagner</td>
</tr>
<tr>
<td>B 4 Surgical Treatment of Invasive Breast Cancer</td>
<td>Kreienberg, Berg, Jackisch, Kühn, Lebeau, G. Maiwald, Marx, Untch, Wagner</td>
</tr>
<tr>
<td>B 5 Pathomorphological Examination</td>
<td>Lebeau, Kühn, Kreipe, Possinger, Schlake, Thomssen</td>
</tr>
<tr>
<td>B 6 Adjuvant Radiotherapy for Breast Cancer</td>
<td>Souchon, Budach, Dunst, Engel, Hölzel, Kreienberg, Kühn, Sauerbrei, Thomssen, Untch</td>
</tr>
<tr>
<td>B 7 Systemic Adjuvant Treatment (Endocrine Treatment, Chemotherapy, Immune Therapy)</td>
<td>von Minckwitz, Jackisch, König, A. Maiwald, G. Maiwald, Marschner, Ortmann, Possinger, Thomssen, Untch, Wagner</td>
</tr>
<tr>
<td>B 8 Management of Locally and Locoregionally Advanced Breast Cancer</td>
<td>Wagner, Kreienberg</td>
</tr>
<tr>
<td>Chapter/Subject Area</td>
<td>Chairperson and Members of the Working Group</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td><strong>Section C Recurrent Breast Cancer</strong></td>
<td></td>
</tr>
<tr>
<td>C 1 Definition and Prognosis</td>
<td>Wagner, Budach, Engel, Jackisch,</td>
</tr>
<tr>
<td>C 2 Diagnostic Procedures</td>
<td>Link, Lück, A. Maiwald,</td>
</tr>
<tr>
<td>C 3 Treatment of Local or Locoregional Recurrence</td>
<td>G. Maiwald</td>
</tr>
<tr>
<td>C 4 Distant Metastases</td>
<td>Possinger, Lück, Dunst, Jackisch, Leining, Lück, Marschner, v. Minckwitz, Thomssen</td>
</tr>
<tr>
<td><strong>Section D Treatment, Support, Continuing Care</strong></td>
<td></td>
</tr>
<tr>
<td>D 1 General Concept</td>
<td>Kreienberg</td>
</tr>
<tr>
<td>D 2 Psychosocial Aspects and Psychooncology</td>
<td>Beckmann, Albert, Bartsch, Bick, Ernst, Henscher, Hölzel, König, Leining, Link, A. Maiwald, G. Maiwald, Nass-Griegoleit, Schulte, Souchon, Weiss</td>
</tr>
<tr>
<td>D 3 Supportive Therapy</td>
<td></td>
</tr>
<tr>
<td>D 4 Rehabilitation</td>
<td></td>
</tr>
<tr>
<td>D 5 Follow-up Care Including Diagnostic Workup of Metastases and Support during Therapy</td>
<td></td>
</tr>
<tr>
<td>D 6 Palliative Medicine</td>
<td></td>
</tr>
<tr>
<td><strong>Section E Quality Management and Coordination of Patient Care</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kreienberg, Albert, Berg, du Bois, Engel, Ernst, Geraedts, Hölzel, Kopp, Lebeau, Reiter, Sauerbrei, Souchon, Thomssen, Wagner</td>
</tr>
</tbody>
</table>
Appendix 10: List of Statements

A 2 Patient Information

Statement Info-1

The provision of qualified, competent and accurate information material (printed or Internet material) should meet the quality standards of the Leitlinie Fraueninformation [Guide-line Women’s Information] and should provide the patient with easily understood risk information (e.g. specification of absolute risk reduction instead of relative percentages) to help women arrive at a self-determined decision for or against a particular medical procedure.

GCP (Albert, U et al. 2003; Albert, US et al. 2008)

Statement Info-2

When conveying information to the patient doctors should follow the following basic principles of patient-centered communication:

– Display empathy and listen actively.
– Address difficult topics directly and with empathy.
– Whenever possible, avoid medical terminology. If medical terms cannot be avoided they should be explained.
– Employ strategies that improve understanding (e.g. repeating, summarizing the salient points, using graphics, etc.).
– Encourage the patient to ask questions.
– Allow and even encourage her to express her feelings.
– Offer further assistance (Cf. Psycho-oncology).

LOE 1b, Grade of Recommendation A (Bruera, E et al. 2002; Butow, P et al. 2007; Elkin, EB et al. 2007; Ford, S et al. 2006; Politi, MC et al. 2007)
The consultation to inform the patient about the treatment should cover at least the following points:

- Surgical therapy: possibilities for breast-conserving therapy (surgery followed by radiation therapy), possibilities for reconstruction or external prostheses following mastectomy
- Systemic therapy: principles of adjuvant or palliative therapy (endocrine therapy, chemotherapy, immunotherapy).
- Radiotherapy: underlying principles, duration and follow-up surveillance, possible acute and late sequelae
- Participation in clinical studies, principles behind the treatment, duration and mode of administration of the therapy; treatment targets, effects and side-effects known to date, special features (e.g. monitoring, additional measures, cooperation, data storage and processing)
- Miscellaneous: possibilities for prevention and treatment of therapy-related side-effects (e.g. emesis, osteoporosis, lymphedema, etc.), necessity for follow-up care, possibilities for rehabilitation and psycho-oncological support as well as services offered by self-help groups, aspects that are the responsibility of the patient and the need for cooperation (e.g. reporting symptoms and problems, treatment compliance)

Multidisciplinary counseling and genetic testing should be carried out at special centers and offered to every woman with one or more of the following constellations in her family:

- at least three women who developed breast cancer
- at least two women (including one below age 50) who developed breast cancer
- at least one woman who developed breast cancer and one who developed ovarian cancer
- at least two women who developed ovarian cancer
- at least one woman who developed breast and ovarian cancer
- at least one woman who developed breast cancer before age 36
- at least one woman who developed cancer in both breasts before age 51
- at least one man who developed breast cancer and one woman who developed breast or ovarian cancer.
**Statement Risk-2**

The treatment of BRCA-associated carcinoma of the breast is based on the therapeutic guidelines for sporadic carcinoma of the breast.

**GCP**

Mastectomy can be performed in the contralateral breast to reduce the patient’s risk of developing a second carcinoma in this breast as well; however, an advantage of this approach in terms of survival is not substantiated by empirical evidence.

**LOE 3a, Grade of Recommendation 0** (Hartmann, LC et al. 2001; Meijers-Heijboer, H et al. 2001; Rebbeck, TR et al. 2004)

Bilateral oophorectomy can be performed to reduce the risk of a second carcinoma of the breast and the ovaries. However, an advantage of this approach in terms of survival has also not been substantiated by empirical evidence.

**LOE 3a, Degree of Recommendation 0** (Metcalfe, K et al. 2004; Pierce, LJ et al. 2006)

**Statement Risk-3**

BRCA1-associated carcinomas of the breast frequently exhibit a characteristic histopathological and immunohistochemical phenotype:

– invasive carcinoma (NOS) with a growth pattern similar to that of medullary carcinoma
– G3 morphology
– negativity for estrogen receptors, progesterone receptors and HER2/neu (triple negative)

**LOE 2a** (Honrado, E et al. 2006; Lakhani, SR et al. 1998; Lakhani, SR et al. 2005)

In cases where these characteristics are present, the pathologist should draw attention to the possibility of an inherited susceptibility to breast cancer.

**GCP**
B 2 Pretherapeutic Diagnostic Measures to Assess the Spread of Cancer in Symptomatic Patients

Statement Stag-1: Basic diagnostic measures

The following examinations are considered essential elements of a basic diagnostic workup:

– clinical examination of the breast: inspection and palpation of both breasts and the efferent lymphatic system
– mammography
– diagnostic ultrasound

If the clinical breast examination produces abnormal findings, diagnostic imaging and histological examination should be performed to complete the diagnostic workup.

Grade of Recommendation A (Calman, K et al. 2002; NBCC 2001; NBCC 2006a; NBCC 2006b; NCCN 2007; SIGN 2005)

For the investigation of symptomatic findings in women under age 40, sonography is the imaging method of first choice.

LOE 3b, Grade of Recommendation A (Nothacker, M et al. 2007)

The effects of endogenous and exogenous hormones are to be taken into account during the performance and interpretation of diagnostic procedures.

LOE 2b, Grade of Recommendation B (Calman, K et al. 2002; NBCC 2006b; NHMRC 2004; Schulz, KD et al. 2003)

Statement Stag-2: Mammography

At present mammography is the only method generally recognized to be effective for the detection of precursor or early stages of breast cancer.

LOE 1a, Grade of Recommendation A (Calman, K et al. 2002; NBCC 2006a; NCCN 2006; NCCN 2007; SIGN 2005)

High mammographic density (ACR 3 and 4) is, next to the BRCA1/2 mutation, the highest-ranking individual risk factor; consequently, the limited sensitivity of mammography in this situation should be countered by performing sonography as a supplementary study.

LOE 3b, Grade of Recommendation B (Nothacker, M et al. 2007)
**Statement Stag-3: Sonography**

Sonography is a supplementary study performed to investigate indeterminate lesions.

**Grade of Recommendation A** (Calman, K et al. 2002; NBCC 2006a; NBCC 2006b; NCCN 2007; Schulz, KD et al. 2003; SIGN 2005)

Sonography should be used to investigate clinically non-palpable mammographic lesions with the classifications BI-RADS 0, III, IV and V.

**LOE 2b, Grade of Recommendation B** (Nothacker, M et al. 2007)

The aim of standardized breast sonography is the systematic and reproducible examination of both breasts and the axilla.

**LOE 2b, Grade of Recommendation B** (Madjar, H et al. 2006; NCCN 2007; Schulz, KD et al. 2003)

Structural and process quality, as well as quality of outcomes, should also be demonstrated as a prerequisite for the use of breast sonography.

**GCP (DEGUM 2006)**

**Statement Stag-4: MRI with Contrast Medium**

An MRI scan with contrast medium (CM-MRI) should be recommended preoperatively for the local staging (excision margins) of lobular breast carcinoma.

**LOE 3b, Grade of Recommendation B** (Schwartz, GF et al. 2006)

To realize the benefits associated with this recommendation, strict coupling of CM-MRI and the possibility of performing MRI-guided interventions should be assured.

For other indications (e.g. multicentricity, occult breast carcinoma, etc.), CM-MRI should be performed only if there are possibilities for MRI-guided interventions.

**GCP**
Statement Stag-5: Imaging-guided minimally invasive biopsy

The histological diagnostic investigation of unclear findings should be carried out via core biopsy, vacuum-assisted biopsy or open biopsy. Percutaneous interventions should be carried out in accordance with the quality recommendations.

**LOE 3a, Grade of Recommendation A** (NCCN 2007; NICE 2006a; Perry N, et al. 2006; Schulz, KD et al. 2003)

Fine-needle biopsy should not be employed as the standard biopsy method.

**LOE 2b, Grade of Recommendation A** (NCCN 2007; NICE 2006a; Schulz, KD et al. 2003)

Intervention-guided tissue biopsy for histopathological confirmation of the diagnosis and for therapeutic planning should be performed in patients with the following findings: mammographic classification BI-RADS IV and V and/or sonographic classification US-BI-RADS IV or V and/or MRI classification MRT-BI-RADS IV or V.

**LOE 3a, Grade of Recommendation A** (NCCN 2007; Schulz, KD et al. 2003)

During intervention-guided (preferably sonography-guided) core biopsy, ≥ 3 representative specimens should be taken at ≤ 16G.

**LOE 3b–2b, Grade of Recommendation B** (Crystal, P et al. 2004; Fishman, JE et al. 2003)

In the presence of microcalcifications, stereotactically guided vacuum-assisted biopsy should preferably be performed.

**LOE 3b–2b, Grade of Recommendation A** (Nothacker, M et al. 2007)

Vacuum-assisted biopsy should also be used for MRI-guided tissue sampling.

**GCP**

Following minimally invasive imaging-guided tissue sampling, the results should be verified by correlating the results of the imaging diagnostic studies with the histopathological findings.

**Grade of Recommendation A** (NBCC 2006a; NCCN 2007; NICE 2006b; Perry, N et al. 2006; Schulz, KD et al. 2003)

If the histopathological examination reveals a benign lesion, a follow-up imaging study should be performed with the appropriate imaging method in six months’ time.

**Grade of Recommendation B** (NCCN 2007; NICE 2006b)
Statement Stag-6: Open Excisional Biopsy

The operative quality assurance for the open diagnostic excision of screen-detected lesions should take place in conformance with the guidelines of the European Commission. The surgical objective (diagnostic or therapeutic) should be defined in a non-ambiguous manner.

**Grade of Recommendation A** (O’Higgins, N et al. 2006; Schulz, KD et al. 2003)

During the preoperative wire marking of non-palpable lesions, the wire should penetrate the focal lesion and project beyond the lesion by less than 1 cm. In cases where the wire does not penetrate the focal lesion, the distance between the wire and the margin of the lesion should be ≤ 1 cm. In non-space-occupying processes, marking of the surgically relevant target volume may be useful.

**LOE 3b, Grade of Recommendation A** (O’Higgins, N et al. 2006; Schulz, KD et al. 2003)

In the case of non-palpable changes, it is always important to perform preoperative marking and to demonstrate adequate resection via imaging methods.

**LOE 3b, Grade of Recommendation A** (NBCC 2001; O’Higgins, N et al. 2006; Schulz, KD et al. 2003)

The material collected during the operation should be clearly marked and sent to the pathologists without any incision of the tissue material obtained.

**Grade of Recommendation A** (Carlson, RW et al. 2006; Perry N, et al. 2006; Schulz, KD et al. 2003)

Intraoperative determination of malignancy by frozen section should be the exception. Frozen section of breast specimens can be performed in cases satisfying the following criteria:

– The lesion is palpable intraoperatively and in the specimen.
– The lesion is large enough (in general > 10 mm).

**Grade of Recommendation A** (O’Higgins, N et al. 2006; Schulz, KD et al. 2003)

---

Statement Stag-7

In patients with locally advanced carcinomas and in cases where metastasis is suspected, the following individual studies should be performed for staging prior to the institution of treatment:

– chest x-ray
– ultrasound examination of the liver
– bone scan

**LOE 5, Grade of Recommendation B** (Alderson, PO et al. 1983; Crump, M et al. 1996)
## B 3 Preinvasive Lesions

**Statement DCIS-1**

In cases where a potential precursor lesion or preinvasive lesion is suspected on the basis of the radiological studies or has been demonstrated by core biopsy or vacuum-assisted biopsy, the therapeutic strategy should be elaborated by an interdisciplinary team consisting of a specialist in diagnostic radiology, a surgeon and if necessary a pathologist.

**GCP**

**Statement DCIS-2**

An individualized treatment strategy should be elaborated for and offered to every patient with ductal carcinoma in situ (DCIS). The patient must be briefed on the arguments for and against the particular therapies and combinations of these therapies (including possible adverse reactions), possible subsequent therapies, the effect of each therapeutic option on the frequency of recurrence, and the absence of an effect on the probability of survival (Houghton, J et al. 2003).

**GCP**

**Statement DCIS-3**

Axillary staging (sentinel node biopsy or axillary dissection) is generally not indicated for patients with DCIS.

**GCP**

**Statement DCIS-4**

Postoperative radiotherapy after breast-conserving surgery for DCIS lowers the rate of invasive and non-invasive local recurrences.

**LOE 1a** (Bijker, N et al. 2006; Clarke, M et al. 2005; Cutuli, B et al. 2002)

There is evidence that the effect of radiotherapy depends on individual factors such as patient age, extent of tumor, grading, surgical procedure and resection status.

**GCP**
B 4 Surgical Treatment of Invasive Breast Cancer

Statement Gen-1

Excision of the tumor with a negative resection margin (R0) is the basis of therapy for all non-advanced breast carcinomas.

LOE 1b, Grade of Recommendation A (Blichert-Toft, M et al. 1998; Renton, SC et al. 1996)

Statement Gen-2

The microscopically measured safety distance between the tumor and the resection margin should be 1 mm or more for invasive carcinoma.

GCP (NHMRC 2001; NHSBSP et al. 2003; O’Higgins, N et al. 1998; O’Higgins, N et al. 2006)

Statement Gen-3

The microscopically measured safety distance between the tumor and the resection margin should be 5 mm or more for intraductal carcinoma (DCIS).

GCP

Statement Gen-4

The objective of surgical treatment is removal of the tumor. Breast-conserving therapy (BCT) with subsequent radiotherapy is equal, with respect to survival, to modified radical mastectomy (MRM) alone.

LOE 1a (EBCTCG 1995; Fisher, B et al. 2002a; Veronesi, U et al. 2002; Wald, NJ et al. 1995; Weaver, DL et al. 2000)

For this reason, all patients should be briefed on the options of breast-conserving therapy (BCT) or modified radical mastectomy (MRM) with the possibility of primary or secondary reconstruction. The patient’s preference is decisive.

GCP
Statement Gen-5

The following constitute indications for modified radical mastectomy:

– diffuse, extensive calcifications of the malignant type
– multicentricity
– incomplete removal of the tumor (including the intraductal component), even after repeat excision
– inflammatory carcinoma of the breast, possibly following pre-treatment
– likelihood of an unsatisfactory cosmetic result
– postoperative radiotherapy clinically contraindicated after breast-conserving treatment
– informed preference for mastectomy voiced by the patient

LOE 2b, Grade of Recommendation A (Fisher, B et al. 1994; Voogd, AC et al. 2001)

Statement Gen-6

Every patient who undergoes a breast amputation should be informed about the possibility of immediate or later breast reconstruction or of not having any reconstructive procedure performed at all; contact to a support group should also be offered.

GCP

Statement Gen-7

Determination of the histological node status (pN status) is part of the surgical treatment of invasive breast cancer. It should be performed by means of sentinel node biopsy (SNB)


Sentinel node biopsy is equal to axillary dissection with regard to local control.

LOE 1b (Palest, JA et al. 2006; Smidt, ML et al. 2005; Veronesi, U et al. 2005a; Zavagno, G et al. 2005)

The morbidity after SNB is significantly reduced compared with axillary dissection.

LOE 1a (Fleissig, A et al. 2006; Mansel, RE et al. 2006; Veronesi, U et al. 2003)

In patients in whom SNB is not possible or in whom the sentinel node is positive, axillary dissection with removal of at least 10 lymph nodes from levels I and II must be carried out.

GCP
Statement Gen-8

If the sentinel node is excised, the quality criteria set out by the medical associations must be satisfied.

GCP (Kuehn, T et al. 2005; Lyman, GH et al. 2005)

B 5 Pathomorphological Examination

Statement Patho-1: General principles for surgical specimens

Normally the material removed during the operation is to be furnished with unambiguous topographical markings and sent to the pathologist without any prior taking of specimens by the clinician, surgeon or other physician.

GCP (Amendoeira, I 2006b; Carlson, RW et al. 2006a)

Statement Patho-2: Histological classification of invasive carcinomas

All invasive carcinomas are classified histologically (according to WHO 2003).


Statement Patho-3: Grading of invasive carcinomas

All invasive carcinomas are to be graded according to the WHO system (Elston and Ellis modification of the Bloom and Richardson grading; Elston and Ellis 1991).

**Statement Patho-4: Hormone receptor (ER/PgR) and HER2 status of invasive carcinomas**

In patients with invasive breast carcinoma the primary diagnostic procedures should include determination of the estrogen and progesterone receptor status and the HER2 status.

**LOE 2a, Grade of Recommendation A** (Carlson, RW et al. 2006a; ICSI Institute for Clinical System Improvement 2005; NHMRC 2001) re hormone receptor status, (Carlson, RW et al. 2006a; ICSI Institute for Clinical System Improvement 2005; NCRI Breast Clinical Studies Group 2005; Wolff, AC et al. 2007) re HER2 status.

The estrogen and progesterone receptor status should be determined by immunohistochemistry assay, preferably in the core biopsy already. The percentages of tumor cell nuclei positive for estrogen and progesterone receptors, respectively, should be stated; this may be done by giving summation scores, in which case the procedure used should be specified (Allred (Quick) Score, Immunoreactive Score of Remmele and Stegner).

**GCP** (Goldhirsch, A et al. 2005)

HER2 positivity as precondition for trastuzumab therapy is defined as protein overexpression with a score of 3+ demonstrated by immunohistochemistry assay or gene amplification demonstrated preferably by fluorescence in situ hybridization (FISH) or chromogenic in situ hybridization (CISH).

**LOE 1b, Grade of Recommendation A** (Carlson, RW et al. 2006b; Carlson, RW et al. 2006a; Crump M 2005; NCRI Breast Clinical Studies Group. 2005; Wolff, AC et al. 2007)

The reliability of the detection method used for determination of the hormone receptor and HER2 status must be ensured. For this purpose internal test validation, the use of standardized protocols and internal controls and the regular successful participation in external quality assurance measures are necessary.

**GCP** (Carlson, RW et al. 2006b; Wolff, AC et al. 2007)
Statement Patho-5

Documentation of the tumor characteristics and the patient’s situation are necessary in order to be able to assess the course of the disease (prognosis) and the expected effect of systemic therapies (prediction).

The following prognostic factors are to be documented:

– pTNM status (tumor size, axillary lymph node involvement, distant metastasis)
  **LOE 1a, Grade of Recommendation A** (Bundred, NJ 2001; Carter, CL et al. 1989; Page, DL et al. 1992; Page, DL et al. 1998; Rosen, PP et al. 1991; Rosen, PP et al. 1993)

– Resection margin (R classification)
  **LOE 1b, Grade of Recommendation A** and safety distances
  GCP (Bundred, NJ 2001; Kurtz, JM et al. 1989; Park, CC et al. 2000)

– Histological type
  **LOE 2b, Grade of Recommendation A** (Fisher, ER et al. 1990)

– Grading
  **LOE 2a, Grade of Recommendation A** (Elston, CW et al. 1991)

– Lymphatic and vascular invasion (Lx, Vx)
  **LOE 1b, Grade of Recommendation B** (Colleoni, M et al. 2007; Gasparini, G et al. 1994; Goldhirsch, A et al. 2007; Kato, T et al. 2003)

– Age
  GCP

Documentation of the following predictive factors is mandatory:

– Estrogen/progesterone receptor status for hormone therapy
  **LOE 1a, Grade of Recommendation A** (Bundred, NJ 2001; EBCTCG 1992; EBCTCG 1998; Osborne, CK 1998)

– HER2/neu status for treatment with trastuzumab
  **LOE 1b, Grade of Recommendation A** (Bundred, NJ 2001; Cobleigh, MA et al. 1999; Piccart-Gebhart, MJ et al. 2005; Romond, EH et al. 2005; Slamon DJ et al. 2001; Wallgren, A et al. 2003) (Nabholtz)

– Menopausal status for use of GnRH analogs
  **LOE 1c, Grade of Recommendation A** (EBCTCG 2000)

In the case of node-negative breast carcinomas the invasion factors uPA and PAI-1 can provide additional prognostic information.

**LOE 1a** (Harris, L et al. 2007; Janicke F et al. 2001; Look, MP et al. 2002)

The use of gene expression analyses – PCR-based or by microarray – for evaluation of the prognosis or response to treatment (prediction) is not yet validated for routine use and can therefore not be recommended.

**LOE 5, Grade of Recommendation B** (Paik, S et al. 2004; Paik, S et al. 2006)
**Statement Patho-6: Frozen section examination**

The decision as to whether a lesion is benign or malignant should only be made intraoperatively on the basis of a frozen section in exceptional cases.

The following are prerequisites for intraoperative frozen section examination of breast specimens:
- The lesion must be palpable intraoperatively and in the specimen.
- The lesion must be sufficiently large (generally >10 mm).

*GCP* (Amendoeira, I 2006b; NHMRC 2001; O’Higgins, N et al. 1998)

**Statement Patho-7: Lymph node status**

Lymph node status is determined on the basis of the histological examination of all lymph nodes removed.

Documentation of the following is mandatory: number of lymph nodes removed and involved, capsule penetration, pN category (according to TNM classification, 6th Edition, UICC 2002).


---

**B 6  Adjuvant Radiotherapy for Breast Cancer**

**Statement RT-1: Radiotherapy after BCT (general)**

In patients with invasive carcinoma, irradiation of the affected breast is indicated after breast-conserving surgery.


Percutaneous high-volt radiotherapy brings about improvements in local tumor control and overall survival.

Statement RT-2: Administration of radiotherapy after BCT

The target volume of percutaneous adjuvant radiotherapy encompasses the entire residual breast and the adjoining thoracic wall.


The dose should amount to approx. 50 Gy fractionated in the conventional manner (5 x 1.8–2.0 Gy/week).

**LOE 1a, Grade of Recommendation A** (Clarke, M et al. 2005; EBCTCG 2000; EBMG 2006; NCCN 2007; NHMRC 2001; SIGN 2005; Whelan, T et al. 2002)

The application of a local boost dose to the tumor bed in addition to whole-breast irradiation reduces the rate of local recurrence in the breast in all age groups without conferring an advantage in terms of survival (Antonini, N et al. 2007; Bartelink, H et al. 2007; Romestaing, P et al. 1997). Boost irradiation is indicated as a rule. The recommended boost dose amounts to 10–16 Gy fractionated in the conventional manner (5 x 1.8–2.0 Gy/week).

**LOE 1b, Grade of Recommendation B** (Antonini, N et al. 2007; Bartelink, H et al. 2007)

In postmenopausal patients with a very low risk of local recurrence (in particular patients > 60 years of age and patients with small tumors), the advantage conferred by boost irradiation is small in absolute terms. In this subgroup the administration of boost irradiation can possibly be waived

**LOE 2a, Grade of Recommendation B** (NCCN 2006; NCCN 2007; NHMRC 2003; SIGN 2005)

Statement RT-3: Partial breast irradiation

The use of partial breast irradiation as the sole intraoperative or postoperative radiation treatment, without homogeneous irradiation of the entire breast, represents an experimental approach at present and should not be undertaken outside of studies.

**LOE 3, Grade of Recommendation A** (NCCN 2006; NCCN 2007)
Statement RT-4: Radiotherapy after mastectomy

Postoperative irradiation of the thoracic wall after mastectomy lowers the risk of a locoregional recurrence.

**LOE 1a** (Clarke, M et al. 2005; EBMG 2006; NCCN 2006; NCCN 2007; NHMRC 2001; Peto, R 2006; Shafiq, J et al. 2007; SIGN 2005; Whelan, T et al. 2007)

In patients with a high risk of a local recurrence, overall survival is also improved.

**LOE 1a** (Clarke, M et al. 2005; Gebski, V et al. 2006; Peto, R 2006; Whelan, T et al. 2007).

Postoperative irradiation of the thoracic wall after mastectomy is therefore indicated in the following situations:

– **T3/T4**
  
  **LOE 2a, Grade of Recommendation A** (NCCN 2007; SIGN 2005; Truong, PT et al. 2004)

– **R1/R2 resection**
  
  **LOE 2a, Grade of Recommendation A** (NCCN 2007; SIGN 2005; Truong, PT et al. 2004)

– **pN+ (> 3)**
  
  **LOE 1a, Grade of Recommendation A** (NCCN 2006; NCCN 2007; SIGN 2005; Truong, PT et al. 2004)

Patients with 1–3 positive lymph nodes can benefit from radiotherapy.

**LOE 1a, Grade of Recommendation 0** (NCCN 2007; Peto, R 2006; Truong, PT et al. 2005b)

After primary (neoadjuvant) systemic therapy the decision to institute radiotherapy should be made on the basis of the pretherapeutic T and N scores regardless of the degree of response to the primary systemic therapy.

**LOE 2a, Degree of Recommendation A** (Huang, EH et al. 2006; Kaufmann, M et al. 2003; NCCN 2007)
Statement RT–5: Irradiation of the regional lymphatic drainage system

So far the value of adjuvant irradiation of the regional lymphatic drainage system has not been substantiated by the results of prospective and randomized studies; as a result, the decision to irradiate the regional lymphatic drainage system must be made from case to case.

**LOE 3b** (EBMG 2006; NCCN 2007; NHMRC 2001; Recht, A et al. 2001; SIGN 2005; Truong, PT et al. 2004)

In patients with negative sentinel node biopsy results, irradiation of the axilla is not indicated.

**LOE 1b, Grade of Recommendation A** (Veronesi, U et al. 2005b; Veronesi, U et al. 2005a)

Irradiation of the axilla is recommended only in the following situations:

- residual tumor in the axilla
  
  **LOE 2b, Grade of Recommendation A** (NCCN 2007; SIGN 2005; Truong, PT et al. 2004; Truong, PT et al. 2005b)

- clear-cut clinical involvement or positive SN status in patients in whom no axillary dissection or only incomplete axillary dissection has been performed
  
  **LOE 3b, Grade of Recommendation A** (Louis-Sylvestre, C et al. 2004; NCCN 2007; SIGN 2005; Truong, PT et al. 2004)

No substantial body of data is available which could validate the advantage of irradiating the axilla in patients with histologically demonstrated tumor growth beyond the capsule. Irradiation of the axilla is thus not indicated in this group of patients.

Irradiation of the internal mammary nodes is generally not recommended (NCCN 2007).

Irradiation of the supraclavicular and infraclavicular lymphatic drainage channels is recommended in the following situations:

- patients with > 3 positive axillary lymph nodes
  
  **LOE 2a, Grade of Recommendation B**

- involvement of Level III of the axilla
  
  **LOE 3b, Grade of Recommendation B**

- cases where irradiation of the axilla is indicated
  
  **LOE 3b, Grade of Recommendation B**

In cases where a decision is made to irradiate lymphatic drainage areas, radiotherapy is administered with approx. 50 Gy fractionated in the conventional manner (5 x 1.8–2.0 Gy/week). For irradiation of the supraclavicular lymphatic drainage region, preference should be given to a single dose of 1.8 Gy.
Statement RT-6: Radiotherapy for patients with locally very advanced tumors or primary inoperability

| For patients with primarily inoperable carcinomas (Stage IIIB), primary systemic therapy is recommended followed by surgery and postoperative radiotherapy. |
| LOE 1b, Grade of Recommendation A (Kaufmann, M et al. 2003; NCCN 2007; Shenkier, T et al. 2004; SIGN 2005; Truong, PT et al. 2004) |
| If the systemic therapy fails to achieve operability, radiotherapy – possibly in combination with simultaneous systemic therapy – is indicated. |
| Grade of Recommendation B (Kaufmann, M et al. 2003; NCCN 2007; Shenkier, T et al. 2004; Truong, PT et al. 2004) |

Statement RT-7: Sequencing of chemotherapy and radiotherapy

| The superiority of a particular sequence of chemotherapy and radiotherapy has not been sufficiently established. As a basic rule the postoperative sequence depends on the type of recurrence most likely to occur, especially since the optimal time for starting adjuvant therapy is not substantiated by a sufficient body of data. |

Statement RT-8: Sequencing of antibody therapy and radiotherapy

| No sufficient body of data is available on the sequencing of trastuzumab and radiotherapy. The concurrent administration of trastuzumab and radiotherapy does not appear to increase the side effects of radiotherapy dramatically and can be justified as long as no irradiation of the internal mammary nodes is planned. |
| LOE 3a (Belkacemi Y et al. 2006; Belkacemi Y et al. 2007; Halyard MY et al. 2006; Romond, EH et al. 2005) |

Statement RT-9: Sequencing of tamoxifen and radiotherapy

| Anti-estrogen treatment modalities can be carried out concurrently with or sequential to radiotherapy. |
B7 Systemic Adjuvant Therapy (Endocrine Therapy, Chemotherapy, Immune Therapy)

Statement Adj-1

Pharmacotherapy for the primary disease is carried out before or after surgery in the form of chemotherapy, endocrine therapy, immune therapy or a combination of these forms of therapy.

LOE 1a (EBCTCG 2005; EBCTCG 2006; NCCN et al. 2006)

Statement Adj-2

The rate of recurrence and the mortality can be reduced by systemic therapy. This is true of polychemotherapy (in particular, the administration of anthracyclines and taxanes, pharmacological suppression of ovarian function, tamoxifen, aromatase inhibitors and trastuzumab). The magnitude of this effect in absolute terms depends on the level of risk.

LOE 1a (EBCTCG 1998a; EBCTCG 2005; EBCTCG 2006; NIH 2001)

Statement Adj-3

An optimal supportive therapy (e.g. anti-emetic medication, provision of wigs, etc.) is an integral part of all systemic therapies. All patients must be briefed on possible side-effects and late sequelae and offered prophylactic measures.

GCP

Statement Adj-4

Older patients should receive a systemic adjuvant therapy comparable to that given to younger patients. The altered organ function and comorbidities should be taken into account when establishing the indication for, and carrying out, adjuvant therapy measures.

GCP
Statement Adj-5

In patients with tumors positive for estrogen and/or progesterone receptors, endocrine treatment is indicated.

**LOE 1a, Grade of Recommendation A**

This treatment should not be initiated until after completion of the chemotherapy.

**LOE 2, Grade of Recommendation B** (EBCTCG 1998a; Fisher, B et al. 1997c; Thuerlimann B et al. 2001)

Statement Adj-6

Adjuvant anti-estrogen therapy with tamoxifen 20 mg per day is carried out over a period of 5 years or until recurrence.

**LOE 1a, Grade of Recommendation A** (EBCTCG 1998b)

If the duration of therapy is distinctly shorter than 5 years, it is worthwhile to reinitiate the therapy in order to complete the 5 years.

**LOE 2a, Grade of Recommendation B** (Gradishar, WJ et al. 2002; Peto, R 1996; Stewart, HJ et al. 1996; Swedish Breast Cancer Cooperative Group 1996)

Statement Adj-7

In premenopausal women, suppression of ovarian function via GnRH analogs, oophorectomy or ovarian ablation via radiotherapy can have a positive impact on the disease. This treatment is comparable in effect to CMF chemotherapy. Treatment with GnRH analogs should be carried out for at least 2 years.

**LOE 1b, Grade of Recommendation A** (Cuzick, J et al. 2007)

The efficacy of suppression of ovarian function after chemotherapy is uncertain.

Statement Adj-8

In women who are unmistakably postmenopausal, third-generation aromatase inhibitors are superior to tamoxifen. In women with a corresponding risk constellation, these can be administered as primary therapy for 5 years, for 2-3 years alternating after 2-3 years of tamoxifen therapy, or for 5 years after 5 years of tamoxifen therapy.

**LOE 1b, Grade of Recommendation A** (Boccardo, F et al. 2006; Coombes, RC et al. 2007; Goss, PE et al. 2005; Jakesz, R et al. 2005; Kaufmann, M et al. 2007; Thurlimann, B et al. 2005)
Statement Adj-9

Chemotherapy should be administered at the recommended dosages.

**LOE 1a, Grade of Recommendation A** (Budman, DR et al. 1998; Fisher, B et al. 1997a; French Adjuvant Study Group 2001; Fumoleau, P et al. 2003)

A reduction of either the dosage or the number of cycles may result in a loss of effectiveness.

**LOE 1a, Grade of Recommendation A** (Bonadonna, G et al. 1995; Budman, DR et al. 1998; Cady, B et al. 1993; Fisher, B et al. 1990; French Adjuvant Study Group 2001)

Increasing the doses of cyclophosphamide or doxorubicin does not improve effectiveness.

**LOE 1b, Grade of Recommendation A** (Fisher, B et al. 1999; Fumoleau, P et al. 2003; Henderson, IC et al. 2003)

Statement Adj-10

Cytotoxic agents can be administered concurrently or sequentially.

For patients with an elevated risk of recurrence, dose-dense treatments should be administered; however, these therapies should be carried out only at experienced centers.

**LOE 1b, Grade of Recommendation B** (Bonadonna, G et al. 1995; Citron, ML et al. 2003; Henderson, IC et al. 2003; NIH 2001; Wilking, N et al. 2000)

Statement Adj-11

An adjuvant combination chemotherapy (three-drug combination) should contain an anthracycline.

The decision to institute this therapy should not be influenced by nodal status or receptor status.

**LOE 1a, Grade of Recommendation A** (EBCTCG 2005; EBCTCG 2006; EBM Reviews 2003; NIH 2001)

Statement Adj-12

Patients with axillary lymph-node involvement should receive an adjuvant combination therapy with taxanes.

**LOE 1b, Grade of Recommendation B** (Bria, E et al. 2006; Citron, ML et al. 2003; Clavarezza, M et al. 2006; Estevez, LG et al. 2007; Henderson, IC et al. 2003; Mamounas, EP et al. 2005; Roche, H et al. 2006)
Statement Adj-13

Neoadjuvant (primary, preoperative) systemic therapy is now deemed the standard treatment for patients with locally advanced, primarily inoperable or inflammatory breast carcinoma. This treatment should be administered within the framework of a multimodal therapeutic strategy.

**LOE 1c, Grade of Recommendation A** (Brito, RA et al. 2001; Fisher, B et al. 1997b; Kaufmann, M et al. 2006)

Statement Adj-14

Neoadjuvant chemotherapy represents an alternative treatment option in cases where mastectomy is indicated but the patient wants to have a breast-conserving operation.

**LOE 1b, Grade of Recommendation 0** (Kaufmann, M et al. 2006)

This kind of therapy has the greatest effect on hormone-receptor-negative carcinoma.

**LOE 2b** (Bear, HD et al. 2006; von Minckwitz, G et al. 2005)

Resection according to the new tumor margins is a possibility if RO resection with a sufficient safety distance can thereby be achieved.

**LOE 3b, Grade of Recommendation 0** (Kaufmann, M et al. 2003)

Statement Adj-15

Primary hormonal therapy represents an option for postmenopausal patients with receptor-positive tumors in cases where an operation is contraindicated or is refused by the patient.

**Grade of Recommendation 0**

Statement Adj-16

Patients with HER2-positive (immunohistochemical score 3+ and/or FISH positive) tumors should receive trastuzumab treatment for one year. Trastuzumab can be administered concurrently with a taxane or sequential to anthracycline/taxane-containing chemotherapy.

**LOE 1b, Grade of Recommendation A** (Joensuu, H et al.; Piccart-Gebhart, MJ et al. 2005; Romond, EH et al. 2005; Slamon, DJ et al. 2006)


C 3 Treatment of Local or Locoregional Recurrence

Statement Rec-1

In patients with an in-breast recurrence (DCIS or invasive carcinoma), the best local tumor control is achieved by secondary mastectomy.

**LOE 3b** (Borner, M et al. 1994; Dalberg, K et al. 1998)

In patients with a favorable baseline, e.g. patients with DCIS or invasive carcinoma with a long recurrence-free interval, no skin involvement and a large spatial distance between the site of the first tumor and the recurrence, an organ-conserving surgical procedure can be performed in cases where this is deemed justified.

**LOE 4, Grade of Recommendation 0** (Deutsch, M 2002; Haffty, BG et al. 1996; Kurtz, JM et al. 1991; Whelan, T et al. 1994)

Patients who undergo organ-conserving surgery must be advised of the associated higher risk for a repeat in-breast recurrence.

GCP

Statement Rec-2

An isolated recurrence in the chest wall is to be removed completely by surgery (R0) if possible.

**LOE 2a, Grade of Recommendation A** (Schmoor, C et al. 2000)

Statement Rec-3

In patients with an isolated regional recurrence, the therapeutic objective should be to achieve local control of the disease via surgery and/or radiotherapy.

**Grade of Recommendation A**

Statement Rec-4

The benefits of postoperative systemic therapy following surgical resection of a locoregional recurrence in terms of improved overall survival have not been sufficiently substantiated.

There is evidence that the disease-free interval can be prolonged by systemic therapy.

**LOE 1b, Grade of Recommendation B** (Haffty, BG et al. 1996; Rauschecker, H et al. 2001)
Statement Rec-5

The need for radiotherapy after surgery for a recurrence should be discussed and decided upon within an interdisciplinary team. Postoperative radiotherapy is indicated if radiotherapy was not administered previously or radical surgical excision of the local recurrence was not performed (R1–2). In patients with an inoperable local recurrence, palliative radiotherapy may be beneficial.

LOE 4, Grade of Recommendation 0 (Aberizk, WJ et al. 1986)

C 4 Distant Metastases

Statement Met-1

A patient with demonstrated distant metastases of breast cancer should be given an especially detailed briefing on the therapeutic options and be involved in the decision-making process. The patient’s request for information on all pertinent available measures, including supportive and complementary treatment options, should be met.

GCP

Statement Met-2

The therapy should be selected and modified to reflect the expectations, value concepts and preferences of the individual patient as well as her symptoms, age and general condition. It should also take account of any co-morbidity, the aggressiveness of the disease, the location of the metastases, the type of prior adjuvant and palliative treatment, HER-2 status, hormone-receptor status and menopausal status.

GCP

Statement Met-3

The following prognostic and predictive factors can be defined for the employment of the various palliative therapies:

– hormone-receptor status for hormonal therapy
– HER-2 status for therapy with trastuzumab or lapatinib
– bone metastases for the administration of bisphosphonates
– the previous response to a chemo-endocrine therapy for further systemic and local therapies
– the performance status for the effect of chemotherapy.

LOE 2, Grade of Recommendation B (Andersson, M et al. 1999; Cheung, KL et al. 1997; Hortobagyi, GN et al. 1996)
Statement Met-4

Endocrine therapy is the therapy of choice for patients with a positive hormone-receptor status. In general hormonal therapy should be given preference over chemotherapy.

**LOE 2b, Grade of Recommendation B** (Fossati, R et al. 1998; Stockler M et al. 1997; Stockler, M et al. 2000)

Statement Met-5

Endocrine therapy is not indicated in the following cases:

– if there is a need to achieve rapid remission to prevent pronounced symptoms in the affected organ
– negative hormone-receptor status
– brain metastases (not an adequate/sufficient therapy).

**LOE 2b, Grade of Recommendation A** (Fossati, R et al. 1998; Stockler M et al. 1997; Stockler, M et al. 2000)

Statement Met-6

Combined chemo-endocrine therapy is not recommended. Although it can raise remission rates, it causes increased toxicity without prolonging either the progression-free interval or overall survival.

**LOE 1a, Grade of Recommendation B** (Sledge, GW, Jr. et al. 2000)

Statement Met-7

In postmenopausal patients with metastases, the first step in endocrine treatment – following adjuvant therapy with tamoxifen or no hormonal therapy – is the administration of an aromatase inhibitor.

**LOE 1a, Degree of Recommendation A** (Ellis MJ et al. 2000; Fossati, R et al. 1998; Hayes, DF et al. 1995; Mouridsen H et al. 2001; Mouridsen, H et al. 2001)

Statement Met-8

Depending on the prior anti-hormonal treatment, the further steps in the cascade of endocrine therapy used to treat postmenopausal women are the administration of anti-estrogens, estrogen receptor antagonists and high-dose progestins or the switch from a steroidal to a non-steroidal aromatase inhibitor (or vice versa).

**LOE 3b, Grade of Recommendation 0** (Fossati, R et al. 1998; Robertson, JF et al. 2003)
Statement Met-9

In premenopausal patients, suppression of ovarian function (e.g. with GnRH analogs, oophorectomy, ovarian ablation via radiotherapy) in combination with tamoxifen is the first-choice therapy.

LOE 1b, Grade of Recommendation A (Klijn, JG et al. 2001)

Statement Met-10

In premenopausal patients, ovarian suppression can subsequently be carried out in combination with the administration of an aromatase inhibitor. Treatment with high-dose progesterins (MA/MPA) represents a further step.

LOE 2c, Grade of Recommendation 0 (Taylor, CW et al. 1998; von Minckwitz G et al. 1991)

Statement Met-11

Prior to the administration of chemotherapy, the patient’s general condition and compliance must be assessed.

GCP

Statement Met-12

The toxicity of the therapy administered must be assessed both objectively and subjectively at regular intervals during the therapy. The doses administered, as well as the time intervals aimed at, must conform to generally accepted standard, or currently published, therapeutic regimens. After a suitable and representative measurement parameter (e.g. symptoms, tumor markers, indicator metastasis) has been selected prior to the institution of therapy, the therapeutic effect should be evaluated at least every 3 months. Cytotoxic maintenance therapy increases toxicity without improving survival. For this reason, cytotoxic therapy is recommended only in the event of increased symptomatology and/or cancer progression.

GCP

Statement Met-13

The therapy should be stopped immediately if progression or intolerable toxicity is observed.

GCP
Statement Met-14

The administration of combination chemotherapy, instead of single-agent chemotherapy, may confer a slight advantage in terms of survival. However, combination chemotherapy is often associated with higher toxicity rates.

**LOE 1a, Grade of Recommendation 0** (Fossati, R et al. 1998)

In patients with mild symptoms and slow tumor growth — as well as cases where endocrine therapy is ineffective — single-agent chemotherapy is useful.

However, in patients with severe symptoms and rapidly growing or aggressive tumors (i.e. in cases where there is a strong pressure to achieve remission), combination chemotherapy may be indicated.

**LOE 1a, Grade of Recommendation B** (Fossati, R et al. 1998)

Statement Met-15

The following substances, for example, may be used for single-agent chemotherapy: anthracyclines (including liposomal anthracyclines), anthraquinones, taxanes, vinorelbine and fluoropyrimidine. If polychemotherapy is administered, these cytotoxic agents can be combined with each other or with other substances. The highest remission rates are achieved by using a taxane in combination with an anthracycline or antimetabolite.

**LOE 1b, Grade of Recommendation B** (Fossati, R et al. 1998)

Statement Met-16

After the benefits of anthracycline and taxane chemotherapies have been fully exploited, patients should not be denied further chemotherapies, e.g. to stabilize the disease or to alleviate symptoms.

**LOE 2b, Grade of Recommendation B** (Feher, O et al. 2002; Vogel, C et al. 1999).

Statement Met-17

Dose-intensified and high-dose therapies do not result in any improvement in survival.

**LOE 1b** (Stadtmauer, EA et al. 2000)

Statement Met-18

HER-2 status should be determined in advance of any potential therapy with HER-2 inhibitors. This status can be determined in the primary tumor or in a new biopsy.

**LOE 1c, Grade of Recommendation A** (Schaller, G et al. 2001)
Statement Met-19

Treatment with HER-2 inhibitors is indicated in patients with HER-2-overexpressing tumors. It can be administered in combination with chemotherapy or as a single-agent therapy in patients previously treated with taxanes and anthracyclines.

**LOE 1b, Grade of Recommendation B** (Burstein, HJ et al. 2001; Seidman, AD et al. 2001; Slamon DJ et al. 2001)

Statement Met-20

Monitoring of cardiac function before and during therapy with potentially cardiotoxic substances is essential.

**GCP**

Statement Met-21

In patients with metastatic breast cancer receiving paclitaxel as the first-line cytotoxic therapy, bevacicumab can be administered to improve the therapeutic outcome.

**GCP**

Statement Met-22

In patients with symptomatic bone metastases or bone metastases posing a risk of fracture, radiotherapy is the local therapy of choice. The following constitute indications for radiotherapy:

- local pain symptomatology
- danger to stability (if necessary in combination with surgical stabilization)
- impairment of mobility and/or function, in particular neurological symptoms (emergency: spinal cord compression)
- pathological fractures which cannot be treated surgically
- as a postoperative therapeutic modality following the surgical treatment of bone metastases (insofar as only non-resecting methods have been used).

**LOE 1a, Grade of Recommendation B** (Hoskin PJ et al. 2001; Roos, DE et al. 2000; Steenland, E et al. 1999)
Statement Met-23

Surgical therapy of skeletal metastases is carried out for pain management and to restore or preserve function and stability in order to improve the patient’s quality of life. The decision to operate is made as a function of the urgency and of the therapeutic objective of this surgery: If necessary the decision may be made by an interdisciplinary team including the surgeon (general surgeon, orthopedic surgeon or neurosurgeon), the radio-oncologist, the medical specialist with oncological expertise, and the pain therapist.

LOE 1c, Grade of Recommendation B (Ali, SM et al. 2003; Wunder, JS et al. 2003)

Statement Met-24

The following constitute indications for operative therapy:

– pathological fractures (especially in the lower extremities and the acetabulum)
– unstable pathological vertebral fractures
– progressive spinal or radicular compression (the option of radiotherapy should be considered)
– impending fractures of the lower extremities.


Statement Met-25

The following constitute indications for bisphosphonate therapy: hypercalcemia, bone pain caused by metastases, osteolytic metastases, and manifest osteoporosis induced by cancer therapy.

LOE 1b, Grade of Recommendation A (Conte, PF et al. 1996; Hortobagyi, GN et al. 1998; O’Rourke, N et al. 1995; Rosen, LS et al. 2001; Theriault, RL et al. 1999)

Statement Met-26

An isolated brain metastasis can be treated by surgery, by single-session stereotactic irradiation or by fractionated radiotherapy (SFRT) especially if the extracerebral disease is under control.

LOE 2a, Grade of Recommendation 0 (Alderson, PO et al. 1983; Antoniades J et al. 1993; Kundziolka D et al. 1999)
Statement Met-27

In patients with multiple brain metastases, percutaneous irradiation of the entire cranium (whole brain radiotherapy), supported by steroid medication in patients with perifocal edema, is indicated for the control of existing neurological symptoms. Substantial (including transient complete) improvement of symptoms is achieved in 50–70% of patients with headache, 30–40% with paresis, and 40–50% with cerebral dysfunction.

**LOE 2a, Grade of Recommendation A** (Kundziolka D et al. 1999)

Statement Met-28

In individual cases satisfying the criteria listed below, local therapy may be indicated for patients with visceral metastases (i.e. metastases located in the liver, lungs or other organs):
- no disseminated metastases
- no local recurrence or second primary
- metastases in only one lobe of the lungs or liver (if both lobes are affected, surgery is not indicated)
- the metastases did not occur during the first year after primary treatment.

**LOE 3b, Grade of Recommendation 0** (Bathe, OF et al. 1999; Vogl, TJ et al. 1999)

Statement Met-29

In cases where pleural carcinosis occurs together with symptomatic effusion, pleurodesis may be indicated.

**LOE 2b, Grade of Recommendation 0** (Cardillo, G et al. 2002)

**D 2 Psychosocial Aspects and Psychooncology**

Statement Psych-1

Psychooncological treatment measures should be integrated into the overall plan for the cancer therapy.

**LOE 1b, Grade of Recommendation B** (Edwards, AG et al. 2004; Sheard, T et al. 1999)

All patients should receive information from doctors at an early stage concerning all the types of psychooncological assistance that are available.

**GCP** (Luker, KA et al. 1996; Street, RL, Jr. et al. 1995)
Statement Psych-2

Psychooncological interventions should be tailored to the patient’s individual needs and made available at the earliest possible opportunity as required. In addition to clinical judgment, validated measuring instruments – e.g. psychooncological basic documentation (PO BaDo), the German version of the Hospital Anxiety and Depression Scale (HADS), the Hornheide Questionnaire and the Distress Thermometer – may be used to assess the need for psychooncological intervention.

LOE 1b, Grade of Recommendation B (Edwards, AG et al. 2004; Weis, J et al. 2006)

Statement Psych-3

To guarantee the continuity of the psychooncological support provided after inpatient treatment, the patient should be informed about continuing aftercare options in the outpatient and community settings (cancer counseling centers, registered psychotherapists, self-help groups, social counseling services, etc.).

GCP

Statement Psych-4

The patient’s quality of life should be assessed regularly throughout the course of the disease. Standardized questionnaires for assessing quality of life may be used.

LOE 2, Grade of Recommendation B (Velikova, G et al. 1999; Velikova, G et al. 2004)

D 4 Rehabilitation

Statement Reha-1

The use of surgery, radiotherapy and systemic therapy to treat a patient with breast cancer can result in therapeutic sequelae of varying severity that require targeted somatic and psychosocial rehabilitation. The patients should be informed at an early date about the options for outpatient and inpatient rehabilitation and about additional claims arising under German social law. The patient’s preferences should be taken into consideration when establishing the necessity for, and recommending, a particular type of rehabilitation.

GCP
D 5 Follow-up Care Including Diagnostic Workup of Recurrences and Metastases and Support During Therapy

Statement FU-1

Follow-up care for breast cancer begins after the completion of local primary treatment. It consists of history-taking, a physical examination, and guidance, support and continuing care provided by physicians.

**LOE 1c, Grade of Recommendation A**

Follow-up care should be symptom-oriented, if required.


Statement FU-2

As part of her follow-up care the breast cancer patient requires intensive interdisciplinary support and continuing care. Doctors specializing in oncology and also other healthcare professionals (e.g. psychooncologists, physiotherapists, oncological nursing staff, etc.) should be involved as needed. The patient should be given information appropriate to her individual needs about the options for further treatment and support.

**LOE 2a, Grade of Recommendation B** (Selby, P et al. 1996)

Statement FU-3

In asymptomatic women who have undergone breast-conserving therapy, imaging studies (e.g. mammography and ultrasound) of the ipsilateral breast are indispensable.

**GCP** (Grunfeld, E et al. 2002; Khatcheressian, JL et al. 2006; Loprinzi, CL 2004)

Statement FU-4

All patients should receive annual follow-up mammograms of the contralateral breast.

Statement FU-5

Laboratory tests and apparative diagnostic methods should be employed in cases where the history or clinical findings yield grounds for suspecting a recurrence and/or metastases.


A routine search for remote metastases is not indicated in asymptomatic women, owing to the uncertainty of the methods used and of the intervals between examinations. Patients with persistent symptoms should undergo a targeted diagnostic workup.

**GCP**

Statement FU-6

All patients who have undergone axillary lymph node dissection must be informed of the options for detection, prophylaxis and treatment of lymphedema.


Statement FU-7

For breast cancer patients sentinel lymph node biopsy without more extensive axillary lymph node dissection constitutes primary prophylaxis of lymphedema in the arm. These patients should be informed after surgery about normal use of the arm and should contact the medical specialist treating them if functional disturbances or signs of lymphedema occur.

**LOE 1b, Grade of Recommendation A** (Francis, WP et al. 2006; Golshan, M et al. 2003; Sanjuan, A et al. 2005; Torrenga, H et al. 2004)

Statement FU-8

Follow-up visits should be scheduled four times a year during the first three years after the local primary therapy and twice a year during the fourth and fifth year; starting in the sixth year, the visits should be scheduled annually and include the normal gynecological checkups for early cancer detection.

**LOE 2a, Grade of Recommendation A** (Khatcheressian, JL et al. 2006)
Methodology Report

Update of the S3 Guidelines for the Diagnosis, Treatment and Follow-up Care of Breast Cancer 2007

Version 1.1 of 21 Dec. 2007
Authors:

PD Dr. Ina B. Kopp
PD Dr. U.-S. Albert
Prof. Dr. Rolf Kreienberg

Address for correspondence:

Prof. Dr. Rolf Kreienberg,
Ärztlicher Direktor der Universitätsfrauenklinik
Prittwitzstrasse 43
D-89075 Ulm

Fon: +49 731 500-58500
Fax: +49 731 500-58502
E-mail: rolf.kreienberg@uniklinik-ulm.de

This work is subject to German copyright law. It may not be used without the written consent of the authors. No part of this work may be reproduced in any form without written permission from the authors. This applies in particular to copies, translations, microfiches and storage, and other uses including those on electronic systems, intranets and the Internet.
Contents

List of Abbreviations ........................................................................................................................ 260

1 Background and Starting Point for Updating the S3 Guidelines .............................................. 261
2 Rationale, Objectives and Improvement Potential of the S3 Guidelines 2007 ............................. 265
3 Target Readership and Scope of Application ........................................................................... 267
4 Members of the Guidelines Group ............................................................................................... 269
4.1 Publisher, Coordinator, Guidelines Steering Group and their tasks ........................................ 269
4.2 Selection criteria for the panel of experts, working groups and their tasks ..................... 270
4.3 Professional societies/organizations involved, authors and voting rights ............................ 270
5 Updating Method ......................................................................................................................... 271
5.1 Methodological accuracy: evidence base ............................................................................... 273
5.1.1 Systematic literature review and selection ........................................................................ 273
5.1.2 Systematic search for guidelines ......................................................................................... 273
5.2 First consensus process: methodological approach, prioritizing ......................................... 275
5.3 S3 Guidelines 2007: new developments, organization and questions addressed .............. 276
5.4 Formulation and rating of core statements and recommendations .................................... 278
5.5 Second consensus process: voting and grading of recommendations .................................. 279
5.6 Quality assurance measures for Guidelines updating ............................................................... 280
6 Quality Indicators: Updating, Prioritizing and Consensus Process ........................................ 282
7 External Appraisal, Distribution and Implementation ................................................................. 283
8 Assessment .................................................................................................................................. 284
9 Duration of Validity and Updating .............................................................................................. 285
10 Financing/Editorial Independence ............................................................................................... 286

Literature .......................................................................................................................................... 287

Appendices
I Strategy for Updating the S3 Guidelines for the Diagnosis, Treatment and Follow-up Care of Breast Cancer .................................................................................................................................... 288
II Members of the Guidelines Group ............................................................................................... 289
III Project Outline of Work Sequences in the Updating Process, Methodological Steps, and Assignment of Responsibilities ........................................................................................................... 291
IV Algorithm for Literature Review, Selection and Rating of Sources ..................................... 293
V Methodological Quality of the Empirical Evidence: Classification of Level of Evidence ............................................................................................................................. 294
VI From Evidence to Recommendation: Classification of Grade of Recommendation ............. 295
VII Form for Declaring Possible Conflicts of Interests ................................................................. 296
VIII Link to Electronic Appendix: Statement-specific Literature Search .................................. 297
IX Link to Electronic Appendix: Methodology Report for the S3 Guidelines 2004 .................. 298
List of Abbreviations

ADT Arbeitsgemeinschaft Deutscher Tumorzentren e.V. [Working Group of German Cancer Centers]

AWMF Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. [Association of the Scientific Medical Societies in Germany]

ÄZQ Agency for Quality in Medicine

BÄK Bundesärztekammer [German Medical Association]

BQS Bundesgeschäftsstelle Qualitätssicherung gGmbH [Federal Office for Quality Assurance]

DGS Deutsche Gesellschaft für Senologie e.V. [German Society of Senology]

DELBI German Instrument for Methodological Guideline Appraisal

DKG Deutsche Krebsgesellschaft e.V. [German Cancer Society]

DKH Deutsche Krebshilfe e. V. [German Cancer Aid]

GEKID Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. [Association of Population-Based Cancer Registries in Germany]

GIN Guidelines International Network

KoQK Collaboration on Quality Assurance by means of Clinical Cancer Registries

NGP Nominal Group Process

NVL National Health Care Guideline
1 Background and Starting Point for Updating the S3 Guidelines

Breast cancer is the most frequent malignant neoplasm occurring in women. It is estimated that around 60,000 women develop this type of cancer in the Federal Republic of Germany every year. This means that breast cancer accounts for 27% of all new cancers in women. According to the German Federal Statistical Office, 17,455 women died of breast cancer in the year 2005 [1, 2]. At present health policy discussions and scientific discussions on breast cancer focus on reducing breast cancer mortality, and improvements and quality assurance of health-care delivery along the entire chain stretching from early detection and diagnosis to treatment and follow-up care, while at the same time enhancing the quality of patients’ lives. For example the project “gesundheitsziele.de” has elaborated the objectives of “reducing mortality and improving quality of life” in women with breast cancer [3].

One of the major aspects on which the overall concept for improved patient care is based is the development and implementation of national, high-quality, evidence-based and consensus-based guidelines (S3). Other aspects are approval of disease management programs (DMPs), accreditation of breast centers, recording of epidemiological and clinical data on breast cancer in cancer registries, and external, comparative quality assurance using guideline-based quality indicators.

The first version of the S3 Guidelines for the Diagnosis, Treatment and Follow-up Care of Breast Cancer in Women was published in June 2004. The Guidelines were developed in accordance with the following stipulations of the Guidelines Manual of the AWMF and the ÄZQ [4]:

– systematic consideration of high-quality international guidelines for breast cancer (search, selection according to methodological quality, synopsis of the recommendations and of the literature cited, cf. Appendix IX)

– systematic search, selection and evaluation of the literature for priority issues

– classification of studies and recommendations according to the criteria of evidence-based medicine

– structured, interdisciplinary consensus-building involving representatives of all stakeholders contacted

– outcomes analysis: presentation of results expected and early and late sequelae of various treatment options

– clinical algorithms: simple flow charts of the major treatment steps

– identification of resources and interfaces for patient care

– quality assurance: presentation of the (minimum) scope of documentation

– formulation of quality objectives and indicators with targets and reference ranges for process and outcome quality
The S3 Guidelines pursued the following objectives:

– provide support for doctors and patients when taking medical decisions by presenting evidence-based recommendations approved in a formal consensus process
– create a basis for measures for targeted initial, further and continuing training for doctors
– the nationwide implementation of an interdisciplinary, quality-controlled and cross-sectoral approach to the management of breast cancer
– optimize the diagnostic chain and the stage-appropriate treatment of the first occurrence of the disease as well as any recurrences and/or metastases

Implementing these objectives in the medium and long term should reduce the mortality of breast cancer patients and enhance their quality of life. They are intended to complement and link in with the current principles of early detection (S3 Guidelines for Early Detection of Breast Cancer in Germany [5]) and the additional above-mentioned projects and measures for an overall plan to improve quality.

The S3 Guidelines were published both electronically and in print. They were made publicly accessible via the Internet portals of the AWMF (www.awmf-leitlinien.de, AWMF register no. 032/045), the German Cancer Society (www.krebsgesellschaft.de, under evidence-based guidelines) and the German Society of Senology (www.senologie.org), in the following versions:

– full version:
  complete text, recommendations and algorithms with extensive background information and brief methodology report giving a rationale for individual recommendations and a comprehensive literature list
– abridged version in the appendix to the full version:
  summary of the patient care recommendations, including the level of evidence and grade of recommendation
– Methodology Report:
  comprehensive description of the methodology of the development process.

The full version of the S3 Guidelines was also published as a book [6] and its English translation was made publicly accessible via the Internet portal of the “Guidelines International Network” (www.g-i-n.net).

The S3 Guidelines for the Diagnosis, Treatment and Follow-up Care of Breast Cancer in Women were planned to be valid for three years. The update procedure was therefore started in early 2006. Its methodological approach was analogous to the first plan for updating the S3 Guidelines, set out in the Methodology Report in the S3 Guidelines for the Early Detection of Breast Cancer in Germany 2007 (www.awmf-leitlinien.de). It is reproduced as an overview in Appendix I. It is based on the requirements of the German Instrument for Methodological Guideline Appraisal (DELBI [8]).

Guidelines aim to set out explicitly the current knowledge on certain problems in the provision of medical care. They evaluate scientific evidence and practical experience from both the methodological and the clinical point of view, clarify opposing standpoints and define the current approach of choice, weighing up both benefit and harm. For this reason it is necessary to continually re-examine the validity of the knowledge contained in the Guidelines and to update
it [8]. It is only the application of a set of guidelines in hospitals or medical practices which determines its benefit for patients, for the doctors involved and for the health care system as a whole [9]. Guideline updates should therefore also take into account their impacts on patient care, i.e. the extent to which they are disseminated and implemented and the results of doing so. This can reveal room for improvement in terms of their design, content and implementation strategy. Updating and revising the S3 Guidelines is thus part of a guideline quality management cycle.

The update (cf. Appendix I) was therefore designed to include the following:

1. an analysis of the current demand for and implementation of the S3 Guidelines
2. a systematic literature search for the period between initial publication and update (cf. Chapter 5.1)
3. assessment of the need for an update by a process of consensus in the Guidelines Group (cf. Chapter 5.2)

The statistics on pages accessed in the AWMF register (www.awmf-leitlinien.de) indicate that since the S3 Guidelines were published, the full version has continuously been among the five most popular guidelines. They were downloaded by individual users over 30,000 times in the year 2005, over 40,000 times in the year 2006 and over 50,000 times in the first half of 2007.

Since 2003 breast centers have been reviewed and accredited according to the accreditation system of the German Cancer Society (DKG) and the German Society of Senology (DGS). The interdisciplinary cooperation enshrined in quality agreements and the recording of process and outcome indicators of the S3 Guidelines are an integral part of quality management and subject to annual internal and external review (auditing). This system fulfills one of the structural requirements for implementing quality-controlled patient care. In the summer of 2007 over 140 breast centers were accredited [http://www.onkozert.de; accessed on 25 Sept. 2007].

The quality targets and indicators of the S3 Guidelines on breast cancer are applied nationwide ([5]; a detailed overview is provided in the Methodology Report for the S3 Guidelines on the Early Detection of Breast Cancer 2007, www.awmf-leitlinien.de). The quality indicators represent an indirect measure of care quality, supporting the implementation and auditing of the guidelines in practice. In addition, they are interdisciplinary in nature and accordingly entail a certain amount of documentation work. The following criteria were applied by the Federal Office for Quality Assurance (BQS) during the external, comparative quality assurance. These criteria and the corresponding quality indicators were subject to continual appraisals in the years 2004 to 2006 which provide comparative data for the period from initial publication of the Guidelines to the update [http://www.bqs.de, accessed on 25 Sept. 2007]. The criteria are:

– postoperative specimen x-ray
– hormone receptor analysis
– safety distance
– axillary dissection in patients with DCIS or papillary carcinoma in situ
– indication for breast-conserving treatment (exhaustively evaluated up to 2005)
– reporting to cancer registry (exhaustively evaluated up to 2005)
– time interval between diagnosis and operation
The results for hormone receptor analysis have been consistently very good. The time between diagnosis and operation is increasing and should continue to be monitored. The remaining criteria showed improvements but the quality targets (reference ranges) have not yet been achieved. It has been compulsory since the year 2006 for hospitals to publish the results of the quality indicators for the postoperative specimen x-ray, hormone receptor analysis and information about the safety distance in their quality reports. These indicators are recommended on the basis of a methodological audit using the QUALIFY tool [7] [http://www.bqs.de, accessed on 25 Sept. 2007].

The following documentation requirements for DMPs (resolution of the Joint Federal Committee of 21 June 2005) apply, analogously to the guidelines: recording of the diagnosis of breast cancer, the diagnostic interventions (ultrasound, open biopsy and core biopsy), the surgical procedures (breast-conserving treatment, mastectomy, sentinel lymph node biopsy and axillary lymph node dissection), the pathological reporting (pTNM, grading, resection and receptor status, lymph nodes), and adjuvant therapy (radiation, chemotherapy and endocrine therapy) [http://www.g-b-a.de, accessed on 25 Sept. 2007].
The main rationale for updating the Guidelines is the continuously great epidemiological significance of breast cancer and the associated disease burden. It has been observed that there is a trend towards a slight increase in the incidence and a slight decrease in the mortality [1, 2]. In this context, the effects of implementing new patient management strategies (mammographic screening, DMPs, and accredited breast centers) are to be examined. The Guidelines also need to be updated as new scientific findings become available and in the light of results from the overview of guidelines application to date (cf. also Chapter 5.3: New developments, organization and questions addressed in the S3 Guidelines 2007). Finally, the continuing development of the Guidelines’ methodology necessitates a review of editorial aspects and content, and revision of the core statements and recommendations of the Guidelines [8].

The objectives of the S3 Guidelines for the Diagnosis, Treatment and Follow-up Care of Breast Cancer in Women were kept in the 2007 update and, where necessary, supplemented and adapted:

– taking into account current findings from evidence-based medicine and recognized treatment strategies when updating and implementing the Guidelines
– taking into account findings from disseminating the Guidelines and nationwide recording of the guideline-based quality indicators when updating and implementing the Guidelines
– support for involving the patients in treatment decisions, taking account of their individual needs
– nationwide implementation of interdisciplinary, quality-controlled and cross-sectoral management of breast cancer with the specific intention of
  – improving needs-oriented and quality-controlled psychosocial support and rehabilitation
  – supporting the documentation of epidemiology and clinical course of breast cancer by means of clinical cancer registries
  – systematic inclusion of the recommendations in initial and continuing training and in quality management systems
  – systematic inclusion of the recommendations and the quality indicators derived from them in disease management programs, accreditation procedures for breast centers, cancer registries, external comparative quality assurance and standardization of the documentation requirements.

Improving knowledge of the disease among non-affected persons and patients is an important objective where there is clearly room for improvement. This is required if women are to be empowered to take an active part in treatment decisions. At present information for lay persons is becoming increasingly available in print form and on the Internet, but in many cases the quality is very variable and in some cases unacceptable [10]. There is a veritable flood of information material available on breast cancer in particular whose quality is largely regarded
as deficient [10]. For this reason, as a backup to the two S3 Guidelines concerning management of breast cancer, updated, understandable, standardized, neutral and comprehensive information is being drawn up for potential patients, healthy women and those actually with breast cancer (taking account of the various stages of the disease) and also for their families. This information is based on the S3 Guidelines and is being collated under the auspices of the DKG and the DGS, in collaboration with patient organizations and self-help groups and supported by the AWMF jointly with the Agency for Quality in Medicine (ÄZQ).
3 Target Readership and Scope of Application

The recommendations of the Guidelines are intended for all doctors and professionals who are involved in the care of breast cancer patients (gynecologists, general practitioners, radiologists, pathologists, radiooncologists, hematooncologists, psychooncologists, physiotherapists, nursing staff, etc.), and all women with breast cancer and their families. The scope of application of the Guidelines covers the outpatient and inpatient treatment sectors.

Additional target groups are:

- medical and scientific societies and professional associations
- women’s interest groups (women’s health organizations, patients’ and self-help organizations)
- quality assurance facilities and projects at national and state level in Germany (BQS, KoQK, ADT, GEKID, “gesundheitsziele.de”)
- health policy facilities and decision-makers at German national and state level
- persons responsible for contracts for disease management programs (DMP) and integrated care programs
- third-party payers
- and the public, to provide information about good medical practices

The S3 Guidelines on the Early Detection of Breast Cancer in Germany give extensive treatment to the topic of early detection. These Guidelines were published for the first time in 2003 and an updated version is appearing in 2008 [5]. In addition, questions and definitions of structural quality, treatment interfaces and the minimum requirements for communication among all parties involved are dealt with in the DKG and DGS requirements for the accreditation of breast centers, and the current Disease Management Programs (DMPs). The diagnosis, treatment and follow-up care of breast cancer in men are not given any separate consideration in these Guidelines; their recommendations are basically also applicable to breast cancer in men. Any deviations in individual points must be decided by the experts in the individual case.

These Guidelines – as is the case with any medical guidelines – are explicitly not a set of regulations dictating what is to be done (or not), finalized by a legally legitimized institution, set forth in writing and published in order to be binding on an institution with non-compliance resulting in defined sanctions.

Guidelines only become effective when their recommendations are taken into account appropriately in the care of individual patients. They must be checked for applicability at regional or local level before they are applied in individual cases and they must be adapted if neces-
sary. The decision on whether to follow a particular recommendation must be taken by the doctor, taking into consideration the details of the individual case and the resources available [11].

Appendix II gives an overview of the members of the Guidelines Group.
4 Members of the Guidelines Group

4.1 Publisher, Coordinator, Guidelines Steering Group and their tasks

The *Guidelines* are published by the Information Center for Standards in Oncology (ISTO) of the German Cancer Society (DKG). The DKG is the professional society that bears primary responsibility. The co-editors are the professional societies and organizations involved in developing the *Guidelines*.

The Coordinator was commissioned by the leading professional society (DKG). The Coordinator determined the members and tasks of the Guidelines Steering Group as follows:

Guidelines coordination:  
Prof. Dr. Rolf Kreienberg, Ulm  
Dipl. math. oec. Thomas Zemmler, Ulm

Project management:  
Dipl.-Ing. Anita Prescher, ISTO/DKG, Frankfurt

Methodological support:  
PD. Dr. Ina Kopp, AWMF, Marburg  
PD Dr. Ute-Susann Albert, Marburg  
Prof. Dr. Klaus-Dieter Schulz, Marburg †

The tasks of the Steering Group included making initial contact to and coordination with the professional societies and organizations involved, implementing the methodological requirements for the *S3 Guidelines* using a project plan, managing the financial resources, supporting the experts’ work on Guidelines’ content, collating and editing the draft texts prepared by the experts in working groups, and compiling the Guidelines Methodology Report. Additional experts were brought in by the Steering Group to provide support on issues concerning the content of the *Guidelines*, supplement the specialist expertise in the Guidelines Group and provide support for working groups tackling specific topics:

Panel of experts:  
Prof. Dr. Matthias W. Beckmann, Erlangen  
Prof. Dr. Max Geraedts, Düsseldorf  
Prof. Dr. Christian Jackisch, Offenbach  
Prof. Dr. M. Koller, Regensburg  
Prof. Dr. Thorsten Kühn, Esslingen  
PD Dr. Annette Lebeau, Hamburg  
Prof. Dr. Uwe Wagner, Marburg
4.2 Selection criteria for the panel of experts, working groups and their tasks

The Guidelines Group was convened by the Coordinator in consultation with the Steering Group. All of the professional societies, working groups and organizations already involved in drawing up the first version of the *S3 Guidelines* were contacted. They were asked to appoint experts to represent them in the coordination processes (finding a consensus) and in working on the content of the *Guidelines* in topic groups. All the experts were selected and invited to participate on the basis of their specialist expertise. The board of each co-editing professional society, organization and working group in the Guidelines Group confirmed its representatives’ mandate in writing. The aim was to ensure an interdisciplinary and multiprofessional Guidelines Group appropriate to the *Guidelines*’ content and the scope of application. Representatives of the self-help organizations were actively integrated in the process of updating the *Guidelines* right from the beginning with the objective of better addressing the problems of the disease and its treatment from the patient’s perspective.

In the first consensus-building process, work on the content of the text was shared by 18 topic groups (cf. Table III, Chapter 5.3 for their composition). Each working group appointed a speaker. The speakers functioned primarily as contact persons for the Steering Group and bore the main responsibility for elaborating a group’s topic, compliance with the methodological requirements and project schedule, compiling and presenting the group’s results, core statements and recommendations at the consensus conferences and for elaborating the background text in consultation with the working group. The topic groups had the task of presenting the current medical knowledge of their own topic and the cross-disciplinary aspects relevant to the patient care strategy including proposals for interfaces. The Steering Group provided materials and instructions to all the working group members for ensuring compliance with the methodological requirements according to DELBI for literature review, formulating and grading of recommendations, including indication of the level of evidence and elaboration of the background texts (cf. Chapter 5.6).

4.3 Professional societies/organizations involved, authors and voting rights

The members of the Guidelines Steering Group, the experts appointed by the participating professional societies and organizations, and the experts invited in by the Steering Group are the members of the working groups and the authors of the *Guidelines* (Guidelines Group). Only the experts appointed by the participating professional societies and organizations (cf. Table I) had voting rights in the consensus-building process. The other members of the Steering Group and the invited experts only had a consultative role and were not entitled to vote.

During the first consensus-building process, the group for updating the *S3 Guidelines* was checked by the experts to determine how representative it was. Appointing additional experts was considered unnecessary.
**Table I. Guidelines Group: Professional Societies and Organizations Involved.**

<table>
<thead>
<tr>
<th>Working Party/Professional Society/Organization</th>
<th>Authors entitled to vote</th>
</tr>
</thead>
<tbody>
<tr>
<td>Working Group on Psychooncology (PSO)</td>
<td>Prof. Dr. Joachim Weis</td>
</tr>
<tr>
<td>Working Group on Rehabilitation, Follow-up Care and Social Medicine (ARNS)</td>
<td>Prof. Dr. Hans-Helge Bartsch</td>
</tr>
<tr>
<td>Working Group on Gynecological Oncology (AGO)</td>
<td>Prof. Dr. Hans-Joachim Lück Prof. Dr. Gunter von Minckwitz Prof. Dr. Christoph Thomssen Prof. Dr. Michael Untch</td>
</tr>
<tr>
<td>Working Group on Medical Oncology (AIO)</td>
<td>Dr. Norbert Marschner Prof. Dr. Kurt Possinger</td>
</tr>
<tr>
<td>Working Group on Radiological Oncology (ARO)</td>
<td>Prof. Dr. Wilfried Budach Prof. Dr. Jürgen Dunst Prof. Dr. Rainer Souchon</td>
</tr>
<tr>
<td>Working Group on Supportive Measures in Oncology (ASO)</td>
<td>Prof. Dr. Andreas du Bois Prof. Dr. Hartmut Link</td>
</tr>
<tr>
<td>Professional Association of Gynecologists</td>
<td>Dr. Klaus König</td>
</tr>
<tr>
<td>German Professional Association of Pathologists</td>
<td>Prof. Dr. Werner Schlake</td>
</tr>
<tr>
<td>Federal Office for Quality Assurance (BQS)</td>
<td>Dr. Anne Reiter</td>
</tr>
<tr>
<td>German Federal Self-Help Organization for Women after Cancer</td>
<td>Hilde Schulte</td>
</tr>
<tr>
<td>Working Group on Surgical Oncology (CAO)</td>
<td>PD. Dr. Steffen Leinung</td>
</tr>
<tr>
<td>German Society of Plastic, Reconstructive and Esthetic Surgeons</td>
<td>Dr. Gernot Maiwald Dr. Mario Marx</td>
</tr>
<tr>
<td>German Society for General and Family Medicine (DEGAM)</td>
<td>Dr. Brigitte Ernst</td>
</tr>
<tr>
<td>German Society of Gynecology and Obstetrics (DGGG)</td>
<td>Prof. Dr. Dietrich Berg</td>
</tr>
<tr>
<td>German Association for Medical Informatics, Biometry and Epidemiology (GMDS)</td>
<td>PD Dr. Willi Sauerbrei</td>
</tr>
<tr>
<td>German Society of Pathology</td>
<td>Prof. Dr. Hans Kreipe</td>
</tr>
<tr>
<td>German Society of Senology (DGS)</td>
<td>PD Dr. Ute-Susann Albert  Prof. Dr. Ingrid Schreer Prof. Dr. K.-D. Schulz † Prof. Dr. H. Madjar</td>
</tr>
<tr>
<td>German Society for Ultrasound in Medicine (DEGUM)</td>
<td></td>
</tr>
<tr>
<td>German Radiological Society</td>
<td>Prof. Dr. Ulrich Bick</td>
</tr>
<tr>
<td>Clinical Epidemiology, Munich Cancer Registry (TRM)</td>
<td>PD Dr. Jutta Engel Prof. Dr. Dieter Hölzel Andrea Maiwald</td>
</tr>
<tr>
<td>Conference on Oncological Nursing and Pediatric Nursing (KOK)</td>
<td></td>
</tr>
<tr>
<td>Coordinator of the Centers for Hereditary Breast and Ovarian Cancer</td>
<td>Prof. Dr. Rita Schmutzler</td>
</tr>
<tr>
<td>Women’s Health Coalition e.V. (WHC)</td>
<td>Irmgard Nass-Griegoleit</td>
</tr>
<tr>
<td>Central Association of Physiotherapists (ZVK)</td>
<td>Ulla Henscher</td>
</tr>
</tbody>
</table>
5 Updating Method

The methodological approach for updating the *S3 Guidelines* is described in Appendix I. Appendix III gives an overview (project outline) of how the methodology was elaborated in the course of the updating process, the methodological steps and the responsibilities. The starting point for the procedure was the compilation of a tabular overview of all the Statements to date (core statements and recommendations in the 2004 *Guidelines*) and the supporting evidence and/or the sources quoted (Guidelines Updating Synopsis) drawn up by the Coordinator and the Project Manager. This formed the basis for a systematic literature search for the update. The search encompassed all the former Statements and the period from the initial compilation to the update of the *Guidelines* (cf. Chapter 5.1, Appendix VIII). Furthermore, this was followed by a systematic guideline search. The existing and newly found sources formed the basis for auditing the statements, and if necessary reformulating them. In order to make a balanced and useful update of the *Guidelines* that also takes account of diverging values, the work on the content of the *Guidelines* was backed up by a two-stage formal consensus-building process (cf. Chapters 5.2, 5.5). This used the techniques of the nominal group process (NGP), the Delphi technique and formal consensus conferences [12, 13]. The voting processes were conducted by neutral facilitators trained and experienced in the consensus techniques. The voting processes, including all the contributions regarding content, the results of the ballots and the assessment of the strength of the consensus, and the areas where no consensus was found, were documented along with the reasons, e.g. minority opinions (Table II).

<table>
<thead>
<tr>
<th>Strength of Consensus</th>
<th>Percentage of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong consensus</td>
<td>≥ 95 %</td>
</tr>
<tr>
<td>Consensus</td>
<td>&gt; 75–95 %</td>
</tr>
<tr>
<td>Consent of majority</td>
<td>&gt; 50–75 %</td>
</tr>
<tr>
<td>No consensus</td>
<td>≤ 50 %</td>
</tr>
</tbody>
</table>

Applications to inspect the complete documentation on the consensus-finding procedure may be submitted to the coordinator in writing.

The major new developments as compared to the 2004 *Guidelines* (in terms of structure and content) are summarized in Chapter 5.3.


5.1 Methodological accuracy: evidence base

5.1.1 Systematic literature review and selection

The literature search was carried out centrally in the Guidelines Coordination Office with support from a specialist (medical documenting expert). The search strategy for the update was determined as follows:

Databases: via Ovid: Medline, BIOSIS Previews, CDSR, ACP Journal Club, DARE, CCTR, CINAHL

Search terms: (breast$ or mamma$) and (cancer or carcinom$ or neoplasm$) and (randomi$ or meta$analysis$)

Period: 2003 to 2006

This identified 10,094 publications. On this basis targeted searches were made for each individual statement in the old Guidelines, to facilitate the allocation of the sources in the Guideline Updating Synopsis and the selection (limitation according to relevance to content) (for strategies, search terms and numbers of hits, cf. electronic Appendix VIII). After preliminary sifting of the abstracts by the Coordinator, and the exclusion of duplicates, items not available in either English or German, and those of no relevance, 243 new sources were selected. The Guidelines Coordination Office fed these sources into the existing literature database, a pdf library (full text of all publications) and the Guideline Updating Synopsis.

For the topic of diagnostic workup (e.g. mammography, value of ultrasound breast examination, indications for stereotactic vacuum-assisted biopsy in comparison to stereotactic core biopsy, benefit of excision of the core biopsy tract following minimally invasive biopsy to avoid spread of tumor cells, assessment of the HER-2/neu determination methods, etc.) the literature was systematically reviewed by an external working group at the ÄZQ. The Evidence Report was commissioned by members of the Steering Group (Prof. Schulz and PD Albert) in their capacity as Coordinators of the S3 Guidelines on the Early Detection of Breast Cancer and is publicly accessible as an Appendix to the Methodology Report of the S3 Guidelines on the Early Detection of Breast Cancer 2007 on the Internet: www.awmf-leitlinien.de.

5.1.2 Systematic search for guidelines (sources for adapting the recommendations)

International guidelines are important sources for the creation of new guidelines. In addition to the literature search, therefore, a specific guideline search was carried out with the following strategy:

– database: Guidelines International Network (GIN), www.g-i-n.net
– search term: breast cancer

This process identified 87 publications. Publications were excluded that contained the words screening/early detection in their titles, and those whose full text was not available in either English or German, and also publications that had been withdrawn, were still being prepared, second publications and those that did not have a Methodology Report and did not fulfill the
minimum requirements for evidence-based work and consensus-finding according to DELBI [8]. This was followed by a comparison with the results of the literature search and the exclusion of duplicates. This resulted in the following list of guidelines that were possible sources for the working groups:

1. *S3 Guidelines for Early Detection in Germany*, Internet: www.awmf-leitlinien.de (AWMF register no. 77/001)
   - Cancer care Ontario Program in Evidence Based Care (PEBC)
     Internet: http://www.cancercare.on.ca/index_breastCancerGuidelines.htm
   - Publications by the Breast Cancer Disease Site Group:
     2. 2003: Adjuvant Systemic Therapy for node negative breast cancer
     3. 2003: Surgical Management of Early-Stage Invasive Breast Cancer
     4. 2003: The Role of Aromatase Inhibitors in the Treatment of Postmenopausal Women with Metastatic Breast Cancer
     5. 2003: The Role of the Taxanes in the Management of Metastatic Breast Cancer
     6. Capecitabine in Stage IV Breast Cancer
     7. 2004: The Role of Taxanes in Neoadjuvant Chemotherapy for Women with Non-metastatic Breast Cancer
     8. 2004: Use of Bisphosphonates in Women with Breast Cancer
     9. 2005 The Role of Trastuzumab (Herceptin?) in the Treatment of Women with HER-2/neu-overexpressing Metastatic Breast Cancer
     10. 2006: Management of Ductal Carcinoma in Situ of the Breast
   - Publication by the Supportive Care Guidelines Group:
     12. 2003: The Treatment of Lymphedema Related to Breast Cancer
   - American Society of Clinical Oncology (ASCO)
     Internet: http://jco.ascopubs.org/cgi/content/full/21/21/4042
   - Scottish Intercollegiate Guidelines Network (SIGN)
   - National Institute of Clinical Excellence (NICE)
   - National Breast Cancer Centre/National Health and Medical Research Council (NBCC/NHMRC)

In addition, the following guidelines located via a manual search were included for their practical relevance to the *S3 Guidelines*:

20. Arbeitsgemeinschaft für Gynäkologische Onkologie e.V. [ Working Group on Gynecological Oncology]: Leitlinien gynäkologische Onkologie 2006, Breast Commission
5.2 **First consensus process: methodological approach, prioritizing**

On the basis of the Guidelines Updating Synopsis, the need for revision was determined by identifying the recommendations to be updated and prioritizing the topics and questions for the systematic literature evaluation. This took place in a two-staged process:

1. **Modified Delphi process [12]:**
   - written survey of opinions with the aid of a structured questionnaire. The questionnaire was sent to all members of the Guidelines Group. The members were asked to respond to the following items for each Guideline Statement:
     - keep the Statement
     - check the strength of evidence and/or the strength of recommendation
     - revise the contents
     - delete the Statement

2. **Nominal group process [13]**
   Discussion and taking of a decision at the first meeting of the Guidelines Group.
   - Part 1: Short introductory presentations (Coordinator, Methodology Expert)
     - Introduction to the current methodological principles of guideline development (DELBI)
     - Presentation of the revision plan and the preliminary work (Guideline Updating Synopsis, literature search)
     - Presentation of the results of the written survey conducted to determine the need for revision
     - Overview of the implementation of the Guidelines since 2004
     - Methodological instructions for the work to be carried out in the working groups (WG) constituted for specific topics
     - Explanation and collection of declarations on conflicts of interest
   - Part 2: Discussion and taking of decisions via the formal consensus process (NGP)
     - Determination of the need for revision on the basis of the Guideline Updating Synopsis including old and new sources, recommendations for additions and deletions, and setting down of the revision strategy
     - Ascertainment of the completeness of the Guidelines Group
     - Composition of the working groups on specific topics
     - Formulation of the task assignments for the particular working groups, appointing of responsible parties

The formal consensus process took place in 6 steps [13]:

- Phase of quiet work: making notes of opinions
- Registration of opinions of individual participants on a “round robin” basis by the Moderator
- Clarification and justification of alternative proposals
- Preliminary vote on the first draft and all alternatives
- Identifying points of discussion and dissent
- Debate and discussion
- Final vote
Three possible strategies were given for prioritizing and determining the strategies for processing the Statements in the working groups for the specific topics (cf. Appendix IV):

1. Processing on the basis of the consensus reached in the Guidelines Group (“consensus”)
   This strategy could be selected if a Statement from the former version of the Guidelines was to be accepted with unchanged contents or deleted entirely. Likewise, it could be selected if no information on strength of evidence was deemed necessary, i.e. the contents were considered good clinical practice. In concrete terms, the working group then elaborated a proposal which was formally voted upon in the subsequent consensus process and given the grade of “good clinical practice” (GCP).

2. Processing by adapting recommendations contained in current guidelines of high methodological quality (“guideline adaptation”)
   This strategy was to be selected if either no information on strength of evidence was deemed necessary or if the contents and information on strength of evidence were taken in unchanged form from a reference guideline. For this purpose only guidelines were to be used for which clear-cut information could be found – either in the guidelines themselves or in the accompanying Methodology Report – on the origins of the Statements, recommendations and grading in accordance with the requirements of DELBI [8]. The grades could be taken over in unchanged form if a reason had been given for the grading.

3. Processing on the basis of a systematic selection and evaluation of the literature (“de-novo processing of evidence”)
   This strategy was specified as necessary if the changes in the contents of a guideline, along with the information on the strength of evidence and a grade of recommendation and/or checking of the strength of evidence and/or strength of recommendation was deemed necessary and an adaptation was not deemed worthwhile or appropriate. In this context the working groups were to check the reasons for the selection of sources from the systematic literature search and/or cite sources on the basis of their own supplementary searches; they were also to check the methodological quality of the sources (study design, quality of study implementation and quality of study evaluation) using structured assessment forms (Basis: SIGN 50. [15]).

5.3 S3 Guidelines 2007: new developments, organization and questions addressed

During the first consensus process, the following basic revisions were decided upon:

– writing of a new chapter “Preinvasive Lesions”
– complete revision of the chapter “Pathology” (former Statements 14–21, Addendum)
– complete revision of the chapter “Adjuvant Radiotherapy” (former Statements 23–30)
– reorganization of the chapters on adjuvant and neoadjuvant treatment (former Statements 41–46)
– complete revision of the chapter on follow-up care including additional information on the aspects of supportive therapy, rehabilitation, psychosocial therapy and palliative medicine.
During the first consensus process it was decided to revise two of the former 96 Statements (core statements and recommendations) contained in the 2004 version of the Guidelines via systematic de novo evaluation of evidence. A total of 58 Statements were prioritized for revision to be carried out by adapting recommendations contained in current guidelines of high methodological quality. For 26 Statements the choice between these two strategies was left up to the working groups. For 10 Statements a decision was taken to carry out revision via a structured consensus-building process. The revision of Statements was carried out in the working groups for the particular topics. These groups also wrote the new Statements.

The organization of the Guidelines is based on the instructions in the Guideline Clearing Report on Breast Cancer [16]. An overview of the chapter structure showing the working groups responsible for the particular chapters is provided in Table III.

Table III. Organization of the S3 Guidelines 2007.

<table>
<thead>
<tr>
<th>Chapter/Topic</th>
<th>Speaker, Working Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Section A  General</strong></td>
<td></td>
</tr>
<tr>
<td>A 1 Introduction</td>
<td>Kreienberg, Engel, Hölzel</td>
</tr>
<tr>
<td>A 2 Patient Information</td>
<td>Kreienberg, Albert, Ernst, König, Nass-Griegoleit, Schulte, Schulz</td>
</tr>
<tr>
<td>A 3 Early Detection, Mammographic Screening</td>
<td>Albert, Schulz, Guidelines Group for Early Breast Cancer Detection 2007</td>
</tr>
<tr>
<td>A 4 Women at Increased Risk of Developing Breast Cancer</td>
<td>Schmutzler, Kreipe, Schreer</td>
</tr>
<tr>
<td><strong>Section B  Locoregional Primary Disease</strong></td>
<td></td>
</tr>
<tr>
<td>B 1 General Diagnostic and Therapeutic Concepts</td>
<td>Kühn, Berg, duBois, Engel, Kreienberg, Kreipe, Lebeau, Madjar, Nass-Griegoleit, Schlake, Schreer, Schulz, Souchon</td>
</tr>
<tr>
<td>B 3 Preinvasive Lesions</td>
<td>Beckmann, Kühn, Lebeau, Marx, Schreer, Souchon, Possinger, Wagner</td>
</tr>
<tr>
<td>B 4 Surgical Treatment of Invasive Breast Cancer</td>
<td>Kreienberg, Berg, Jackisch, Kühn, Lebeau, G. Maiwald, Marx, Untch, Wagner</td>
</tr>
<tr>
<td>B 5 Pathomorphological Examination</td>
<td>Lebeau, Kühn, Kreipe, Possinger, Schlake, Thomssen</td>
</tr>
<tr>
<td>B 6 Adjuvant Radiotherapy for Breast Cancer</td>
<td>Souchon, Budach, Dunst, Engel, Hölzel, Kreienberg, Kühn, Sauerbrei, Thomssen, Untch</td>
</tr>
<tr>
<td>B 7 Systemic Adjuvant Treatment (Endocrine Treatment, Chemotherapy, Immune Therapy)</td>
<td>von Minckwitz, Jackisch, König, A. Maiwald, G. Maiwald, Marschner, Ortmann, Possinger, Thomssen, Untch, Wagner</td>
</tr>
<tr>
<td>B 8 Management of Locally and Locoregionally Advanced Breast Cancer</td>
<td>Wagner, Kreienberg</td>
</tr>
</tbody>
</table>
Table III (cont’d.)

<table>
<thead>
<tr>
<th>Chapter/Topic</th>
<th>Speaker, Working Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Section C  Recurrent Breast Cancer</strong></td>
<td></td>
</tr>
<tr>
<td>C 1 Definition and Prognosis</td>
<td>Wagner, Budach, Engel, Jackisch,</td>
</tr>
<tr>
<td>C 2 Diagnostic Procedures</td>
<td>Link, Lück, A. Maiwald,</td>
</tr>
<tr>
<td>C 3 Treatment of Local or Locoregional Recurrence</td>
<td>G. Maiwald</td>
</tr>
<tr>
<td>C 4 Distant Metastases</td>
<td>Possinger, Lück, Dunst, Jackisch,</td>
</tr>
<tr>
<td></td>
<td>Leining, Lück, Marschner,</td>
</tr>
<tr>
<td></td>
<td>v. Minckwitz, Thomssen</td>
</tr>
<tr>
<td><strong>Section D  Treatment, Support, Continuing Care</strong></td>
<td></td>
</tr>
<tr>
<td>D 1 General Concept</td>
<td>Kreienberg</td>
</tr>
<tr>
<td>D 2 Psychosocial Aspects and Psychooncology</td>
<td>Beckmann, Albert, Bartsch, Bick,</td>
</tr>
<tr>
<td>D 3 Supportive Therapy</td>
<td>Ernst, Henscher, Hölzel, König,</td>
</tr>
<tr>
<td>D 4 Rehabilitation</td>
<td>Leining, Link, A. Maiwald,</td>
</tr>
<tr>
<td>D 5 Follow-up Care Including Diagnostic Workup of</td>
<td>G. Maiwald, Nass-Griegeleit,</td>
</tr>
<tr>
<td>Metastases and Support during Therapy</td>
<td>Schulte, Souchon, Weiss</td>
</tr>
<tr>
<td>D 6 Palliative Medicine</td>
<td></td>
</tr>
<tr>
<td><strong>Section E  Quality Management and</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Coordination of Patient Care</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kreienberg, Albert, Berg, du Bois,</td>
</tr>
<tr>
<td></td>
<td>Engel, Ernst, Geraedts, Hölzel,</td>
</tr>
<tr>
<td></td>
<td>Kopp, Lebeau, Reiter, Sauerbrei,</td>
</tr>
<tr>
<td></td>
<td>Souchon, Thomssen, Wagner</td>
</tr>
</tbody>
</table>

5.4 Formulation and rating of core statements and recommendations

The present Guidelines use the evidence categories of the Oxford Centre for Evidence-Based Medicine (cf. Appendix VI [17]) as the basis for presenting evidence. The grading of the recommendations was carried out with reference to the current Methodology Report of the Program for National Health Care Guidelines in Germany (cf. Appendix VII [14]).

The strength of evidence is an indicator of the methodological validity of the studies on which a statement or recommendation is based. In addition to the study design, the assignment of levels of evidence takes account of the quality of the study’s performance and evaluation. The strength of the recommendation corresponds to the results of the clinical assessment of the information value and applicability of the methodologically processed evidence. In English this process is also referred to as “considered judgment.” The assignment of grades of recommendation is based on both explicit and implicit judgments and is carried out within the scope of the final structured consensus process. In addition to the evidence on which the statement or recommendation is based, this grading takes account of ethical obligations, the clinical relevance of the effectiveness of the studies, the applicability of the study results to the target patient group, the German health care system and the patient’s preferences. It also takes consideration of the extent to which the Statement or recommendation can be implemented during the everyday practice of medicine, especially in the different areas of patient care. Owing to these consensus-related aspects, deviations from this procedure are permissible in justified cases (Cf. specifications in Chapter 5.2, Appendix VII). The terms used in the Guidelines and a scheme for converting levels of evidence to grades of recommendation have been presented in summarized and simplified form in Table IV.
Table IV. Simplified Scheme for Converting Levels of Evidence to Grades of Recommendation.

<table>
<thead>
<tr>
<th>LoE CEBM</th>
<th>Simplified Definition of Sources</th>
<th>Grade of Recom.</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>Diagnostics</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Randomized controlled studies</td>
<td>A</td>
<td>Strong recommendation</td>
</tr>
<tr>
<td>II</td>
<td>Controlled studies w/o randomization</td>
<td>Exploratory cohort studies</td>
<td>B</td>
</tr>
<tr>
<td>III or IV</td>
<td>Observational studies, expert opinions</td>
<td>0</td>
<td>Recom. open</td>
</tr>
<tr>
<td>Structured consensus process/Clinical judgment</td>
<td>GCP</td>
<td>Consensus regarding “good clinical practice”</td>
<td></td>
</tr>
</tbody>
</table>

The recommendations are formulated analogously to the grading if possible:

Strong recommendation: “shall;” recommendation: “should;” recommendation open: “can” (action option) or “unclear.” Negative recommendations are expressed in words (“not”) with the same symbols. The grading in the formulations is used analogously manner for the GCP recommendations.

5.5 Second consensus process: voting and grading of recommendations

The tasks of selecting sources, formulating core statements and recommendations, presenting the strength of the evidence on which the statements and/or recommendations are based, and grading of recommendations on the basis of the source guidelines and/or the primary literature were carried out by the members of the working groups. During the second formal consensus process, all the core statements and recommendations proposed in this way (including the grading) were discussed and voted on in accordance with the criteria (consensus aspects) specified for the grading of recommendations. Reasons were given for any deviations of the level of evidence from the grade of recommendation. In the Guidelines levels of evidence have been included for all core statements and recommendations; in addition, grades of recommendation have been included for all recommendations. Guideline recommendations citing a guideline adaptation as a source are presented in the same way. The consensus-building took place at two structured two-day Consensus Conferences of the entire Guidelines Group held in October 2006 and March 2007, respectively.

The agenda of the Consensus Conferences comprised several steps [12]:

Part 1: Short Presentations

– Introduction of the formal consensus technique by the Moderator
– Presentation of the state of scientific and medical knowledge in each topic by the speaker of the corresponding working group.
– Opportunity for questions from the floor on the methodological approach taken to reach the results
Part 2: Structured Consensus-Building

– Chapter-by-chapter approach, reading aloud of each proposed core statement or recommendation by the Moderator
– Recording of opinions from the floor by the Moderator
– Clarification and justification of alternative proposals
– Preliminary vote on the first draft and all alternatives
– Identification of points of discussion and dissent
– Debate and discussion
– Final vote

A final revision of Statements for which consensus is still to be reached, the background texts for the recommendations, the elaboration of algorithms and the standards for quality assurance including the parameters used for assessment (Quality Indicators, cf. Chapter 6) were carried out after the second consensus process. The final vote on the revised complete draft was taken as part of the Delphi process during which a questionnaire was sent to all members of the Guidelines Group and the ADT. Each member was asked to respond to the following items for each chapter:

– agree
– disagree
– propose specific changes and state reasons

The results of this first survey of opinion (first Delphi round) were summarized and returned to the Guidelines Group. The chapters for which consensus was not achieved in the first round were put to the vote again in a revised form incorporating the proposed changes (second Delphi round, cf. also Chapter 7). For a discussion of the consensus process for quality indicators, refer to Chapter 6.

5.6 Quality assurance measures for Guidelines updating

To support the work on the Guideline contents in the working groups on the specific topics and to implement quality assurance of the process, the Steering Group enacted the following measures:

1. Provision of work materials including instructions (DVD)
   – Guideline Updating Synopsis (core statements and recommendations of the previous Guidelines along with former and new sources)
   – pdf library containing all complete texts from the systematic literature search (reference guidelines, systematic reviews, primary literature)
   – Algorithm for processing the literature in the working groups
   – Specified strategy for elaborating and formulating new recommendations (structured consensus-building or guideline adaptation or systematic selection and evaluation of evidence)
   – Literature evaluation forms and model evidence table
   – Scheme for assigning levels of evidence and grades of recommendation
2. Formalized, guided correspondence (e.g. confirmation, reminder system)
3. Preparing a written transcript of all work sessions and votes
4. Process sequences set down in advance
   – Methodology, Time and Financing Plans
   – Selection and evaluation of sources used for the revision of the Guidelines’ contents
   – Consensus process and votes
5. Transparency of the development process and responsibilities (Methodology Report)
6. Consultation process before publication
   – Delphi process within the Guidelines Group and external appraisal of the long version, abridged version, quality indicators and Methodology Report
7. Written consent of the participating organizations and authors before publication

A written application to inspect the comprehensive documentation of the guideline development process, the guideline updating process or the consensus process may be submitted to the Coordinator.

In both the abridged version and final complete text of the Guidelines, all Statements (core statements and recommendations) are accompanied by the Level of Evidence and Grade of Recommendation as well as the primary sources cited by the working groups and the strengths of consensus ascertained.
6 Quality Indicators: Updating, Prioritizing and Consensus Process

The revision of the quality indicators encompassed:

1. the simple derivation of quality indicators from the Guideline Statements approved during the second consensus process (already available quality indicators were included) as a List of Proposed Indicators by the Working Group on Quality Management and Coordination of Patient Care (48 indicators)

2. the prioritizing of quality indicators by the Guidelines Group according to the aspects of validity, feasibility and consensus during the Delphi process

During the first Delphi round prioritization was undertaken using the RAND/UCL method [18] as a Quality Assessment (QA) tool. The quality indicators were assessed according to the criteria of “validity” and “feasibility” and rated on a scale of 1 to 9. The highest score (9) was given for “extremely valid or feasible” while the lowest score (1) was given for “not valid or feasible at all.” These two criteria were defined by the following characteristics:

Validity (according to RAND-UCLA)
- The QI is supported by sufficient scientific evidence or a sufficient professional consensus.
- Patients treated as specified by the QI derive noticeable health benefits.
- It can be verified, on the basis of the professional experience of the appraisers, that service providers who follow the specifications of the QI significantly more often are deemed to be “of high quality.”
- The majority of factors determining the level of the QI is within the control of (or can be influenced by) the service provider.

Feasibility (according to RAND-UCLA)
- The information which is required to measure a QI can be found, with a high degree of probability, in a typical patient’s file.
- Estimates of the level of a QI on the basis of data from the patient’s file are, with a high degree of probability, reliable and non-distorted.
- The absence of documentation of relevant data on a QI is in itself a sign of poor quality.

The results of the first Delphi round were quantitatively evaluated and the results were returned to the Guidelines Group for the consensus process in the second Delphi round. The quality indicators which were prioritized and attained consensus in this manner are included in both the abridged and long versions of the Guidelines as recommended for use.
The draft of the updated *Guidelines* was presented to the Guidelines Group as a consultation version in October 2007 and voted upon (first Delphi round of final voting). In December 2007 the revised draft was submitted to the ADT for external appraisal and was approved by the Guidelines Group (second Delphi round of final voting). Finally, the *Guidelines* were presented to the participating professional societies for formal approval.

The updated S3 *Guidelines for the Diagnosis, Treatment and Follow-up Care of Breast Cancer in Women* will be published in the following formats:

1. abridged version in German and English, abridged version of the Information for Patients (peer-reviewed journal)
2. long version: publication in book form
4. full version in English in the Internet (Guidelines International Network, GIN: www.g-i-n.net)

The special formats are part of the implementation strategy, which explicitly proposes that the publications listed under 1–4 above be used to put the *Guidelines* into practice. The measures foreseen for this purpose include:

- implementation of algorithms in hospitals and doctors’ practices (clinical local treatment paths, training seminars and appropriate local development of implementation aids, e.g. labcoat pocket formats, incorporation in supportive media, and incorporation in electronic information systems installed in hospitals and doctors’ practices within the framework of quality management
- use of the information for women as part of a public relations campaign, e.g. postcard formats, Internet presentations, brochures.

The distribution and implementation of the *Guidelines* are supported actively by the Steering Group by means of:

- presentation of the *Guidelines*, by the sponsors of the *Guidelines*, in a manner that captures the attention of the media
- preparation of a press release for the Scientific Information Service idw (idw-online.de)
- press conferences
- a series of presentation events in the first six months of 2008 (Dresden, Cologne, Munich, Berlin): short talks on the contents supplemented by case studies and followed by interactive discussion
- directly approaching the target readership of the *Guidelines*
- articles in professional journals, contributions to books, lectures (including presentations at conferences), seminars, etc.
- support of production of materials for CPD/CME (CME accreditation by the Medical Associations in the individual German states)
8 Assessment

The assessment should be geared to the objectives of the Guidelines. In addition, the quality indicators presented in the Guidelines for assessing structural, process and outcomes quality are suitable parameters for such assessment. Research requirements and research questions that emerged during the preparation and revision of the Guidelines have been identified in the updated long version of the Guidelines. The impact of implementation, in particular the questions concerning the effectiveness and efficiency of patient care, require further investigation. In this context there is a need for research studies on patient care.

The targets of the assessment are:

– clinical cancer registries
– breast centers
– the Federal Office for Quality Assurance (BQS) (www.bqs-online.de)
– projects carried out within the framework of the German health care goals (www.gesundheitsziele.de)

The accompanying assessment within the framework of research on patient care is a central concern. Applications for grants (e.g. within the scope of Invitations to Tender) should be encouraged.
9 Duration of Validity and Updating

The updated S3 Guidelines for the Diagnosis, Treatment and Follow-up Care of Breast Cancer in Women were completed in December 2007. In January 2008 they were formally approved by the professional societies and organizations which participated in drawing up and editing the Guidelines and were subsequently published. The Guidelines are valid until December 2010 at the latest. A complete revision and new edition of the Guidelines are slated to take place at this time. New knowledge emerging in the interim which might make it necessary to update individual chapters or recommendations will be monitored by the Guidelines Group. Helpful information on this subject from the target readership of the Guidelines is expressly desired, moreover, and should be addressed to the Coordinator. The aim is to use this information to continuously update the Guidelines to bring them into line with evolving requirements.

The date of publication, the date of the next planned revision and the registration of planned updates or updates made in the interim will be published in the Directory of the AWMF (http://www.awmf-leitlinien.de) accessible to the public. In each case only the most recent version shown in the AWMF Directory is valid.
10 Financing/Editorial Independence

The updating of the *S3 Guidelines* has been supported by a grant of 80,000 euros from Deutsche Krebgesellschaft e. V. [German Cancer Society] These funds have been used to meet personnel costs (contract for literature search), expenses related to the planning meetings, and costs incurred for the consensus process (travel expenses for all participants, hall rental, technical support and catering), costs for office supplies, and reimbursement of expenses of external experts who provided methodological support. The *Guidelines* were drawn up and updated by a team of authors and editors who worked independently of the organization financing the project.

The authors and the participants in the consensus process are to be thanked for their work, which was provided exclusively on a voluntary basis. All members of the Guidelines Group submitted a written declaration of any existing conflicts of interest, especially with respect to industry (Form, cf. Appendix VII).
Literature


Appendix I: Strategy for Updating the S3 Guidelines for the Diagnosis, Treatment and Follow-up Care of Breast Cancer

Coordinator, Steering Group
Initialization, preparation, overview of implementation, collation of Statements for needs analysis

Steering Group
Analysis of present situation: assessment of overview of implementation
Needs analysis: preparation and assessment of Delphi procedure, Guidelines updating synopsis
Review of Guidelines rationale and goals
EBM: systematic literature review, guidelines research
Preparation for 1st consensus procedure

Professional societies/organizations (Guidelines Group)
Appointment of representative, needs analysis: examination of statements, new proposals or deletion from Delphi procedure if appropriate

1st consensus procedure
Coordination of the strategy (presentations, discussion, coordination of need for revision on the basis of the analysis of present situation, needs analysis and results of literature review), Prioritization: determination of revision strategy for each core statement and recommendation

Conveying of results to Steering Group

Formation of working groups for individual theme-based modules

Elaboration, collation of results from working groups, quality indicators, algorithms, preparation for consensus conference

EBM: Selection and rating of sources

Drafts of updated Statements/QI/algorithms (comparison of old versus new) and background texts

2nd consensus procedure
Updated core statements, recommendations and algorithms, quality indicators: presentations, discussion, coordination of content, grading

Coordination (in writing)

Elaboration (texts)

External appraisal: abridged version, full version, Methodology Report; formal approval; compilation of patient information

Publication: abridged version, full version, Methodology Report, patient information
Appendix II: Members of the Guidelines Group

Coordination of the Guidelines: Prof. Dr. Rolf Kreienberg, Ulm  
Dipl. math. oec. Thomas Zemmler, Ulm

Project management: Dipl.-Ing. Anita Prescher, ISTO/DKG, Frankfurt

Methodological support: PD. Dr. Ina Kopp, AWMF, Marburg  
PD Dr. Ute-Susann Albert, Marburg  
Prof. Dr. Klaus-Dieter Schulz, Marburg †

Panel of experts: Prof. Dr. Matthias W. Beckmann, Erlangen  
Prof. Dr. Max Geraedts, Düsseldorf  
Prof. Dr. Christian Jackisch, Offenbach  
Prof. Dr. Michael Koller, Regensburg  
Prof. Dr. Thorsten Kühn, Esslingen  
PD Dr. Annette Lebeau, Hamburg  
Prof. Dr. Uwe Wagner, Marburg

Participants in the consensus process

<table>
<thead>
<tr>
<th>Professional Society/Working Group/Organization</th>
<th>Authors entitled to vote</th>
</tr>
</thead>
<tbody>
<tr>
<td>Working Group on Psychooncology (PSO)</td>
<td>Prof. Dr. Joachim Weis</td>
</tr>
<tr>
<td>Working Group on Rehabilitation, Follow-up Care</td>
<td>Prof. Dr. Hans Helge Bartsch</td>
</tr>
<tr>
<td>and Social Medicine (ARNS)</td>
<td></td>
</tr>
<tr>
<td>Working Group on Gynecological Oncology (AGO)</td>
<td></td>
</tr>
<tr>
<td>Working Group on Medical Oncology (AIO)</td>
<td>Dr. Norbert Marschner</td>
</tr>
<tr>
<td>Working Group on Radiological Oncology (ARO)</td>
<td>Prof. Dr. Ute-Susann Albert</td>
</tr>
<tr>
<td>Working Group on Supportive Measures in Oncology (ASO)</td>
<td>Prof. Dr. Hans-Joachim Lück</td>
</tr>
<tr>
<td>Professional Association of Gynecologists</td>
<td>Prof. Dr. Gunter von Minckwitz</td>
</tr>
<tr>
<td>German Professional Association of Pathologists</td>
<td>Prof. Dr. Christoph Thomssen</td>
</tr>
<tr>
<td>Federal Office of Quality Assurance (BQS)</td>
<td>Prof. Dr. Michael Untch</td>
</tr>
<tr>
<td>German Federal Self-Help Organization for Women after Cancer</td>
<td>Prof. Dr. Andreas du Bois</td>
</tr>
<tr>
<td>Working Group on Surgical Oncology (CAO)</td>
<td>Dr. Klaus König</td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. Werner Schlake</td>
</tr>
<tr>
<td></td>
<td>Dr. Anne Reiter</td>
</tr>
<tr>
<td></td>
<td>Hilde Schulte</td>
</tr>
<tr>
<td></td>
<td>PD. Dr. Steffen Leinung</td>
</tr>
<tr>
<td>Professional Society/Working Group/Organization</td>
<td>Authors entitled to vote</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>--------------------------</td>
</tr>
</tbody>
</table>
| German Society of Plastic, Reconstructive and Esthetic Surgeons | Dr. Gernot Maiwald  
Dr. Mario Marx |
| German Society for General and Family Medicine (DEGAM) | Dr. Brigitte Ernst |
| German Society for Gynecology and Obstetrics (DGGG) | Prof. Dr. Dietrich Berg |
| German Association for Medical Informatics, Biometry and Epidemiology (GMDS) | PD Dr. W. Sauerbrei |
| German Society of Pathology | Prof. Dr. Hans Kreipe |
| German Society of Senology (DGS) | PD Dr. Ute-Susann Albert  
Prof. Dr. Ingrid Schreer  
Prof. Dr. Klaus-Dieter Schulz † |
| German Society for Ultrasound in Medicine (DEGUM) | Prof. Dr. Helmut Madjar |
| Germany Radiological Society | Prof. Dr. Ulrich Bick |
| Clinical Epidemiology, Munich Cancer Registry (TRM) | PD Dr. Jutta Engel  
Prof. Dr. Dieter Hölzel |
| Conference on Oncological Nursing and Pediatric Nursing (KOK) | Andrea Maiwald |
| Coordinator of the Centers for Hereditary Breast and Ovarian Cancer | Prof. Dr. Rita Schmutzler |
| Women’s Health Coalition e.V. (WHC) | Irmgard Nass-Griegoleit |
| Central Association of Physiotherapists (ZVK) | Ulla Henschler |
Appendix III: Project Outline of Work Sequences in the Updating Process, Methodological Steps and Assignment of Responsibilities

<table>
<thead>
<tr>
<th>Work steps</th>
<th>Persons responsible</th>
<th>Tasks</th>
<th>Time period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initialization</td>
<td>Coordinator, Steering Group</td>
<td>Creation of project schedule, application for promotional funding, formation of Guidelines Steering Group</td>
<td>Early 2006</td>
</tr>
<tr>
<td>Preparation</td>
<td></td>
<td>- Invitation to the professional societies/organizations, appointment of representatives, invitation to the panel of experts</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Creation of synopsis of all previous statements and recommendations in the Guidelines, allocation of each source cited (Guidelines updating synopsis)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Creation of reference database and pdf library</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Review of Guidelines implementation since 2004</td>
<td></td>
</tr>
<tr>
<td>Needs analysis</td>
<td>Guidelines Group</td>
<td>Delphi procedure for prioritizing the revision (preparation for 1st consensus)</td>
<td></td>
</tr>
<tr>
<td>Literature review</td>
<td>Coordinators and methodological support</td>
<td>- Search strategy: all statements and recommendations from the 2004 Guidelines in full; derivation of search terms from the synopsis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Goal: Guidelines, sources of reviewed evidence and primary literature for the period 1 Jan. 2003 to 30 June 2006 (cf. Annex IV)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Preselection: restriction to relevant sources, publication of complete document in English or German</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Additions to Guidelines updating synopsis: allocation of sources found, marked as new literature</td>
<td></td>
</tr>
<tr>
<td>1st consensus procedure: methodological concept, needs analysis, prioritization, formation of working groups for specific topics</td>
<td>Guidelines Group</td>
<td>Part 1: Brief presentations as introduction (coordinators, methodologists)</td>
<td>29 June 2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Presentation of DELBI, consensus technique, revision strategy and preliminary work</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Overview of Guidelines implementation since 2004</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Instructions on methodology for work in working groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Explanation and obtaining of declarations of conflicts of interests</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Part 2: Discussion and taking of decisions by consensus</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Determination that Guidelines Group is complete</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Determination of need for revision using the Guidelines updating synopsis with old and new sources, proposals for additions and deletions, prioritization: determination of revision strategy in NGP</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Compiling working groups for specific topics (18 groups)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Formulation of task assignments for working groups, appointment of persons responsible</td>
<td></td>
</tr>
<tr>
<td>Preparation for working groups for specific topics</td>
<td>Steering Group</td>
<td>Sending all authors the minutes of the meeting incl. resolutions and a DVD with materials, instructions on procedure, Guidelines updating synopsis and pdf library of all complete texts from systematic literature search</td>
<td>July 2006</td>
</tr>
<tr>
<td>Work steps</td>
<td>Persons responsible</td>
<td>Tasks</td>
<td>Time period</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Work in working groups for specific topics</td>
<td></td>
<td>Literature check for plausibility and completeness, provision of relevant works not found during the search from the in-house collection/hand search, revision of core statements/recommendations in line with consent strategy (methodological requirements, cf. Annex IV)</td>
<td>July–October 2006</td>
</tr>
<tr>
<td>Preparation for consensus</td>
<td>Steering Group</td>
<td>Ordering original works, entering them in the databases, working group communication, collating the texts, revising the synopsis</td>
<td></td>
</tr>
</tbody>
</table>
| 2nd consensus procedure, first meeting |                      | Part 1: Brief presentations:                                                 – Introduction to the formal consensus-building technique  – Presentation of current scientific medical knowledge (working group spokespersons) for each thematic complex  
Part 2: Consensus procedure, structured coordination of each thematic complex, pathomorphology, DCIS, adjuvant radiation therapy, adjuvant systemic therapy, management of advanced tumors, follow-up care, recurrence, distant metastases, operative treatment, rehabilitation  – Decisions on need for further revision and continuing procedure | 6–7 October 2006  |
| Further processing              | Working groups      | In accordance with the decisions and methodological requirements (cf. Annex IV)                                                                                                                                                                             | October 2006–March 2007 |
| Preparation for consensus       | Coordinator         | Formal registration of the Guidelines project with the AWMF                                                                      | 2 February 2007   |
|                                 | Steering Group      | Working group communication, checks and feedback on methodological and clinical assessment of the evidence and the proposed recommendations                                                                                                                   | October 2006–March 2007 |
| 2nd consensus procedure, second meeting | Guidelines Group    | Part 1: Brief presentations:                                                 – Report on work status (Coordination/Coordinator)  – Presentation of current scientific medical knowledge (working group spokespersons) for the revised thematic complexes  
Part 2: Consensus-building procedure, structured coordination of the thematic complexes, women with increased risk, preinvasive lesions, adjuvant radiation therapy, management of locally advanced tumors, treatment of local recurrence, distant metastases, treatment – support – continuing care, quality indicators | 23–24 March 2007  |
| Consultation phase and final vote | Steering Group      | Collation of the texts, final editing, production of the full version, abridged version, algorithms, quality indicators and Methodology Report, request for external appraisal                                                                 | October 2007      |
|                                 | Guidelines Group    | Consenting process and decision by the authors in two-stage Delphi procedure, formal decision by professional society/organization                                                                                                                            | October–December 2007 |
| Publication                     | Coordinators        | Patients’ version                                                                                                                                                                                                                                           | Summer 2008       |
Appendix IV: Algorithm for Literature Review, Selection and Rating of Sources

<table>
<thead>
<tr>
<th>Literature search</th>
</tr>
</thead>
<tbody>
<tr>
<td>Search terms: (breast$ or mamma$) and (cancer or carcinom$ or neoplasm$) and (random$ or meta$analysis) + statement-specific</td>
</tr>
<tr>
<td>Period: January 2003 to June 2006</td>
</tr>
<tr>
<td>Databases: Ovid (Medline + all EBM Reviews)</td>
</tr>
<tr>
<td>Hits: 10,094, of which n=243</td>
</tr>
</tbody>
</table>

| Complete texts (DVD) sent to the Guidelines Group members |

| Revision in working groups for specific topics, strategy defined in accordance with the decision from the 1st consensus procedure |

<table>
<thead>
<tr>
<th>Strategy 1: Consensus-building in the Guidelines Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>– unchanged inclusion/rejection of Statements and recommendations from the 2004 version</td>
</tr>
<tr>
<td>– consensus statements/recommendations without grading (GCP)</td>
</tr>
</tbody>
</table>

| or |

<table>
<thead>
<tr>
<th>Strategy 2: Adaptation from reference guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>– unchanged inclusion of content and grading when formulating statements and recommendations, giving source</td>
</tr>
</tbody>
</table>

| or |

<table>
<thead>
<tr>
<th>Strategy 3: De novo processing of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Review of abstracts</td>
</tr>
<tr>
<td>– Addition of relevant publications/publications not found during the search/current publications if appropriate</td>
</tr>
<tr>
<td>– Rejection of irrelevant sources, giving reason</td>
</tr>
<tr>
<td>– Assessment of full versions in relation to methodological quality, applying a series of hierarchical steps:</td>
</tr>
<tr>
<td>1. Search for and assessment of publications with the best available study design (Level 1 strength of evidence according to the Oxford system, termination if questions can be answered sufficiently)</td>
</tr>
<tr>
<td>2. Search for and assessment of works with the next best available study design (Level 2 strength of evidence, Level 3 if applicable)</td>
</tr>
<tr>
<td>– Use of the most readily available sources for formulating and grading statements and recommendations</td>
</tr>
<tr>
<td>– Creation of evidence tables for priority issues</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Draft Guidelines:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statements and recommendations, linked with levels of evidence and grades of recommendation; background texts</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consensus conference:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discussion, resolution on recommendations, grades of recommendation</td>
</tr>
</tbody>
</table>
**Appendix V: Methodological Quality of the Empirical Evidence, Classification of Level of Evidence**


<table>
<thead>
<tr>
<th>Level</th>
<th>Studies on Treatment/Prevention/Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Systematic overview of randomized controlled trials (RCT)</td>
</tr>
<tr>
<td>1b</td>
<td>RCT (with narrow Confidence Interval)</td>
</tr>
<tr>
<td>1c</td>
<td>All-or-none principle</td>
</tr>
<tr>
<td>2a</td>
<td>Systematic overview of well planned cohort studies</td>
</tr>
<tr>
<td>2b</td>
<td>Well planned cohort study or a lower quality RCT</td>
</tr>
<tr>
<td>2c</td>
<td>Outcome studies, ecological studies</td>
</tr>
<tr>
<td>3a</td>
<td>Systematic overview of case control studies</td>
</tr>
<tr>
<td>3b</td>
<td>One case control study</td>
</tr>
<tr>
<td>4</td>
<td>Case series or cohort studies/case control studies of lower quality</td>
</tr>
<tr>
<td>5</td>
<td>Expert opinions without explicit critical appraisal of evidence or based on physiological models/bench research</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level</th>
<th>Studies on Diagnostic Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Systematic overview of Level 1 diagnostic studies or diagnostic decision-making rules, based on 1b studies, validated at several different clinical centers</td>
</tr>
<tr>
<td>1b</td>
<td>Validation cohort study with a good reference standard or diagnostic decision-making rule, validated at one center</td>
</tr>
<tr>
<td>1c</td>
<td>All-or-none principle (absolute SpPins and SnNouts)</td>
</tr>
<tr>
<td>2a</td>
<td>Systematic overview of Level 2 diagnostic studies</td>
</tr>
<tr>
<td>2b</td>
<td>Exploratory cohort study with a good reference standard</td>
</tr>
<tr>
<td>3a</td>
<td>Systematic overview of Level 3 diagnostic studies</td>
</tr>
<tr>
<td>3b</td>
<td>Non-consecutive study or studies without consistently applied reference standards</td>
</tr>
<tr>
<td>4</td>
<td>Case control study, poor or non-independent reference standards</td>
</tr>
<tr>
<td>5</td>
<td>Expert opinions without explicit critical appraisal of evidence or based on physiological models/bench research</td>
</tr>
</tbody>
</table>
Appendix VI: From Evidence to Recommendation: Classification of Grade of Recommendation


* As proposed by the Oxford Centre of Evidence-based Medicine
** Symbol used for assigning grades to recommendations in the Program for National Guidelines on Patient Care

The recommendations are formulated analogously if possible:
Strong recommendation: “shall”; recommendation: “should;” recommendation open: “can” (action option). Negative recommendations are expressed in words (“not”) using the same symbols.
Appendix VII

Form for Declaring Possible Conflicts of Interest

Apart from professional expertise, the development of guidelines for medical care demands a strict avoidance of commercial dependencies and other conflicts of interest which could exert a systematic effect on the contents of the Guidelines. The declarations made by the authors and participants in the consensus process are pivotal for the assessment of guideline quality but also for their general legitimization and credibility as perceived by the general public and policy-makers.

For this reason, we ask you to sign the declaration printed below.

The declaration of interest refers to financial and commercial interests as well as interests of the members themselves or of their personal or professional partners. The declarations are submitted to the Coordinator. The Guidelines Coordinator ensures that the information is treated as confidential. Please provide specific information on the following points:

1. work as an advisor or consultant for industrial companies, paid work as a member of a scientific advisory council of a pharmaceutical, biotechnology or medical technology company
2. financial remuneration received from pharmaceutical, biotechnology or medical technology companies or commercially oriented contract research institutes above and beyond an appropriate reimbursement of costs for the planning, performance and documentation of clinical or experimental studies
3. proprietary interest in medicinal products or medical devices (e.g. patent, copyright, sales license)
4. possession of shares in the company, share capital or funds of the pharmaceutical or biotechnology industry (information must be provided only for amounts > 50,000 euro per single title)
5. paid authorship or co-authorship of articles commissioned by pharmaceutical, biotechnology or medical technology companies in the past 5 years

Are there any conflicts of interest of a financial or other nature with third parties who may be interested in the contents of the Guidelines? yes no

If yes, please specify.

Place, Date, Signature
Appendix VIII

Electronic Appendix:  
“Statement-specific Literature Search“

Strategies, Search Terms and Hits for each Statement in the S3 Guidelines 2004 (Time Period: 2003-2006)

Available at  www-awmf-leitlinien.de, Directory No. 32/045
Appendix IX

Electronic Appendix: Methodology Report for the S3 Guidelines 2004

Available at www.awmf-leitlinien.de, Register No. 32/045