

Interdisciplinary Screening, Diagnosis, Therapy and Follow-up of Breast Cancer. Guideline of the DGGG and the DKG (S3-Level, AWMF Registry Number 032/045OL, December 2017) – Part 1 with Recommendations for the Screening, Diagnosis and Therapy of Breast Cancer

Interdisziplinäre Früherkennung, Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Leitlinie der DGGG und DKG (S3-Level, AWMF-Registernummer 032/045OL, Dezember 2017) – Teil 1 mit Empfehlungen zur Früherkennung, Diagnostik und Nachsorge des Mammakarzinoms



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Key words

breast cancer, guideline, screening, diagnosis, follow-up

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Bibliography

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ABSTRACT

Purpose The aim of this official guideline coordinated and published by the German Society for Gynecology and Obstetrics (DGGG) and the German Cancer Society (DKG) was to optimize the screening, diagnosis, therapy and follow-up care of breast cancer.

Methods The process of updating the S3 guideline dating from 2012 was based on the adaptation of identified source guidelines which were combined with reviews of evidence compiled using PICO (Patients/Interventions/Control/Outcome) questions and the results of a systematic search of literature databases and the selection and evaluation of the identified literature. The interdisciplinary working groups

took the identified materials as their starting point to develop recommendations and statements which were modified and graded in a structured consensus procedure.

Recommendations Part 1 of this short version of the guideline presents recommendations for the screening, diagnosis and follow-up care of breast cancer. The importance of mammography for screening is confirmed in this updated version of the guideline and forms the basis for all screening. In addition to the conventional methods used to diagnose breast cancer, computed tomography (CT) is recommended for staging in women with a higher risk of recurrence. The follow-up concept includes suggested intervals between physical, ultrasound and mammography examinations, additional high-tech diagnostic procedures, and the determination of tumor markers for the evaluation of metastatic disease.

ZUSAMMENFASSUNG

Ziele Das Ziel dieser offiziellen Leitlinie, die von der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe (DGGG) und der Deutschen Krebsgesellschaft (DKG) publiziert und koordiniert wurde, ist es, die Früherkennung, Diagnostik, Therapie und Nachsorge des Mammakarzinoms zu optimieren.

Methoden Der Aktualisierungsprozess der S3-Leitlinie aus 2012 basierte zum einen auf der Adaptation identifizierter Quelleitlinien und zum anderen auf Evidenzübersichten, die nach Entwicklung von PICO-(Patients/Interventions/Control/Outcome-)Fragen, systematischer Recherche in Literaturdatenbanken sowie Selektion und Bewertung der gefundenen Literatur angefertigt wurden. In den interdisziplinären Arbeitsgruppen wurden auf dieser Grundlage Vorschläge für Empfehlungen und Statements erarbeitet, die im Rahmen von strukturierten Konsensusverfahren modifiziert und graduiert wurden.

Empfehlungen Der Teil 1 dieser Kurzversion der Leitlinie zeigt Empfehlungen zur Früherkennung, Diagnostik und Nachsorge des Mammakarzinoms: Der Stellenwert des Mammografie-Screenings wird in der aktualisierten Leitlinienversion bestätigt und bildet damit die Grundlage der Früherkennung. Neben den konventionellen Methoden der Karzinomdiagnostik wird die Computertomografie (CT) zum Staging bei höherem Rückfallrisiko empfohlen. Die Nachsorgekonzepte beinhalten Untersuchungsintervalle für die körperliche Untersuchung, Ultraschall und Mammografie, während weiterführende Gerätediagnostik und Tumormarkerbestimmungen bei der metastasierten Erkrankung Anwendung finden.

I Guideline Information

Guidelines program of the DGGG, OEGGG and SGGG

Information on the guidelines program is available at the end of the guideline.

Citation format

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Guideline documents

The complete long version, a short version, and a summary of the conflicts of interest of all the authors are available in German on the AWMF homepage under:

<http://www.awmf.org/leitlinien/detail/ll/032-045OL.html> or www.leitlinienprogramm-onkologie.de

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The German Society for Gynecology and Obstetrics (DGGG) was the lead professional organization behind this guideline together with the German Cancer Society (DKG). The updated guideline presented here was supported by German Cancer Aid as part of their oncology guidelines program (OL program). The working groups consisted of members of the guideline steering group (► **Table 1**), specialists appointed by the participating professional societies and organizations (► **Table 2**), and specialists invited by the steering committee (► **Table 3**); they are the authors of this guideline. Only the mandate holders appointed by the participating professional societies and organizations were eligible to vote on a chapter-by-chapter basis during the voting process (consensus process) after they had disclosed and excluded any conflicts of interest. The guideline was compiled with the direct participation of four patient representatives.

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Abbreviations of the S3 Breast Cancer Guideline

| | |
|-------------------|---|
| ADH | atypical (intra) ductal hyperplasia |
| AI | aromatase inhibitor |
| AML | acute myeloid leukemia |
| APBI | accelerated partial breast irradiation |
| ASCO | American Society of Clinical Oncology |
| ADL | activities of daily living |
| AUC | area under the curve |
| BÄK | German Medical Association (Bundesärztekammer) |
| BCT | breast-conserving therapy |
| BI-RADS | breast imaging reporting and data system |
| BMI | body mass index |
| BPM | bilateral prophylactic mastectomy |
| BPSO | bilateral prophylactic salpingo-oophorectomy |
| BRCA1/2 | breast cancer-associated gene 1/2 |
| CAM | complementary and alternative methods |
| CAP | College of American Pathologists |
| CD | cognitive dysfunction |
| CDLT | complex/complete decongestive lymphatic therapy |
| CGA | comprehensive geriatric assessment |
| CHF | chronic heart failure |
| CIPN | chemotherapy-induced peripheral neuropathy |
| CISH | chromogenic in situ hybridization |
| CM | contrast media |
| CNB | core needle biopsy |
| CNS | central nervous system |
| CT | computed tomography |
| DCIS | ductal carcinoma in situ |
| DBT | digital breast tomosynthesis |
| DFS | disease-free survival |
| DGS | German Society for Senology (Deutsche Gesellschaft für Senologie) |
| DKG | German Cancer Society (Deutsche Krebsgesellschaft) |
| EC | expert consensus |
| ECE | extracapsular tumor extension |
| EIC | extensive intraductal component |
| ER | estrogen receptor |
| ESA | erythropoiesis-stimulating agents |
| ESAS | Edmonton Symptom Assessment Scale |
| ET | estrogen therapy |
| FEA | flat epithelial atypia |
| FISH | fluorescent in situ hybridization |
| FN | febrile neutropenia |
| FNA | fine needle aspiration |
| FNB | fine needle biopsy |
| G-CSF | granulocyte colony-stimulating factor |
| GnRH _a | gonadotropin-releasing hormone agonist |
| HADS | Hospital Anxiety and Depression Scale |
| HER2 | human epidermal growth factor receptor 2 |
| HT | hormone therapy |
| IARC | International Agency for Research on Cancer |
| IBC | inflammatory breast cancer |
| IHC | immunohistochemistry |
| IMRT | intensity-modulated radiotherapy |
| IORT | intraoperative radiation therapy |

| | |
|--------------------|---|
| IQWiG | Institute for Quality and Efficiency in Healthcare (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen) |
| ISH | in situ hybridization |
| ITC | intrathecal chemotherapy |
| LABC | locally advanced breast cancer |
| LCIS | lobular carcinoma in situ |
| LN | lymph node |
| GL | guideline |
| LoE | level of evidence |
| LVEF | left ventricular ejection fraction |
| LVI | lymphatic vessel invasion |
| Lsp | lumbar spine |
| MDS | myelodysplastic syndrome |
| MG | mammography |
| MRI | magnetic resonance imaging |
| MSP | mammography screening program |
| NAC | nipple-areolar complex |
| NACT | neoadjuvant chemotherapy |
| NCCN | National Comprehensive Cancer Network |
| NICE | National Institute for Health and Clinical Excellence |
| NNT | number needed to treat |
| NZGG | New Zealand Guidelines Group |
| OP | operation |
| OS | overall survival |
| PBI | partial breast irradiation |
| pCR | pathological complete remission |
| PET | positron emission tomography |
| PFS | progression-free survival |
| PI | proliferation index |
| PMRT | postoperative radiotherapy |
| PNP | polyneuropathy |
| POS | Palliative Outcome Scale |
| PR | progesterone receptor |
| PST | primary systemic therapy |
| QoL | quality of life |
| RCT | randomized controlled trial |
| RFA | radiofrequency ablation |
| ROR | risk of recurrence |
| RR | relative risk |
| RS | recurrence score |
| SABCS | San Antonio Breast Cancer Symposium |
| SBRT | stereotactic radiotherapy |
| SGB | German Social Security Code (Sozialgesetzbuch) |
| SIB | simultaneous integrated boost |
| SIGN | Scottish Intercollegiate Guidelines Network |
| SISH | silver-enhanced in situ hybridization |
| SLN | sentinel lymph node |
| SLNB | sentinel lymph node biopsy |
| SSM | skin-sparing mastectomy |
| TACE | transarterial chemoembolization |
| TILs | tumor-infiltrating lymphocytes |
| TNBC | triple-negative breast cancer |
| TNM classification | tumor-node-metastasis classification |
| UICC | Union for International Cancer Control |
| US | ultrasound |

| | |
|------|---------------------------|
| VMAT | volumetric arc therapy |
| WHO | World Health Organization |

II Guideline Application

Purpose and objectives

The most important reason to update the interdisciplinary guideline was the epidemiological impact of breast cancer and its related burden of disease, which are still high. This is the context in which the impact of new management concepts and their implementation needed to be evaluated.

Targeted areas of patient care

The guideline covers outpatient care, inpatient care and rehabilitative care.

Target patient groups

The recommendations of the guideline are aimed at all women and men who develop breast cancer as well as their relatives.

Target user groups/Target audience

The recommendations of the guideline are addressed to all physicians and professionals who provide screening services to women or care to patients with breast cancer (gynecologists, general practitioners, human geneticists, radiologists, pathologists, radio-oncologists, hemato-oncologists, psycho-oncologists, physiotherapists, nursing staff, etc.).

Adoption of the guideline and period of validity

This guideline is valid from December 1, 2017 through to November 30, 2022. Because of the contents of this guideline, this period of validity is only an estimate. It may be necessary to update the guideline because of new scientific evidence and knowledge as well as new developments in the methodology used for these guidelines. Moreover, it may be necessary to edit and revise the guideline's contents and to re-evaluate and revise the key statements and recommendations of the guidelines at regular intervals.

III Methodology

Basic principles

The method used to prepare this guideline was determined by the class to which this guideline is assigned. The AWMF Guidance Manual (version 1.0) has set out the respective rules and regulations for the different classes of guidelines. Guidelines are differentiated into lowest (S1), intermediate (S2) and highest class (S3). The lowest class is defined as a set of recommendations for action compiled by a non-representative group of experts. In 2004, the S2 class was subdivided into two subclasses: a systematic evidence-based subclass (S2e) and a structural consensus-based subclass (S2k). The highest class (S3) combines both approaches. This guideline is classified as: S3.

Grading of evidence

This guideline used the 2009 version of the system of the Oxford Centre for Evidence-based Medicine (levels 1–5) to classify the risk of bias in identified studies. This system classifies studies according to various clinical questions (benefit of therapy, prognostic value, diagnostic validity). For more detailed information, abbreviations and notes, see: <http://www.cebm.net/?o=1025>.

Grading of recommendations

While the classification of the quality of the evidence (strength of evidence) serves as an indication of the robustness of the published data and therefore expresses the extent of certainty/uncertainty about the data, the classification of the level of recommendation reflects the results of weighing up the desirable and adverse consequences of alternative approaches. This guideline shows the level of the evidence for the underlying studies as well as the strength of the recommendation (level of recommendation) for all evidence-based Statements and Recommendations. This guideline differentiates between three levels of recommendation (► **Table 4**). The levels reflect the strength of the respective recommendation and are also mirrored in the terms used when formulating the recommendation.

► **Table 4** Grading of recommendations.

| Level of recommendation | Description | Terms used |
|-------------------------|---------------------------------------|------------|
| A | strong recommendation, highly binding | must |
| B | recommendation, moderately binding | should |
| 0 | open recommendation, not binding | may |

Statements

Statements are expositions or explanations of specific facts, circumstances or problems with no direct recommendations for action. Statements are adopted after a formal consensus process using the same approach as that used when formulating recommendations and can be based either on trial results or expert opinions.

Expert consensus

As the expression implies, this term refers to consensus decisions taken specifically with regard to Recommendations/Statements

without a previous systematic search of the literature (S2k) or when evidence is lacking (S2e/S3). The term “Expert Consensus” (EC) used here is synonymous with terms such as “Good Clinical Practice” (GCP) or “Clinical Consensus Point” used in other guidelines. The level of recommendation is graded as previously described in the Chapter “Grading of recommendations”, but the grading is only presented semantically (“must”/“must not” or “should”/“should not” or “may”/“may not”) without the use of symbols.

Guideline report

To edit and update the various topic areas, an adaptation of existing guidelines was planned for around 80% of Statements and Recommendations in accordance with the AWMF Guidance Manual. To do this, a systematic search was carried out for source guidelines developed specifically for women with breast cancer and published after 2013. Findings were compared with the IQWiG guideline report No. 224 (Systematische Leitlinienrecherche – und Bewertung sowie Extraktion relevanter Recommendations für das DMP Brustkrebs [Systematic guideline search and appraisal as well as extraction of relevant recommendations for a DMP for breast cancer]). A further inclusion criterion was compliance with methodological standards. Guidelines were included if they complied with at least 50% of Domain 3 (Rigour of Development) of the AGREE II instrument. A corresponding search and evidence assessment was specified in accordance with AWMF guidelines (systematic search, selection, compilation of evidence tables) for those recommendations which could not be adapted or had to be newly created. For Recommendations and Statements which had to be newly developed, the formulation of corresponding key questions and the systematic search were done based on aggregated sources of evidence (meta-analyses, systematic reviews, etc.), in specific cases also on individual publications. The appropriate list of titles and abstracts up until the identification of the full text were selected by two independent raters. After the search and selection processes were completed, the necessary evidence tables which formed the basis for the consensus conferences were compiled by the Methods group (financial support was provided and allowed a researcher to be specifically hired for this purpose). The classification system of the Oxford Centre for Evidence-based Medicine (version 2009) was used to grade the evidence. To update this guideline, Recommendations and Statements were adopted and levels of recommendation (► **Table 4**) was determined during two structured consensus conferences which were preceded by a preliminary online ballot.

The guideline report provides an overview of the search strategies and selection processes used to select the literature and to formulate and grade the recommendations.

IV Guideline

1 Early detection, mammography screening

| No. | Recommendations/Statements | EG | LoE | Sources |
|------|---|----|-----|---------|
| 3.8. | a) The most important population-related risk factor for developing breast cancer in both women and men is advancing age. | A | 2a | [1–3] |
| | b) It is very rare for men to develop breast cancer. Special breast cancer imaging and screening methods must not be recommended to asymptomatic men. A diagnosis is made after the patient presents with clinical symptoms which are then investigated using mammography and ultrasound. The clinical workup must be carried out in accordance with the recommendations for women. (See Chapter: Breast Cancer in Men.) | EC | | |
| 3.9. | <p>a) Early detection of breast cancer is an interdisciplinary task. It requires a quality-assured interdisciplinary combination of clinical examinations, instrument-based diagnostic procedures, histological evaluations and pathomorphological evaluations.</p> <p>b) The chain of care requires complex, quality-assured medical documentation to be able to bring together and coordinate all aspects of quality management.</p> <p>c) Every cancer screening program must be continually evaluated with regard to relevant outcomes (e.g., incidence, mortality, morbidity and patient-related outcomes) and risks (e.g., false-positive and false-negative findings, over-diagnosis). The process data of the screening programs and the breast centers and the data from the population-related cancer registries of the various German federal states are used for this after the respective data have been compared and adjusted. If possible, cancer registries must continuously provide differentiated data for their respective federal state and screening units from the start of the national screening program for Germany in 2005. Patient lists (e.g., about interval cancers, contralateral findings or local recurrences) form part of the continuous re-evaluation of data. It is important to ensure that data evaluation is completely independent.</p> <p>d) To ensure that patients receive the best possible treatment, further therapy to treat breast cancers detected during screening must be carried out in certified breast centers. Good communication between the screening center and certified breast center with careful data collection and registration is needed to ensure a high quality of care.</p> | EC | | |

1.1 Participatory decision-making

| No. | Recommendations/Statements | EG | LoE | Sources |
|-------|--|----|-----|---------|
| 3.10. | <p>a) Screening for the detection of breast cancer may be associated with physical and psychological stress. It is important to take account of this by offering detailed information and using an effective communication strategy.</p> <p>b) The information given to patients during breast cancer screening must not just consist of pre-formulated texts and statements; patients also require medical counselling which takes account of the patient's preferences, worries and fears and permits a form of participatory decision-making. For mammography screening the information provided to patients must be provided primarily in writing; on the invitation letter for screening, patients must additionally be informed that they have the option to request a consultation with a doctor.</p> | EC | | |

1.2 Mammography screening

| No. | Recommendations/Statements | EG | LoE | Sources |
|-------|---|-----|-----|-----------------|
| 3.11. | a) Mammography is the only method associated with a verified reduction in breast cancer mortality rates. | ST | 1a | [1–9] |
| | b) It is recommended that women between the ages of 50 and 69 participate in the (German) national mammography screening program. Women aged 70 and above should be offered screening which takes account of their individual risk profile and health status as well as whether they have a life expectancy of more than 10 years. | A/B | 1a | [1, 2, 7, 9–13] |
| | c) The reduction of breast cancer mortality has also been proven for women between the ages of 40 and 49 years and outweighs any risks arising from exposure to radiation. The reduction in mortality is, however, lower than that reported for women between the ages of 50 and 69 years and, in relative terms, there are more false-positive and false-negative findings in the younger group. The decision to have screening or not should therefore be based on an individual risk analysis, the weighing up of benefits and risk and should take the woman's preferences and objections into account. | B | 1b | [1, 2, 8, 14] |
| | d) The quality of the structures, processes and results for curative mammography must be the equivalent of those described above. | EC | | |
| | e) If the mammography findings are category 0, III, IV or V (unclear or suspicious findings), additional workup procedures should be carried out within one week to minimize the psychological stress for the affected woman. | EC | | |

1.3 Breast cancer screening methods

| No. | Recommendations/Statements | EG | LoE | Sources |
|-------|---|----|-----|---------|
| 3.12. | a) As part of the statutory screening for breast cancer, women must be offered medical counselling which provides them with information about potential risk factors and reviews their medical history and familial risks. | EC | | |
| | b) Breast self-exams are not adequate to reduce breast cancer mortality if they are the only method used for screening, even if women carry out their breast exams regularly and have received training to perform the exam properly. | ST | 1a | [1, 2] |
| | c) Women should receive qualified information which will encourage them to familiarize themselves with normal changes of their own bodies. These include the appearance of the breast and how it should feel. This should help women notice any changes themselves. | EC | | |
| | d) Clinical breast examinations (i.e., the inspection and palpation of the breast and the assessment of lymph drainage) should be offered to women from the age of 30 years as part of statutory breast cancer screening. Clinical examination of the breast and axilla is not recommended as the only method of breast cancer screening. | EC | | |
| | e) The systematic use of ultrasound is not recommended as the only method of breast cancer screening. | EC | | |

Sonography

There are no studies on the use of sonography instead of mammography as the only method for breast cancer screening (For details, see the long version of this guideline [available in German]).

1.4 Additional diagnostic imaging procedures to screen breasts with high mammographic density

| No. | Recommendations/Statements | EG | LoE | Sources |
|-------|---|-----|-----|------------------|
| 3.13. | a) Increased mammographic density is an independent moderate risk factor for breast cancer. Mammographic density and mammography sensitivity are negatively correlated. | B | 3a | [1, 15–17] |
| | b) Evidence on the use of additional imaging procedures is limited. With the exception of high-risk situations, ultrasound currently appears to be a suitable method to supplement mammography. Sonography can increase density-related sensitivity; however, there is no evidence that it reduces mortality. Sonography used for screening purposes is associated with a higher rate of biopsies than the (German) national mammography screening program. | B | 3a | [1, 8, 9, 18–21] |
| | c) Tomosynthesis can increase sensitivity. Trialing tomosynthesis in a quality-assured program should be considered. | B/0 | 1b | [22–24] |

1.5 Women with increased risk of breast cancer, hereditary breast cancer

Around 30% of all women with breast cancer in Germany have a familial risk of breast cancer and meet the inclusion criteria for genetic testing which were established and validated by the German Consortium for Hereditary Breast and Ovarian Cancer (see Statement 3.14) [25]. These are based on a mutation detection rate of at least 10% [26].

| No. | Recommendations/Statements | EG | LoE | Sources |
|-------|---|---|-----|---------|
| 3.14. | Genetic testing should be offered if women have a familial or individual risk with an at least 10% probability of mutation. This applies if, in one line of the family, <ul style="list-style-type: none"> ▪ at least 3 women developed breast cancer ▪ at least 2 women developed breast cancer, one of whom was aged less than 51 years ▪ at least 1 woman developed breast cancer and 1 woman developed ovarian cancer ▪ at least 2 women developed ovarian cancer ▪ at least 1 woman developed breast cancer and ovarian cancer ▪ at least 1 woman aged 35 years or younger developed breast cancer ▪ at least 1 woman aged 50 years or less developed bilateral breast cancer ▪ at least 1 man developed breast cancer and 1 woman developed breast cancer or ovarian cancer. Patients should be given a suitable period for reflection before carrying out diagnostic procedures. | B | | [27] |
| | | EC/2a for the probability of a mutation | | |

Continued next page

| No. | Recommendations/Statements | EG | LoE | Sources |
|-------|---|---|-----|-------------------|
| 3.15. | <p>The consultation must permit participatory decision-making. To ensure they can adequately participate in decision-making, women must receive extensive and detailed information and their preferences must be identified and taken into account in the decision-making process. Evidence-based support can improve the decisions taken by affected women.</p> <p>The following topics must be included in the risk consultation prior to genetic testing:</p> <ul style="list-style-type: none"> ▪ the probability of a mutation ▪ the risk of developing disease if findings are positive ▪ the benefit and harm of preventive and therapeutic options including the option to not do anything ▪ the probability of false-negative findings ▪ the importance of genetic testing for other family members <p>After obtaining genetic findings, the patient's understanding of the following topics must be expanded during the risk consultation before she is offered preventive measures:</p> <ul style="list-style-type: none"> ▪ the risk of developing disease depends on the genetic findings, age and co-morbidities (natural course) ▪ the probability of false-positive and false-negative test results with intensified screening ▪ the benefit of preventive options (intensified screening, prophylactic surgery, drug therapies) for reducing mortality and morbidity and improving quality of life ▪ the risks of preventive options, including long-term sequelae ▪ the concurrent risks, prognosis and treatability in the event that the patient develops disease without undertaking preventive measures, based on the specific manifestation of the genetically defined tumor subtype ▪ the possible risk of associated tumors ▪ the patient should be offered psycho-oncologic counselling | EC/1a for improvements in decision-making | | [28 – 33] |
| 3.16. | <p>a) BRCA1-associated breast cancers often have a characteristic histopathological and immunohistochemical phenotype:</p> <ul style="list-style-type: none"> ▪ invasive carcinoma with medullary features ▪ G3 morphology ▪ estrogen receptor, progesterone receptor and HER2 negativity (triple negative) <p>b) If these characteristics are present, the pathologist should inform the patient that they could have a hereditary propensity to disease.</p> | 2a for histopathological characteristics | | |
| 3.17. | <ul style="list-style-type: none"> ▪ Patients with a pathogenic BRCA1/2 mutation (IARC class 4/5) should and patients with a residual lifetime risk of $\geq 30\%$ can undergo intensified screening including MRI only following a transparent quality assurance process and after appropriate evaluation. ▪ Additional mammography screening after the age of 40 should be carried out as part of a transparent quality assurance process and after appropriate evaluation. | EC | | |
| 3.18. | <p>a)</p> <ul style="list-style-type: none"> ▪ The surgical therapy of BRCA-associated breast cancer corresponds to the guideline recommendations for sporadic breast cancer. ▪ Mastectomy offers no survival benefits compared to breast-conserving therapy. ▪ The drug therapy used to treat BRCA-associated breast cancer corresponds to the guideline recommendations for sporadic breast cancer. <p>b) There are some indications that platinum-based chemotherapy can result in a better response to treatment compared to standard chemotherapy.</p> | | | [34 – 39] |
| 3.19. | <ul style="list-style-type: none"> ▪ Healthy women with a BRCA1 or BRCA2 mutation have an increased lifelong risk of developing breast cancer. ▪ In healthy women with a pathogenic BRCA1 or BRCA2 gene mutation, bilateral prophylactic mastectomy results in a reduction in the incidence of breast cancer. There is not yet sufficient evidence for a reduction in breast cancer-specific mortality or overall mortality following bilateral prophylactic mastectomy. ▪ Every individual decision for or against bilateral prophylactic mastectomy requires in every case that the patient is given detailed information with multidisciplinary counselling about the potential benefits and disadvantages of such a procedure and must include the consideration of potential alternatives. | 2a | | [26, 40 – 48] |
| 3.20. | <ul style="list-style-type: none"> ▪ Women with a pathogenic BRCA1 or BRCA2 mutation have an increased lifelong risk of ovarian cancer, fallopian tube cancer and/or primary peritoneal cancer. ▪ In healthy women with a pathogenic BRCA1 or BRCA2 gene mutation, prophylactic adnexectomy reduces the incidence of ovarian cancer and reduces overall mortality. Prophylactic bilateral salpingo-oophorectomy must therefore be discussed and recommended on a case-by-case basis and as part of extensive multidisciplinary counselling about the potential benefits and disadvantages of such a procedure and must take the lack of effective screening options into account. | 2a | | [40, 44, 49 – 52] |

Continued next page

| No. | Recommendations/Statements | EG | LoE | Sources |
|-------|--|----|-----|--------------|
| 3.21. | <ul style="list-style-type: none"> Women with a pathogenic BRCA1 or BRCA2 gene mutation who have already developed breast cancer have an increased risk of developing contralateral breast cancer. The risk also depends on the affected gene and on the age at which the woman first developed disease and must be taken into account during counselling. In women with a pathogenic BRCA1 or BRCA2 gene mutation, contralateral, secondary prophylactic mastectomy reduces the risk of contralateral cancer. When considering whether contralateral secondary prophylactic mastectomy is indicated, the prognosis for the primary tumor must be taken into account. In patients with a pathogenic BRCA1 or BRCA2 gene mutation, prophylactic adnexectomy reduces breast cancer-specific mortality and increases overall survival. | 2a | | [27, 53–60] |
| 3.22. | The benefit of prophylactic or secondary prophylactic contralateral mastectomy has not been proven for women with verified BRCA1 or BRCA2 gene mutations. | 2a | | [55, 61, 62] |
| 3.23. | <p>Healthy women, women who have developed disease, and men with an increased risk of developing disease should be encouraged to contact cancer self-help organizations to obtain further information if required and to encourage them to insist on their right of self-determination.</p> <p>They should be supported:</p> <ul style="list-style-type: none"> if there is a suspicion of hereditary propensity to disease as they consider genetic testing before undertaking prophylactic measures <p>Appropriate printed information material should be available.</p> | EC | | |

2 Diagnostic Workup of Breast Cancer

| No. | Recommendations/Statements | EG | LoE | Sources |
|------|---|----|-----|---------|
| 4.1. | <p>a) The basic examination consists of:</p> <ul style="list-style-type: none"> taking the patient's history and familial history together with a clinical breast examination consisting of inspection, palpation of the breast and the lymphatic drainage areas mammography ultrasound <p>If the findings of the clinical breast examination are suspicious, the diagnostic workup must include suitable imaging techniques and, if required, a histological examination.</p> | EC | | |
| | b) The effects of endogenous and exogenous hormones should be taken into account when carrying out diagnostic procedures and evaluating the findings of diagnostic procedures. | B | 2b | [63–66] |

2.1 Imaging methods

| No. | Recommendations/Statements | EG | LoE | Sources |
|------|--|----|-----|-----------------|
| 4.2. | <p>a) If the findings are suspicious, women aged 40 and above must have a mammography.</p> <p>b) In women younger than 40 years of age, mammography must be used if the suspicion of malignancy based on clinical examination, ultrasound and percutaneous biopsy (when indicated) cannot be ruled out with sufficient certainty.</p> <p>c) Suitable further imaging procedures must be considered in addition to mammography.</p> <p>d) Bilateral mammography must be carried out prior to starting treatment if malignancy is confirmed.</p> | EC | | |
| | e) Ultrasound must be carried out if the mammographic density is high or assessment based on mammography provides only limited results. | A | 1b | [19, 20, 67–73] |
| 4.3. | a) Sonography must be used to further evaluate clinically unclear findings and to assess category 0, III, IV and V findings detected with mammography or MRI. | | | |
| | b) The goal in standard breast sonography is a systematic and reproducible examination of the breast and axilla. Findings must be reproducibly documented. | EC | | |
| | c) The quality of structures, processes and outcomes should also be verified for breast sonography. | EC | | |
| 4.4. | a) In a diagnostic setting, MRI with CM should be limited to those cases where a lesion cannot be adequately identified using conventional diagnostic methods (MG, US) or percutaneous biopsy. | B | 2a | [74] |
| | b) Carrying out MRI with CM prior to treatment to examine an already diagnosed breast cancer is only justified in specific exceptional cases. The decision that MRI with CM is indicated should be made during a multidisciplinary tumor conference. | B | 1a | [75–77] |
| | c) MRI with CM of the breast must only be carried out if an MRI-supported intervention can be carried out in the same center or it is possible to access MRI-supported interventions, and the histological findings of the MRI intervention are presented to an interdisciplinary conference to document the outcome quality. | EC | | |

2.2 Diagnostic confirmation

| No. | Recommendations/Statements | EG | LoE | Sources |
|------|---|----|-----|----------|
| 4.5. | a) The specimens for the histological workup must be obtained by punch biopsy, vacuum biopsy or, in exceptional cases, by open excision biopsy. | A | 3a | [73, 78] |
| | b) Imaging procedures which clearly show the lesion must be used to guide the biopsy. The choice of biopsy method must take the diagnostic certainty and the risk of side effects into account. The investigator must use suitable measures to ensure that the biopsy site can be found again (e.g. clip placement). | EC | | |
| | c) If a sonographic correlate has been identified for a lesion detected primarily using mammography or MRI, sampling must be carried out with ultrasound-guided punch biopsy. | EC | | |
| | d) Stereotactic vacuum biopsy must be used if micro-calcifications are present without accompanying focal findings. | A | 2b | [79] |
| | e) Vacuum biopsy should be used for mammography-guided or MRI-guided tissue biopsy. | EC | | |
| | f) The correlation between the histological findings and the clinically suspicious findings must be reviewed and documented for all biopsies. | EC | | |
| | g) If the histopathological results of a category 4 or 5 lesion on imaging which was representatively sampled are benign, an appropriate control imaging procedure should be carried out after 6 months. | EC | | |
| | h) Punch biopsy should primarily be used for the fine-tissue clarification of lymph nodes classified as suspicious on imaging. | A | 2a | [80–83] |
| | i) After the target tissue has been clearly identified, ≥ 3 samples should be taken during interventional, preferably ultrasound-guided punch biopsy, using a punch biopsy needle with a diameter of ≤ 14 G. | B | 3b | [84–86] |
| | j) In vacuum biopsies, ≥ 12 samples should be taken using a 10-G needle. If other needle diameters (between 8 G and 11 G) are used, the biopsied specimens obtained should result in an equivalent sample volume. | EC | | |
| 4.6. | Primary open diagnostic excision biopsy must only be carried out in exceptional cases. | A | 3a | [79, 87] |
| | Pre-operative or intraoperative marking must be carried out using a method which can clearly show the lesion, particularly when investigating non-palpable lesions. Evidence of adequate resection must be provided intraoperatively by specimen radiography or specimen ultrasound. If MRI-guided marking is carried out, then a control MR must be carried out within 6 months if the benign lesion was histologically unspecific. | EC | | |
| | When carrying out preoperative wire marking of a non-palpable finding, the wire must be located in the focal area and extend less than 1 cm beyond this area. If the wire does not penetrate the focal area, the distance between the wire and the edge of the focal area must be ≤ 1 cm. In patients with extensive focal findings, it may be useful to place several markings around the surgically relevant target volume. | EC | | |
| | The surgically resected material must be clearly topographically marked and sent to the pathologist without incising the sampled tissue material. | EC | | |
| 4.7. | Staging (of the lungs, liver, and skeleton) should be carried out in high-risk patients newly diagnosed with UICC stage II (and higher) breast cancer and in patients newly diagnosed with stage III or IV breast cancer without symptoms of metastasis. | B | 2a | [88] |
| | Staging based on imaging must be carried out in patients newly diagnosed with breast cancer and a clinical suspicion of metastasis. | A | 2a | [88] |
| | Full-body staging should only be carried out in women with a high risk of metastasis (N+, >T2) and/or aggressive tumor biology (e.g.: Her2+, triple-negative), clinical signs, symptoms, and if systemic chemotherapy/antibody therapy is planned. Full-body staging should be done using a thoracic-abdominal CT scan and skeletal scintigraphy. | EC | | |

2.3 Diagnosis of local/loco-regional recurrence

| No. | Recommendations/ Statements | EG | LoE | Sources |
|------|---|-----|------------------------|---------|
| 5.1. | Patients should be informed about the clinical signs of recurrence. | B | Adapted from guideline | [89] |
| 5.2. | In asymptomatic patients, no other diagnostic methods should be carried out in addition to the standard methods recommended for follow-up. | B | Adapted from guideline | [89] |
| 5.3. | As with primary breast cancer, imaging to clarify a suspicion of local/loco-regional recurrence must consist of mammography and breast ultrasound. (A) Breast MRI should be used if, after considering the patient's level of risk, it is not possible to make a sufficiently certain diagnosis using other methods. (B) | A/B | Adapted from guideline | [90] |
| 5.4. | Breast ultrasound and minimally invasive biopsy methods are suitable methods for the primary histological clarification of loco-regional recurrence. | B | Adapted from guideline | [73] |
| 5.5. | If there is a suspicion of distant metastasis, suitable diagnostic methods can be used to exclude the suspicion. Staging based on imaging must be carried out in patients newly diagnosed with breast cancer and a clinical suspicion of metastasis. Procedures used for staging must include contrast-enhanced CT (of the thorax, abdomen and pelvis) and a bone scan. | A | Adapted from guideline | [88] |
| 5.6. | PET-CT should only be used if the use of other methods has led to a strong suspicion of distant metastasis in symptomatic patients and this metastasis cannot be reliably confirmed or excluded. | B | Adapted from guideline | [88] |

3 Follow-up and Long-term Care

Follow-up in the narrow sense of the word consists of structured examinations for loco-regional or intramammary recurrence and contralateral breast cancer, examinations for distant metastasis, investigations which are part of long-term therapy and the diagnosis and treatment of sequelae and side effects. Because of the wide range of therapy regimens, follow-up starts immediately after concluding primary loco-regional therapy [91].

Because different patients have very different risk constellations, a follow-up period of 5 years is not sufficient. This means that even without being directly based on trial data, the follow-up period has been expanded beyond the current period of 5 years to a period of 10 years [92]. It should be noted that therapy must be monitored for at least 10 years.

| No. | Recommendations/ Statements | EG | LoE | Sources |
|-------|---|----|------------------------------|----------------|
| 6.35. | The follow-up of patients with breast cancer starts once primary loco-regional treatment has been concluded. Follow-up consists of taking the patient's medical history, a physical examination, medical counselling, care and guidance as well as diagnostic imaging procedures to detect local or loco-regional recurrence or contralateral breast cancer. If any of the findings are suspicious, follow-up must take a system-oriented approach. | | EC Adapted from guideline | [91, 93 – 100] |
| 6.36. | If required, specialized oncologists and other medical professionals, for example psycho-oncologists, physiotherapists, lymphologists, specialized oncology nurses, breast care nurses, etc., should also be involved in the individual follow-up of breast cancer patients. Depending on the individual requirements of patients, patients should also receive information about further opportunities for counselling and care including information on available self-help support groups. | | EC Adapted from guideline | [101, 102] |

3.1 Examination for loco-regional/intramammary recurrence or contralateral breast cancer

Local/loco-regional recurrence after mastectomy and/or axillary dissection is usually diagnosed by clinical examination. Palpation of the thoracic wall and the lymph drainage areas is therefore a key aspect in all follow-up examinations [103]. The majority of local/loco-regional or intramammary recurrences in affected patients who underwent breast-conserving surgery can be treated curatively.

| No. | Recommendations/ Statements | EG | LoE | Sources |
|-------|--|----|-----|------------|
| 6.37. | a) Diagnostic imaging procedures for the detection of local and loco-regional recurrence or contralateral cancer should include an annual mammography and a quality-assured ultrasound examination. | B | 2c | [104, 105] |
| 6.38. | b) The addition of quality-assured ultrasound examinations as part of standard follow-up will increase the number of patients who need further investigations and the biopsy rate. The majority of patients (82%) reported that the increased attention and the associated higher security had a psychologically positive impact, with only a few patients (<6%) reporting additional psychological stress due to fear and uncertainty. Ultrasound examinations should therefore only be carried out in addition to mammography. | | | |

Men with breast cancer

| No. | Recommendations/ Statements | EG | LoE | Sources |
|-------|---|----|-----|---------|
| 6.39. | Men with breast cancer must be examined annually using diagnostic imaging procedures in the same way as women with breast cancer, particularly as men have a higher risk of contralateral cancer. | EC | | |

3.2 Examination for metastasis

The 3 most common sites of metastasis for women with breast cancer are the lungs, liver and bones. Depending on the patient's staging, diagnostic procedures are indicated during primary therapy to determine whether metastasis is present. Current prospective studies have shown that intensive follow-up examinations at regular established intervals which include chest X-rays of the lungs, bone scans, ultrasound of the upper abdomen, tumor marker determination and diagnostic CT scans do not provide any additional survival benefit to asymptomatic patients [96, 98].

| No. | Recommendations/ Statements | EG | LoE | Sources |
|-------|--|----|-----|--------------------|
| 6.40. | Intensified diagnostic methods such as chest X-rays, bone scans, CT, PET or MRI and including full blood count tests, serum biochemistry and the determination of tumor markers are used to diagnose metastasis; they are not part of standard follow-up and are only indicated if there are clinical anomalies. | A | 1a | [93, 102, 106–108] |

3.3 Diagnosis and treatment of side effects and sequelae from primary and long-term therapy

Follow-up examinations are also used to control and record the success of primary therapy. The overriding principle is that they should contribute to dispelling the patient's fear of disease recurrence. The 10-year probability of survival for patients with favorable tumor features (pT1 N0 M0) is more than 90%.

The sequelae and toxicities from local therapy such as surgery, radiotherapy and systemic therapies such as chemotherapy, targeted therapy, endocrine therapy, osteo-oncologic therapy or complementary and alternative methods (CAM) can be detected and treated, if necessary. More and more breast cancer patients are treated curatively, with therapy administered over longer periods. This has meant that care and support during long-term therapy and the treatment of side effects or late sequelae of therapy are becoming increasingly important. It is important to differentiate between early and late sequelae, between local and systemic side effects and between the long-term side effects of concluded therapies and the acute side effects of current therapies. The affected patient should be informed about therapy-specific short and long-term side effects and possible late sequelae and should be given recommendations about targeted diagnostic and therapeutic treatments or receive treatment where necessary.

The primary local side effects of therapy include edema, somatosensory disorders, chest or breast pain after breast-conserving therapy, limited mobility, and lymphedema [109]. The sequelae (acute and late toxicity) of systemic drug therapies can include myelotoxicity, hepatotoxicity, alopecia, nephrotoxicity, ototoxicity, pulmonary toxicity, cardiotoxicity, infections, thromboembolic events as well as osteoporosis, sterility, climacteric syndrome, secondary cancers, cognitive disorders and more besides [108].

Lymphedema

Secondary lymphedema of the arm following breast cancer is a common problem after axillary dissection, with a reported incidence of 20–30% [91, 92]. However, because sentinel lymph node excision is now routinely carried out, lymphedema has become much less common now. Morbidity after treatment can include functional limitations, weight gain and associated impairments affecting the patient's quality of life. Diagnosis and treatment of secondary lymphedema should follow the recommendations given in the interdisciplinary S2k guideline [110].

| No. | Recommendations/ Statements | EG | LoE | Sources |
|-------|---|----|-----|---------------|
| 6.41. | All patients who undergo axillary lymphadenectomy must be informed about how to recognize the signs of postoperative lymphedema and the prophylactic options and treatment of postoperative lymphedema. | A | 1b | [73, 111–120] |

Cardiotoxicity

Anthracyclines and trastuzumab may promote cardiotoxicity [121]. The risk of cardiotoxicity is significantly increased if both substance

classes are combined and administered simultaneously, and this approach is therefore not recommended. Predisposing factors include age, obesity, preexisting congestive heart failure, arterial hypertension, diabetes mellitus, status post myocarditis or myocardial infarction, and left-sided radiation therapy. In the development of acute or chronic myopathies with heart failure, it is important to differentiate between the acute and the sub-acute non-dose-related early forms, the chronic form (within one year) and the late form. Cardiotoxicity can range from decreased left ventricular ejection fraction (LVEF) to clinically relevant chronic heart failure (CHF). Any general decrease in performance or reduction in physical resilience in affected patients should be urgently investigated. It is important to detect any cardiac damage as early as possible to initiate appropriate supportive measures such as targeted therapy to treat heart failure, improve the patient's quality of life and avoid any deterioration of the patient's prognosis [122–124].

Leukemia

Leukemia is the most common chemotherapy-induced secondary malignancy. The highest risk for secondary leukemia is in the first ten years. The most common type of leukemia is acute myeloid leukemia following the use of anthracyclines [125, 126].

Climacteric syndrome

Chemotherapy and endocrine systemic therapy can induce climacteric syndrome in premenopausal/perimenopausal patients or intensify the symptoms in postmenopausal patients [127]. How patients experience symptoms is subjective and can differ considerably; it may also depend on the time of onset and the duration of amenorrhea as well as the duration of therapy, particularly of endocrine therapy. Treatment of the symptoms of climacteric syndrome depends on the symptoms experienced. Hormone therapy is contraindicated after breast cancer. Hormone therapy is therefore only prescribed in very exceptional cases, and is discussed with great reluctance and only considered when patients report a serious impairment of their quality of life. According to the data from current studies, hormone therapy is contraindicated in hormone receptor-positive breast cancer patients [128].

Thromboembolic events

Thromboembolic events which take the form of paraneoplastic syndrome can occur during primary therapy. They are often an indication of more extensive tumors or metastasis [129]. Thromboembolic events can occur in patients receiving systemic endocrine therapy, particularly during or after long-term therapy [130]. The diagnosis and therapy of thrombosis and arterial lung embolism and the appropriate prophylactic measures are described in the interdisciplinary S2 and S3 guidelines of other professional societies (AWMF 065/002).

Osteoporosis

Estrogens are among the most important factors regulating bone metabolism. Physiologically, bone mass reduction starts with the commencement of menopause. Therapy may reinforce this process, either because chemotherapy or systemic endocrine therapy triggers premature menopause in premenopausal patients or because the use of aromatase inhibitors in postmenopausal patients

intensifies the process of bone reduction. Patients with a significantly higher risk of developing osteoporosis or who already known to have osteoporosis should be recommended the appropriate medication as outlined in the S3 guideline of the DVO (German Osteology Organization); patients who have not yet developed osteoporosis should be informed about appropriate behavioral measures such as physical exercise, modifications of their diet, and substitution with Vitamin D and possibly calcium, if needed [108, 131–133]. Patients should receive detailed information about the options for osteo-oncologic medication. It is important in all cases to determine the risk of fractures early on by carrying out a DEXA scan to measure bone density before and during any potentially necessary anti-hormone therapy or scheduled chemotherapy.

Fatigue

Patients with chronic fatigue syndrome after treatment for breast cancer must be given information about physical exercise strategies and psychosocial support [134, 135].

Reproduction

Premenopausal breast cancer patients wanting to have children should be informed before and after the successful conclusion of primary breast cancer therapy about the options of preserving fertility and having children [136]. To date, no study has confirmed the originally expected increase in the risk of recurrence arising from endocrine changes occurring during pregnancy [137]. The survival benefit postulated in some studies for patients who became pregnant some years after successful treatment for breast cancer is probably due to a “healthy mother effect” [136, 138]. The basic principle is that any decision for or against having children after concluding primary therapy for breast cancer should be based on personal lifestyle considerations and less on vague medical hypotheses. If preventing pregnancy is indicated, either for medical reasons, for example in the context of endocrine therapy, or because of personal lifestyle choices, contraception should generally not consist of hormonal birth control. The risks associated with hormonal contraception must be weighed up carefully.

3.4 Frequency of follow-up

A follow-up period of at least ten years is necessary because of the tumor biology of breast cancer [91, 139]. Therapy monitoring must be continued for at least 10 years.

| No. | Recommendations/ Statements | EG | LoE | Sources |
|-------|---|----|-----|---------|
| 6.43. | In the first 3 years after concluding primary local therapy, patients should have a follow-up examination every 3 months; in the 4th and 5th year, patients should be followed up bi-annually and in the 6th year and thereafter, patients should have an annual follow-up examination. This includes annual screening. | EC | | |

Follow-up examinations after breast cancer

| Years after primary therapy | Follow-up | | Screening |
|--|---|------------------|------------------|
| | 1st–3rd year | 4th and 5th year | 6 years and more |
| Medical history Physical examination Counselling/information | Every 3 months | Twice a year | Annually |
| Laboratory examinations, examinations using imaging procedures (exceptions: mammography and breast ultrasound) | Only if there is a clinical suspicion of recurrence and/or metastasis | | |

Follow-up examinations for breast cancer – breast diagnostics after BCT and mastectomy

| Years after primary therapy | Year 1 – Year 3 | From Year 4 |
|---|----------------------|-------------|
| Ipsilateral breast (BCT): mammography, breast sonography Mastectomy: ultrasound | At least once a year | Annually |
| Contralateral breast: mammography, ultrasound if required | Annually | Annually |

| No. | Recommendations/ Statements | EG | LoE | Sources |
|-------|--|----|-----|---------|
| 6.44. | During follow-up, patients should be encouraged to do physical exercise (> 2–3 h/ week) and to normalize their body weight (in patients with a high BMI). Patients should be offered support to do so. | EC | | |
| 6.45. | Constant motivation of the patient to regularly take the medication prescribed for adjuvant therapy, particularly endocrine therapy (e.g. tamoxifen or aromatase inhibitors), is an essential part of follow-up care. The patient must be questioned in detail about how well she tolerates the therapy and about any side effects. Appropriate measures must be taken to treat any complaints. Premature discontinuation of therapy can be prevented by changing the endocrine therapy. | EC | | |

5 Rehabilitation

| No. | Recommendation | EG | LoE | Sources |
|-------|--|----|-----|---------|
| 6.46. | Tumor disease and treatment of disease with surgery, radiation therapy and systemic therapy can lead to disorders of varying severity, which require targeted rehabilitative somatic and psychosocial measures. Patients must be informed early on about options for outpatient and inpatient rehabilitation as well as about other forms of support to which they are entitled under German social law. When prescribing rehabilitative measures, the patient's own wishes must be considered when recommending the type of rehabilitation. | EC | | |

6 Palliative Medicine

The development of care structures and the inclusion of palliative medicine into medical training and further training has made it possible for patients with incurable disease and a limited or uncertain prognosis to access palliative care which complements oncologic therapy (Reference: Leitlinienprogramm Onkologie [Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF]: Palliativmedizin für Patienten mit einer nicht heilbaren Krebserkrankung [Palliative Medicine for Patients with Incurable Cancer], long version 1.1, 2015, AWMF registry number: 128/001OL, <http://leitlinienprogramm.onkologie.de/Palliativmedizin.80.0.html>).

| No. | Recommendations/ Statements | EG | LoE | Sources |
|-------|--|----|-----|---------|
| 5.42. | The principles listed below must be followed when offering palliative care to patients with incurable breast cancer: 1. The patient's needs must be considered and addressed on all four levels (physical, psychological, social, and spiritual). 2. The patient's needs must be taken into account. 3. Realistic treatment goals must be defined. 4. The patient must be informed about the different ways in which palliative care is organized. 5. An environment must be created which respects the patient's intimacy. | EC | | |

Conflict of Interest

See guideline report: https://www.awmf.org/uploads/tx_szleitlinien/032-045OLm_S3_Mammakarzinom_2017-12.pdf

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