| EVIDENZBERICHT

Synopse evidenzbasierter Leitlinien-Empfehlungen zur Diagnostik, Therapie und Nachsorge des Mammakarzinoms

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Impressum

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S3-Leitliniengruppe „Diagnostik, Therapie und Nachsorge des Mammakarzinoms – 2. Aktualisierung“
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Titel

Synopse evidenzbasierter Leitlinien-Empfehlungen zur Diagnostik, Therapie und Nachsorge des Mammakarzinoms

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Abkürzungsverzeichnis

ASCO	American Society of Clinical Oncology
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
CCO	Cancer Care Ontario
DCIS	Duktales Karzinom in situ
DEGRO	Deutschen Gesellschaft für Radioonkologie
DMP	Disease Management Program
EGAPP	Evaluation of Genomic Applications in Practice and Prevention
GoR	Grade of Recommendation
LoE	Level of Evidence
MRT	Magnetresonanztomographie
n.a.	nicht angegeben
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NBOCC	National Breast and Ovarian Cancer Centre
NZGG	New Zealand Guideline Group

Tabellenverzeichnis

1. Hintergrund und Auftrag

Die Leitlinien-Gruppe zur Aktualisierung der S3-Leitlinie zur Diagnostik, Therapie und Nachsorge des Mammakarzinoms (2008) beauftragte das ÄZQ im Oktober 2010 mit der Erstellung einer umfassenden Synopse von Empfehlungen aktueller evidenzbasierter Leitlinien. Die Synopse sollte sich am IQWIG-Bericht Nr. 37 aus 2008 orientieren (Titel: Systematische Leitlinienrecherche und –bewertung sowie Extraktion neuer und relevanter Empfehlungen für das DMP Brustkrebs) [Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) 2008].

Die Synopse ist als Grundlage für die Aktualisierung der S3-Leitlinie zur Diagnostik, Therapie und Nachsorge des Mammakarzinoms (2008) vorgesehen. Anhand der extrahierten Empfehlungen soll der Änderungsbedarf ermittelt werden. Gleichzeitig sollen Themen identifiziert werden, für die eine zusätzliche Primärrecherche erforderlich ist.

2. Fragestellung

Die Leitliniengruppe zur Aktualisierung der S3-Leitlinie zur Diagnostik, Therapie und Nachsorge des Mammakarzinoms (2008) beauftragte die Synopse aktueller evidenzbasierter Leitlinien zu allen wesentlichen Themen der Leitlinie ohne spezifische Fragestellungen.

Es wurde mit dem Auftraggeber vereinbart, die Empfehlungen evidenzbasierter Leitlinien zu den folgenden Themen zusammenzufassen:

1. PatientInneninformation und –aufklärung
2. Familiär bedingtes Mammakarzinom
3. Diagnostik (einschließlich Staging)
4. Pathomorphologische Untersuchungen einschl. Prognosefaktoren
5. Operative Therapie
6. Strahlentherapie (adjuvant)
7. Systemtherapie ((neo-)adjuvant))
8. Sonderformen (duktales Carcinoma in situ (DCIS), inflammatorisches Mammakarzinom, inoperables Mammakarzinom)
9. Lokalrezidiv
10. Fernmetastasen
11. Psychosoziale Aspekte
12. Supportivtherapie
13. Rehabilitation
14. Nachsorge

3. Methodik

3.1 Einschluss- und Ausschlusskriterien

Für den vorliegenden Evidenzbericht wurde ausschließlich nach Leitlinien zum Themengebiet Mammakarzinom gesucht, die seit 2006 veröffentlicht wurden. Die Recherche wurde auf Publikationen in deutscher oder englischer Sprache beschränkt. Leitlinien, die bereits in der S3-Leitlinie zur [Deutsche Krebsgesellschaft (DKG) et al. 2008] (1. Aktualisierung 2008; im Folgenden S3-Leitlinie Mammakarzinom 2008) als Quell-Leitlinien dienten, wurden nicht berücksichtigt. Ein weiteres Einschlusskriterium war, dass bei der Erstellung der Leitlinien bestimmte methodische Standards für die Entwicklung evidenzbasierter Leitlinien angewendet wurden. Entsprechend wurden Leitlinien ausgeschlossen, bei denen a) keine systematische Literaturrecherche erfolgt ist; und/oder b) für die Mehrheit der Empfehlungen nicht die zugrundeliegenden Literatur angegeben wird und/oder c) nicht für die Mehrheit der Empfehlungen Evidenz- und/oder Empfehlungseinstufungen („Level of Evidence“ [LoE] und/oder „Grade of Recommendation“ [GoR]) angegeben wurden. Für einen Einschluss mussten alle Kriterien erfüllt sein. In Tabelle 1 sind die Einschlusskriterien und die daraus abgeleiteten Auschlusskriterien für die Auswahl der Leitlinien im Überblick dargestellt.

Tabelle 1: Ein- und Ausschlusskriterien der Leitlinien-Recherche

Einschlusskriterien	
E1: Zielgruppe	PatientInnen mit Mammakarzinom (keine weitere thematische Einschränkung bzgl. Intervention und Erkrankung)
E2: Publikationsdatum	Publikation zwischen 01.01.2006 und 18.11.2010 (Tag der letzten Recherche)
E3: Sprachen	deutsch oder englisch
E4: Publikationstyp	Leitlinie
E5: Methodische Anforderungen	Systematische Literaturrecherche nach Primär- und/oder Sekundärliteratur und Angabe der zugrunde liegenden Literatur für die Mehrheit der Empfehlungen und Verwendung von Evidenzklassifikationen und/oder Empfehlungsgraduierungen
Ausschlusskriterien	
A1	Leitlinie ist nicht spezifisch für die Zielgruppe
A2	Die Leitlinie erfüllt mindestens eine methodischen Anforderung, gemäß E5 (siehe oben) nicht.
A3	Die Leitlinie ist nicht in deutscher oder englischer Sprache verfügbar
A4	Die Leitlinie ist vor 2006 publiziert.
A5	Die Leitlinie wurde bereits in der S3-Leitlinie zur Diagnostik, Therapie und Nachsorge des Mammakarzinoms (2008) als Quell-Leitlinie zitiert

A6	Ein Volltext der Leitlinie ist nicht verfügbar
A7	Publikation ist keine Leitlinie

3.2 Leitlinienrecherche: Datenbanken und Suchstrategien

Es erfolgte eine systematische Recherche in der bibliographischen Datenbank Medline (PubMed), und in den Leitlinien-Datenbanken des National Guideline Clearinghouse (NGC), des Guideline International Network (G-I-N) und des NHS Guidelinesfinder. Des Weiteren wurden die Internetseiten bekannter nationaler und internationaler Leitlinienorganisationen nach Leitlinien zum Thema Mammakarzinom durchsucht.

3.3 Identifizierung relevanter Leitlinien

Die Identifizierung geeigneter Leitlinien erfolgte in zwei Schritten. Im ersten Schritt wurde für alle in den elektronischen Datenbanken identifizierten Zitate anhand der Titel oder, soweit vorhanden, anhand des Abstracts die Einschlusskriterien E1 bis E4 geprüft. Wenn aufgrund des Titels oder Abstracts kein Ausschlussgrund identifiziert werden konnte, wurden die Einschlusskriterien E1 bis E4 anschließend im Volltext geprüft. Bei Leitlinien, die auf den Internetseiten von Leitlinienanbietern oder in Leitlinien-Datenbanken identifiziert wurden, erfolgte eine unmittelbare Überprüfung des Volltextes, wenn dieser vorlag.
In einem zweiten Schritt wurde für alle im Volltext verfügbaren, thematisch relevanten Leitlinien geprüft, ob sie den methodischen Anforderungen (E5) genügten.

3.4 Extraktion der Empfehlungen

Nach Identifikation der relevanten Leitlinien erfolgte eine strukturierte Synthese von Empfehlungen (Synopse) zu prospektiv mit dem Auftraggeber abgestimmten Themen (siehe 3.4.1). Für die Synthese der Leitlinienempfehlungen wurden die Empfehlungen im Original und - wenn vorhanden - die jeweiligen Literaturverweise und Angaben zu Evidenzklassifikation (Level of Evidence) und Empfehlungsgraden (Grades of Recommendation) extrahiert. Als Empfehlungen wurden diejenigen Aussagen identifiziert, welche als solche explizit von den Autoren der Leitlinie gekennzeichnet waren (z. B. durch entsprechende Anführungen, Textfelder oder Markierungen). Wenn die Autoren einer Leitlinie die Empfehlungen nicht eindeutig kennzeichneten, wurden diejenigen Aussagen extrahiert, die durch zwei Reviewer aufgrund der sprachlichen Darstellung eindeutig als Empfehlungen eingestuft wurden. Die extrahierten Literaturverweise wurden nicht auf ihre inhaltliche Angemessenheit geprüft. Für die Extraktion der Empfehlungen wurden sowohl die Leitlinien als auch verfügbare Methoden- bzw. Hintergrundberichte zur Erstellung der Leitlinie verwendet.

3.4.1 Berücksichtigte Themen

Die Auswahl der berücksichtigten Themen orientierte sich an der S3-Leitlinie Mammakarzinom 2008 [Deutsche Krebsgesellschaft (DKG) et al. 2008]. Die Extraktion von Empfehlungen zu folgenden Themen wurde prospektiv festgelegt.

1. PatientInneninformation und –aufklärung
2. Familiär bedingtes Mammakarzinom
3. Diagnostik (einschließlich Staging)
4. Pathomorphologische Untersuchungen einschl. Prognosefaktoren
5. Operative Therapie
6. Strahlentherapie (adjuvant)
7. Systemtherapie ((neo-)adjuvant
8. Sonderformen (DCIS, inflammatorisches Mammakarzinom, inoperables Mammakarzinom)
9. Lokalrezidiv
10. Fernmetastasen
11. Psychosoziale Aspekte
12. Supportivtherapie
13. Rehabilitation
14. Nachsorge

3.4.2 Berücksichtigte Leitlinien

Mit dem Auftraggeber wurde vereinbart, pro Thema die Empfehlungen von maximal drei Leitlinien zu extrahieren. Wenn zu einem Thema mehr als drei relevante Leitlinien identifiziert wurden, sollten die methodisch besten Leitlinien ausgewählt werden. Hierzu sollte eine Bewertung der methodologischen Exaktheit der Leitlinien-Entwicklung dieser Leitlinien anhand der Kriterien der Domäne 3 des Deutschen Instruments zur methodischen Leitlinien-Bewertung (DELBI) erfolgen, um die drei Leitlinien mit der höchsten methodischen Qualität auszuwählen.

3.5 Abgleich der synoptierten Empfehlungen mit den Inhalten der S3-Leitlinie Mammakarzinom 2008

Die Inhalte der zu den jeweiligen Themen synoptierten Empfehlungen, Statements (einschließlich der als „Good Practice Points“ gekennzeichneten Empfehlungen) wurden mit den Inhalten der S3-Leitlinie Mammakarzinom 2008 orientierend abgeglichen. Dabei wurden neben den als Empfehlungen bzw. Statements gekennzeichneten Inhalten der S3-Leitlinie Mammakarzinom 2008 auch die Hintergrundtexte berücksichtigt. Die Empfehlungen oder Statements, deren Inhalte in der S3-Leitlinie Mammakarzinom 2008 fehlten oder die diskrepant im Vergleich

mit den Inhalten der S3-Leitlinie Mammakarzinom 2008 waren, wurden den jeweiligen Synopsen vorangestellt. Auf spezifischere Empfehlungen wurde ggf. hingewiesen. Eine Überprüfung der Angemessenheit der für die Empfehlungen angegebenen Evidenzklassifikation erfolgte nicht.

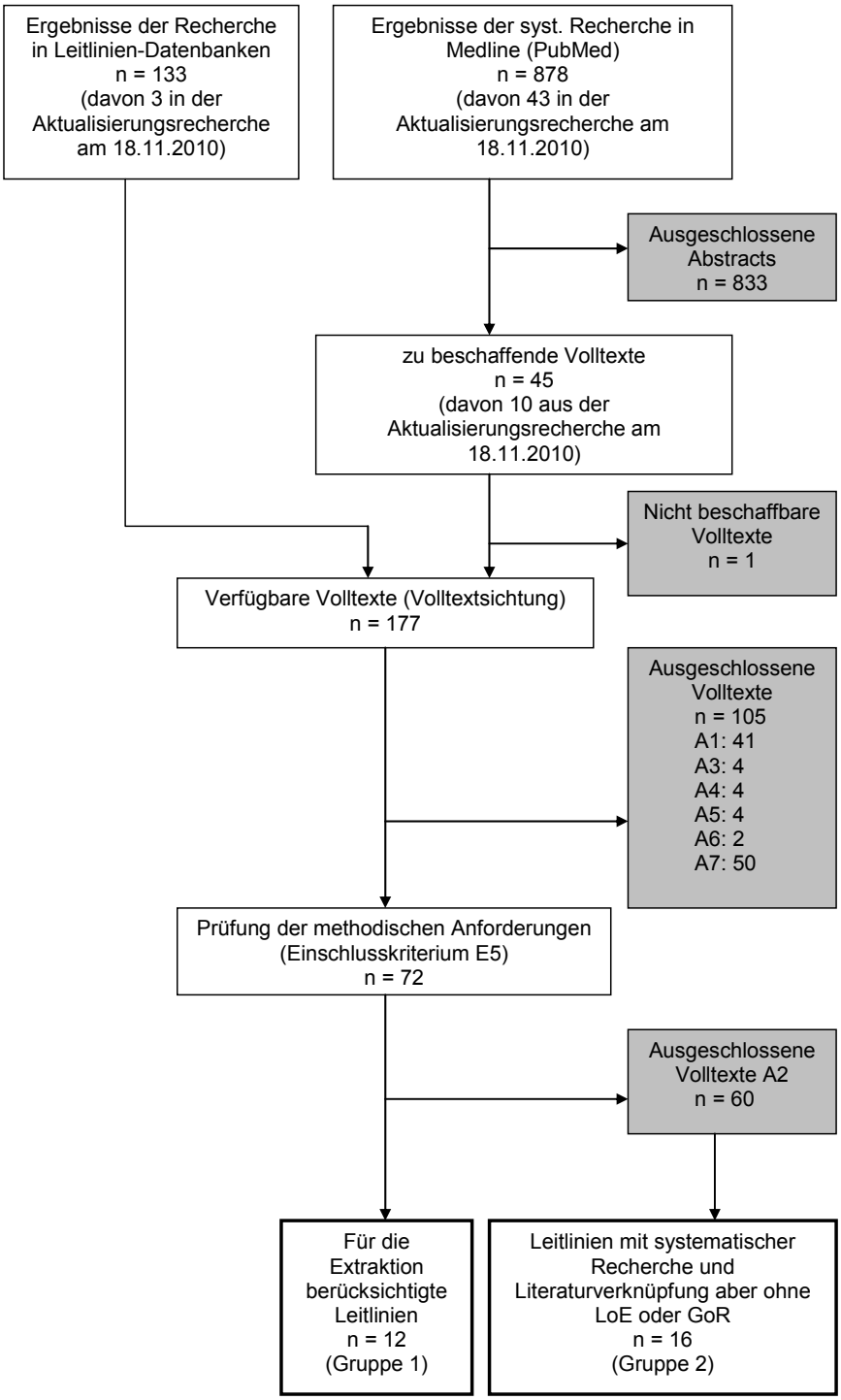
4. Ergebnisse

4.1 Ergebnisse der Leitlinienrecherche

4.1.1 Recherche in bibliographischen Datenbanken

Die Recherche in Medline (PubMed) erfolgte am 21. Juli 2010 und wurde am 18. November 2010 wiederholt (Aktualisierungsrecherche). Die Suche ergab insgesamt 878 Treffer (siehe Suchstrategie und Trefferzahlen in Anhang 5.1). Nach Sichtung von Titel und Abstract wurde für 45 Zitate der Volltext bestellt. Für eine Publikation konnte der Volltext nicht beschafft werden [Yaziji et al. 2008]. 15 Publikationen wurden nach der Sichtung des Volltextes ausgeschlossen (ausgeschlossene Volltexte mit Ausschlussgrund siehe Anhang 5.2). Eingeschlossen wurden demnach aus der Recherche in Medline (PubMed) insgesamt 29 Leitlinien (Siehe auch Abbildung 1).

Abbildung 1: Übersicht der Leitlinienrecherche und des Auswahlprozesses



4.1.2 Recherche in Leitlinien-Datenbanken und bei Leitlinien-Anbietern

Die Recherche in Leitlinien-Datenbanken und bei Leitlinien-Anbietern erfolgte am 21. Juli 2010 und wurde am 18. November 2010 wiederholt (Aktualisierungsrecherche). Die Suche ergab insgesamt 133 potentielle Leitlinien, deren Relevanz durch Sichtung des Volltextes auf den Internetseiten der Anbieter geprüft wurde. In Anhang 5.3 sind die berücksichtigten Leitlinien-Datenbanken und

Leitlinien-Anbieter aufgeführt. Nach Sichtung der Leitlinien wurden 90 Leitlinien ausgeschlossen, so dass aus der Recherche in Leitlinien-Datenbanken und bei Leitlinien-Anbietern insgesamt 43 Leitlinien eingeschlossen wurden (siehe Abbildung Abbildung 1). In Anhang 5.4 werden die ausgeschlossenen Leitlinien der Recherche in Leitlinien-Datenbanken und bei Leitlinien-Anbietern unter Angabe des Ausschlussgrundes aufgeführt.

4.1.3 Überprüfung der methodischen Mindestanforderungen

Die Recherche in Medline (PubMed) und in den Leitliniendatenbanken ergab insgesamt 72 thematisch relevante Leitlinien für die Leitliniensynopse. Nach Überprüfung der methodischen Mindestanforderungen (systematische Recherche, Literaturverknüpfung, Evidenz- oder Empfehlungseinstufung) wurden insgesamt 61 Leitlinien ausgeschlossen. Somit konnten elf Leitlinien, die alle Einschlusskriterien erfüllten, für die weitere Extraktion der Empfehlungen berücksichtigt werden (Gruppe 1). Da für einige Themenbereiche weniger als drei Leitlinien identifiziert wurden, wurden für diese Themen Leitlinien aus der Gruppe der 61 zunächst ausgeschlossenen Leitlinien berücksichtigt. Diese Leitlinien (Gruppe 2) zeichnen sich dadurch aus, dass die Autoren zwar eine systematische Recherche durchgeführt haben und die Literatur, die den Empfehlungen zugrunde liegt, angegeben ist, jedoch keine explizite Einstufung der Evidenz (Level of Evidence) oder der Empfehlungen (Grade of Recommendation) durch definierte Klassifikationssysteme vorgenommen wurde. Die Leitlinien dieser Kategorie wurden zusätzlich berücksichtigt, weil Aussagen zur internen Validität oder Qualität der Evidenz auch ohne Verwendung bestimmter Klassifikationssysteme (Level of Evidence) getroffen werden können, z. B. durch eine Beschreibung der Evidenzgüte im Fließtext (siehe auch [Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) 2008]).

In Tabelle 2 sind die eingeschlossenen Leitlinien der Gruppe 1 und der Gruppe 2 aufgeführt. Anhang 5.5 enthält diejenigen Leitlinien, die aufgrund methodischer Kriterien (keine systematische Recherche, keine Angabe von Literatur zu den Empfehlungen) ausgeschlossen wurden.

Tabelle 2: Eingeschlossene Leitlinien (Gruppe 1 und Gruppe 2)

Gruppe 1	
1.	Belkacemi Y, Fourquet A, Cutuli B, Bourgier C, Hery M, Ganem G, Marsiglia H, Namer M, Gligorov J, Azria D. Radiotherapy for invasive breast cancer: Guidelines for clinical practice from the French expert review board of Nice/Saint-Paul de Vence. Crit Rev Oncol Hematol 2010.
2.	Feyer P, Sautter-Bihl ML, Budach W, Dunst J, Haase W, Harms W, Sedlmayer F, Souchon R, Wenz F, Sauer R. DEGRO Practical Guidelines for palliative radiotherapy of breast cancer patients: brain metastases and leptomeningeal carcinomatosis. Strahlenther Onkol 2010;186(2):63-9.
3.	Souchon R, Wenz F, Sedlmayer F, Budach W, Dunst J, Feyer P, Haase W, Harms W, Sautter-Bihl ML, Sauer R. DEGRO practice guidelines for palliative radiotherapy of metastatic breast cancer: bone metastases and metastatic spinal cord compression (MSCC). Strahlenther Onkol 2009;185(7):417-24
4.	Recommendations from the EGAPP Working Group: can tumor gene expression profiling improve outcomes in patients with breast cancer? Genet Med 2009;11(1):66-73.

5. NBOCC: Recommendations for use of Chemotherapy for the treatment of advanced breast cancer 2010
6. NBOCC: Recommendations for use of Endocrine therapy for the treatment of hormone receptor-positive advanced breast cancer 2008
7. NBOCC: Recommendations for Follow-up of women with early breast cancer 2010
8. NBOCC: Recommendations for use of Taxane-containing chemotherapy regimens for the treatment of early (operable) breast cancer 2008
9. NICE: Advanced breast cancer: diagnosis and treatment 2009
10. NICE: Early and locally advanced breast cancer: diagnosis and treatment 2009
11. NZGG: Management of Early Breast Cancer 2009
12. DRV-Bund: Reha-Therapiestandards Brustkrebs 2009
Gruppe 2
13. Sautter-Bihl ML, Souchon R, Budach W, Sedlmayer F, Feyer P, Harms W, Haase W, Dunst J, Wenz F, Sauer R. DEGRO practical guidelines for radiotherapy of breast cancer II. Postmastectomy radiotherapy, irradiation of regional lymphatics, and treatment of locally advanced disease. Strahlenther Onkol 2008;184(7):347-53.
14. Sautter-Bihl ML, Budach W, Dunst J, Feyer P, Haase W, Harms W, Sedlmayer F, Souchon R, Wenz F, Sauer R. DEGRO practical guidelines for radiotherapy of breast cancer I: breast-conserving therapy. Strahlenther Onkol 2007;183(12):661-6.
15. Smith BD, Arthur DW, Buchholz TA, Haffty BG, Hahn CA, Hardenbergh PH, Julian TB, Marks LB, Todor DA, Vicini FA, Whelan TJ, White J, Wo JY, Harris JR. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). Int J Radiat Oncol Biol Phys 2009;74(4):987-1001.
16. Burstein HJ, Prestrud AA, Seidenfeld J, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, Giordano SH, Hudis CA, Malin J, Mamounas EP, Rowden D, Solky AJ, Sowers MR, Stearns V, Winer EP, Somerfield MR, Griggs JJ. American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. J Clin Oncol 2010;28(23):3784-96.
17. American Society of Clinical Oncology Clinical Practice guideline Update on the Use of Pharmacologic Interventions Including Tamoxifen, Raloxifene, and Aromatase Inhibition for Breast Cancer Risk Reduction 2009
18. American Society of Clinical Oncology 2007 Update of recommendations for the Use of Tumor Markers in Breast Cancer:
19. American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer
20. CCO: The Role of Aromatase Inhibitors in Adjuvant Therapy for Postmenopausal Women with Hormone Receptor-positive Breast Cancer: Guideline Recommendations 2008
21. CCO: Fulvestrant for Systemic Therapy of Locally Advanced or Metastatic Breast Cancer in Postmenopausal Women: Guideline Recommendations 2008
22. CCO: The Role of Gemcitabine in the Management of Metastatic Breast Cancer:A Clinical Practice Guideline 2007
23. CCO: Adjuvant Ovarian Ablation in the Treatment of Premenopausal Women with Early Stage Invasive Breast Cancer 2010
24. CCO: Adjuvant Taxane Therapy for Women with Early-stage, Invasive Breast Cancer: A Clinical Practice Guideline 2006
25. CCO: The Role of Trastuzumab in Adjuvant and Neoadjuvant Therapy in Women with HER2/neu-overexpressing Breast Cancer: A Clinical Practice Guideline 2006
26. NICE: Brachytherapy as the sole method of NICE: adjuvant radiotherapy for breast cancer after local excision 2008

27. NICE Endoscopic mastectomy and endoscopic wide local excision for breast cancer 2009
28. NICE: Image-guided radiofrequency excision biopsy of breast lesions 2009

4.2 Extraktion der Empfehlungen

Für die Extraktion der Empfehlungen wurden zunächst für alle Leitlinien der Gruppen 1 und 2 festgestellt, zu welchen der prospektiv festgelegten Themen Empfehlungen vorlagen. Den einzelnen Themen wurden Leitlinien mit Empfehlungen zu diesen Themen zugeordnet (siehe Tabelle 3). Wenn zu einem Thema weniger als drei Leitlinien der Gruppe 1 identifiziert werden konnten, wurden zusätzlich Empfehlungen aus Leitlinien der Gruppe 2 extrahiert. Dies war für die Themen Diagnostik/Staging, pathomorphologische Untersuchungen und Prognosefaktoren, operative Therapie, adjuvante endokrine Systemtherapie und adjuvante Antikörpertherapie der Fall.

Für das Thema adjuvante endokrine Systemtherapie konnten mehrere Leitlinien der Gruppe 2 identifiziert werden. Diese wurden alle extrahiert, da die entsprechenden Leitlinien unterschiedliche Interventionen adressierten.

Erläuterungen der Verfasser dieses Berichtes, die ein besseres Verständnis der Empfehlungen gewährleisten sollen, sind mit Doppelpfeilen («….») gekennzeichnet.

Tabelle 3: Übersicht der adressierten Themen in den eingeschlossenen Leitlinien (G1 = Gruppe 1, G2 = Gruppe2)

Leitlinie	Patienteninformation/ Aufklärung	Familiärbedingtes Mammakarzinom	Diagnostik/diagnst. Sicherung/Staging	Pathomorphologische Untersuchungen &Prognosefaktoren	Operative Therapie	Strahlentherapie	Systemtherapie/Chemtherapie o	Systemtherapie/endokrine Therapie	Systemtherapie/Antiköprerther apie	Neoadjuvante Systemtherapie	Sonderformen (DCIS, inflamm, MaCa, inoperables MaCa)	Lokalrezidiv	Fernmetastasen/ Systemtherapie	Fernmetastasen/ spezifische Diagnostik und Therapie	Psychosoziale Aspekte	Supportivtherapie	Rehabilitation	Nachsorge
1. American Society of Clinical Oncology Clinical Practice Guideline Update on the Use of Pharmacologic Interventions Including Tamoxifen, Raloxifene, and Aromatase Inhibition for Breast Cancer Risk Reduction 2009							**G2**			**G2**								
2. American Society of Clinical Oncology 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer1			**G2**				**G2**											**G2**
3. American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer				**G2**														

[1] Die Leitlinie wird in der S3-Leitlinie zur Diagnostik, Therapie und Nachsorge des Mammakarzinoms (2008) zitiert, aber nicht als Quell-Leitlinie aufgeführt und wird deshalb bei der Synoptierung berücksichtigt

Leitlinie	Patienteninformation/ Aufklärung	Familiärbedingtes Mammakarzinom	Diagnostik/diagnst. Sicherung/Staging	Pathomorphologische Untersuchungen &Prognosefaktoren	Operative Therapie	Strahlentherapie	Systemtherapie/Chemtherapie	Systemtherapie/endokrine Therapie	Systemtherapie/Antiköpertherapie	Neoadjuvante Systemtherapie	Sonderformen (DCIS, inflamm, MaCa, inoperables MaCa)	Lokalrezidiv	Fernmetastasen/ Systemtherapie	Fernmetastasen/ spezifische Diagnostik und Therapie	Psychosoziale Aspekte	Supportivtherapie	Rehabilitation	Nachsorge
4. Belkacemi et al.. Radiotherapy for invasive breast cancer: Guidelines for clinical practice from the French expert review board of Nice/Saint-Paul de Vence. Crit Rev Oncol Hematol 2010.						**G1**												
5. Burstein HJ et al. American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. J Clin Oncol 2010;28(23):3784-96.								**G2**										
6. CCO: The Role of Aromatase Inhibitors in Adjuvant Therapy for Postmenopausal Women with Hormone Receptor-positive Breast Cancer: Guideline Recommendations 2008								**G2**										
7. CCO: Fulvestrant for Systemic Therapy of Locally Advanced or Metastatic Breast Cancer in Postmenopausal Women: Guideline Recommendations 2008								**G2**					**G2**					
8. CCO: The Role of Gemcitabine in the Management of Metastatic Breast Cancer: A Clinical Practice Guideline 2007													**G2**					
9. CCO: Adjuvant Ovarian Ablation in the Treatment of Premenopausal Women with Early Stage Invasive Breast Cancer 2010								**G2**										

Leitlinie	Patienteninformation/ Aufklärung	Familiärbedingtes Mammakarzinom	Diagnostik/diagnst. Sicherung/Staging	Pathomorphologische Untersuchungen &Prognosefaktoren	Operative Therapie	Strahlentherapie	Systemtherapie/Chemtherapie o	Systemtherapie/endokrine Therapie	Systemtherapie/Antiköpertherapie	Neoadjuvante Systemtherapie	Sonderformen (DCIS, inflamm, MaCa, inoperables MaCa)	Lokalrezidiv	Fernmetastasen/ Systemtherapie	Fernmetastasen/ spezifische Diagnostik und Therapie	Psychosoziale Aspekte	Supportivtherapie	Rehabilitation	Nachsorge
10. CCO: Adjuvant Taxane Therapy for Women with Early-stage, Invasive Breast Cancer: A Clinical Practice Guideline 2006							**G2**											
11. CCO: The Role of Trastuzumab in Adjuvant and Neoadjuvant Therapy in Women with HER2/neu-overexpressing Breast Cancer: A Clinical Practice Guideline 2006									**G2**									
12. DRV-Bund: Reha-Therapiestandards Brustkrebs 2009																	**G1**	
13. Feyer P et al. DEGRO Practical Guidelines for palliative radiotherapy of breast cancer patients: brain metastases and leptomeningeal carcinomatosis. Strahlenther Onkol 2010;186(2):63-9.														**G1**				
14. NBOCC: Recommendations for use of Chemotherapy for the treatment of advanced breast cancer 2010													**G1**					
15. NBOCC: Recommendations for use of Endocrine therapy for the treatment of hormone receptor-positive advanced breast cancer 2008													**G1**					
16. NBOCC: Recommendations for Follow-up of women with early breast cancer 2010																		**G1**

Leitlinie	Patienteninformation/ Aufklärung	Familiärbedingtes Mammakarzinom	Diagnostik/diagnst. Sicherung/Staging	Pathomorphologische Untersuchungen &Prognosefaktoren	Operative Therapie	Strahlentherapie	Systemtherapie/Chemtherapie	Systemtherapie/endokrine Therapie	Systemtherapie/Antiköpertherapie	Neoadjuvante Systemtherapie	Sonderformen (DCIS, inflamm, MaCa, inoperables MaCa)	Lokalrezidiv	Fernmetastasen/ Systemtherapie	Fernmetastasen/ spezifische Diagnostik und Therapie	Psychosoziale Aspekte	Supportivtherapie	Rehabilitation	Nachsorge
17. NBOCC: Recommendations for use of Taxane-containing chemotherapy regimens for the treatment of early (operable) breast cancer 2008							**G1**			**G1**								
18. NICE: Brachytherapy as the sole method of adjuvant radiotherapy for breast cancer after local excision 2008						**G2**												
19. NICE: Advanced breast cancer: diagnosis and treatment 2009	**G1**		**G1**	**G1**									**G1**	**G1**	**G1**	**G1**		
20. NICE: Early and locally advanced breast cancer: diagnosis and treatment 2009	**G1**		**G1**	**G1**	**G1**	**G1**	**G1**	**G1**	**G1**	**G1**	**G1**				**G1**			**G1**
21. NICE Endoscopic mastectomy and endoscopic wide local excision for breast cancer 2009					**G2**													
22. NICE: Image-guided radiofrequency excision biopsy of breast lesions 2009			**G2**															
23. NZGG: Management of Early Breast Cancer 2009	**G1**	**G1**	**G1**	**G1**	**G1**	**G1**	**G1**	**G1**	**G1**	**G1**	**G1**				**G1**			**G1**
24. Recommendations from the EGAPP Working Group: can tumor gene expression profiling improve outcomes in patients with breast cancer? Genet Med 2009;11(1):66-73.				**G2**														

Leitlinie	Patienteninformation/ Aufklärung	Familiärbedingtes Mammakarzinom	Diagnostik/diagnst. Sicherung/Staging	Pathomorphologische Untersuchungen &Prognosefaktoren	Operative Therapie	Strahlentherapie	Systemtherapie/Chemtherapie o	Systemtherapie/endokrine Therapie	Systemtherapie/Antiköprerther apie	Neoadjuvante Systemtherapie	Sonderformen (DCIS, inflamm, MaCa, inoperables MaCa)	Lokalrezidiv	Fernmetastasen/ Systemtherapie	Fernmetastasen/ spezifische Diagnostik und Therapie	Psychosoziale Aspekte	Supportivtherapie	Rehabilitation	Nachsorge
25. Sautter-Bihl ML et al. DEGRO practical guidelines for radiotherapy of breast cancer II. Postmastectomy radiotherapy, irradiation of regional lymphatics, and treatment of locally advanced disease. Strahlenther Onkol 2008;184(7):347-53.						**G2**												
26. Sautter-Bihl ML et al. DEGRO practical guidelines for radiotherapy of breast cancer I: breast-conserving therapy. Strahlenther Onkol 2007;183(12):661-6.						**G2**												
27. Smith et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). Int J Radiat Oncol Biol Phys 2009;74(4):987-1001.						**G2**												
28. Souchon et al. . DEGRO practice guidelines for palliative radiotherapy of metastatic breast cancer: bone metastases and metastatic spinal cord compression (MSCC). Strahlenther Onkol 2009;185(7):417-24														**G1**				

4.2.1 Empfehlungen zum Thema Patienteninformation und Aufklärung

4.2.1.1 Eingeschlossene Leitlinien

Zum Thema Patienteninformation und Aufkärung konnten drei Leitlinien der Gruppe 1 extrahiert werden [National Institute for Clinical Excellence (NICE) 2009; National Institute for Clinical Excellence (NICE) 2009; New Zealand Guidelines Group (NZGG) 2009]. Zwei Leitlinien wurden vom National Institute for Health and Clinical Excellence (NICE) aus Großbritannien in 2009 herausgegeben und adressieren umfassend die Therapie der Primärerkrankung einschließlich lokal fortgeschrittener Tumore und die Therapie des fortgeschrittenen Mammakarzinoms. Für die Extraktion dieser Leitlinien (insbesondere der Evidenzklassifikationen [LoE]) wurden zusätzliche Hintergrund- bzw. Methodendokumente ausgewertet [National Institute for Clinical Excellence (NICE) 2009; National Institute for Clinical Excellence (NICE) 2009]. Zu den Empfehlungen haben die Autoren der NICE-Leitlinien sogenannte ‚Qualifying Statements' angeführt. Diese beschreiben zusammenfassend die zugrundeliegende Evidenz der Empfehlungen. Die ‚Qualifying Statements' wurden mit den Empfehlungen extrahiert, um als Ergänzung zu den berücksichtigten Referenzen auch die entsprechenden zusammenfassenden Einschätzungen der Autoren transparent zu machen. Die Leitlinien von NICE enthalten außerdem Empfehlungen für die weitere Erforschung bestimmter Aspekte (Research Recommendations). Diese Empfehlungen wurden extrahiert und entsprechend gekennzeichnet.

Eine Leitlinie wurde von der New Zealand Guidelines Group (NZGG) 2009 herausgegeben. Diese Leitlinie adressiert umfassend die Diagnostik und Therapie der Primärerkrankung. Für die Extraktion dieser Leitlinie wurden keine weiteren Dokumente ausgewertet.

4.2.1.2 In der S3-Leitlinie Mammakarzinom 2008 nicht enthaltene und diskrepante Empfehlungs-Inhalte

In der NICE early 2009 wird empfohlen, dass die Mitglieder des klinischen Teams ein **Kommunikationstraining** durchlaufen haben sollten (LoE 1+, GoR n.a.), dies ist ebenso Gegenstand einer Empfehlung der NZGG für „practioners" („good practice point" = immer ohne Angaben zu LoE und GoR).

In der NICE early 2009 wird die Zuteilung der Patientinnen zu einer „**breast care nurse"** zur Unterstützung während des gesamten Behandlungsverlaufs empfohlen (LoE 1, GoR n.a.). In der NZGG wird die „breast care nurse" nicht thematisiert, aber als „good practice point" empfohlen, für jede Frau einen **koordinierenden Betreuer („coordinator of care")** zur Erleichterung der Behandlungsplanung und Unterstützung der Patientin festzulegen. Die genannten Aspekte werden in der S3-Leitlinie Mammakarzinom 2008 bisher nicht thematisiert.
Als „good practice point" wird in der NZGG weiterhin empfohlen, Frauen zu ermutigen, zu **Arztterminen eine unterstützende Begleitperson mitzubringen.** Dies wird in der S3-Leitlinie Mammkarzinom 2008 bisher neutral fomuliert (Hintergrundtext: Es liegt im Ermessen der Patientin, ob der Partner oder Angehörige oder auch eine Selbsthilfevertreterin in …die Gespräche einbezogen werden.").

Weitere ‚neue' „good clinical practice points" sind die Empfehlungen der NZGG, dass das **Team und der Koordinator kulturell adäquate Hilfen** und Unterstüzung leisten sollten und **hochwertige evidenzbasierte Patientinneninformationen in verschiedenen Sprachen** bereitgestellt werden sollten. Dies wird in der S3-Leitlinie Mammakarzinom 2008 bisher ggf. implizit vorausgesetzt, jedoch nicht explizit empfohlen.

Die Inhalte der übrigen Empfehlungen finden sich – in ähnlichen bzw. etwas abgewandelten Formulierungen in der S3-Leitlinie Mammakarzinom 2008, zu einem guten Teil auch im Hintergrundtext, ggf. auch im Kapitel D2 „psychosoziale Aspekte und Psychoonkologie". Für strukturelle Aspekte (z.B. Teilnahme an multidiziplinären Besprechungen) wird in der Einleitung der S3-Leitlinie Mammakarzinom 2008 explizit auf den Anforderungskatalog an Brustzentren verwiesen.

Tabelle 4: Patienteninformation und Aufklärung

Leitlinie	Empfehlung	LoE[2]	GoR[1]	Referenzen
Patienteninformation und Aufklärung				
Nice 2009 early	▪ All members of the breast cancer clinical team should have completed an accredited communication skills training programme. ▪ All patients with breast cancer should be assigned to a named breast care nurse specialist who will support them throughout diagnosis, treatment and follow-up. ▪ All patients with breast cancer should be offered prompt access to specialist psychological support, and, where appropriate, psychiatric services. (Qualifying statement: There is evidence from good quality RCTs to support making these recommendations)	1+	n.a.	[Gotay et al. 2007; McArdle et al. 1996; Mutrie et al. 2007; Samarel et al. 2002; Sandgren et al. 2003; Sandgren et al. 2007; Tatrow et al. 2006]
		1	n.a.	[Bantum 2007]
		1-	n.a.	[Allard 2007; Allen 2002; Andersen et al. 2004; Antoni et al. 2006; Badger et al. 2007; Burton et al. 1995; Cohen et al. 2007; Dey et al. 2002; Ritz et al. 2000; Stanton et al. 2005; Zimmermann et al. 2007]

[2] Für Erläuterungen des Level of Evidence (LoE) und Grade of Recommendation (GoR) siehe Anhang 5.6.

Leitlinie	Empfehlung	LoE[2]	GoR[1]	Referenzen
Patienteninformation und Aufklärung				
		2++	n.a.	[Ambler et al. 1999]
		2	n.a.	[Classen et al. 2008; Manne et al. 2007; Meneses et al. 2007; Mock et al. 1997; Vos et al. 2007]
NICE 2009 advanced	▪ Assess the patient's individual preference for the level and type of information. Reassess this as circumstances change ▪ On the basis of this assessment, offer patients consistent, relevant information and clear explanations, and provide opportunities for patients to discuss issues and ask questions. (Qualifying statement: These recommendations are based on moderate-quality evidence from randomised trials.)	1+	n.a.	[Jones et al. 2006; Walker et al. 2005]
		1-	n.a.	[Gaston et al. 2005; Jones et al. 2006; Walker et al. 2005; Williams et al. 2005; Winzelberg et al. 2003]
		2	n.a.	[Aranda et al. 2006]
NICE 2009 advanced	▪ Assess the patient's individual preference for how much they wish to be involved in decision making. Reassess this as circumstances change. ▪ Be aware of the value of decision aids and the range available. Make the most appropriate decision aid available to the patient. (Qualifying statement: These recommendations are based on moderate-quality evidence from randomised trials.)	1++	n.a.	[Whelan et al. 2002; O'Connor et al. 2003],
		1+	n.a.	[Siminoff et al. 2000; Davison et al. 2002]
Nice 2009 early	«Research recommendation» ▪ What is the effectiveness of cognitive behavioural therapy compared with other psychological interventions for breast cancer patients?	n.a.	n.a.	n.a.

Leitlinie	Empfehlung	LoE[2]	GoR[1]	Referenzen
Patienteninformation und Aufklärung				
NZGG 2009	Practitioners should give a woman with early breast cancer information about her diagnosis, treatment options (including risks and benefits) and support services	n.a.	C	Expert opinion, berücksichtigte Quellen: [Kinnersley et al. 2008],[National Breast Cancer Centre (NBCC) 2003; National Institute for Clinical Excellence (NICE) 2004; National Breast Cancer Centre (NBCC) 2001; Cancer Society of New Zealand 2006]
NZGG 2009	Information should be tailored to each woman's individual situation throughout her cancer journey, including follow-up	n.a.	C	Expert opinion, [National Breast Cancer Centre (NBCC) 2003; National Institute for Clinical Excellence (NICE) 2004; National Breast Cancer Centre (NBCC) 2001; Cancer Society of New Zealand 2006]
NZGG 2009	Practitioners, in consultation with the woman, should determine the level and amount of information that will be most effective in enabling her to understand her condition and treatment options	n.a.	C	Expert opinion, berücksichtigte Quellen: [Kinnersley et al. 2008; National Breast Cancer Centre (NBCC) 2003; National Institute for Clinical Excellence (NICE) 2004; National Breast Cancer Centre (NBCC) 2001; Cancer Society of New Zealand 2006]
NZGG 2009	Practitioners should receive training in effective communication skills	n.a.	GPP	n.a.
NZGG 2009	Practitioners, in consultation with the woman, should determine the preferred format and timing of information provision	n.a.	GPP	n.a.

Leitlinie	Empfehlung	LoE[2]	GoR[1]	Referenzen
Patienteninformation und Aufklärung				
NZGG 2009	A woman with early breast cancer should be encouraged to take a support person to consultations to provide support and to assist in retaining information	n.a.	GPP	n.a.
NZGG 2009	A woman with early breast cancer should be encouraged to take notes or record a consultation	n.a.	GPP	n.a.
NZGG 2009	Practitioners should ask the woman what she has understood, to determine how well information has been absorbed. Reflective, open-ended questions (eg, 'We have just covered a lot of information, what have you understood from this discussion?') should be used whenever new information is introduced	n.a.	GPP	n.a.
NZGG 2009	Practitioners should be aware that information provided to a woman with early breast cancer may often need to be repeated	n.a.	GPP	n.a.
NZGG 2009	A woman with early breast cancer should be given adequate time and opportunities to discuss and absorb information and ask questions	n.a.	GPP	n.a.
NZGG 2009	Service providers and practitioners should ensure that high quality evidence-based information resources are available for women with early breast cancer in a variety of formats and languages	n.a.	GPP	n.a.
NZGG 2009	A multidisciplinary team should consider the input from the woman with early breast cancer	n.a.	GPP	n.a.
NZGG 2009	Every specialist involved in early breast cancer care should regularly participate in a multidisciplinary team meeting	n.a.	GPP	n.a.

Leitlinie	Empfehlung	LoE[2]	GoR[1]	Referenzen
Patienteninformation und Aufklärung				
NZGG 2009	A coordinator of care is recommended for each woman with early breast cancer to facilitate the treatment pathway and provide guidance and support from diagnosis through to follow-up	n.a.	GPP	n.a.
NZGG 2009	The multidisciplinary team and coordinator of care should provide culturally appropriate advice and support	n.a.	GPP	n.a.
NZGG 2009	The outcomes of multidisciplinary team meetings should be clearly documented in the medical records and communicated to the individual woman	n.a.	GPP	n.a.
Abkürzungen: GPP = good practice point; n.a. = nicht angegeben				

4.2.2 Empfehlungen zum Thema Familiäres Mammakarzinom

4.2.2.1 Eingeschlossene Leitlinien

Zum Thema Familiäres Mammakarzinom konnte eine Leitlinie der Gruppe 1 extrahiert werden [New Zealand Guidelines Group (NZGG) 2009]. Die Leitlinie wurde von der New Zealand Guidelines Group (NZGG) in 2009 herausgegeben. Diese Leitlinie adressiert umfassend die Diagnostik und Therapie der Primärerkrankung. Darüber hinaus adressiert die Leitlinie explizit Empfehlungen für Frauen mit familiär/genetisch bedingtem hohem Risiko, an Brustkrebs zu erkranken. Für die Extraktion dieser Leitlinie wurden keine weiteren Dokumente ausgewertet. Es wurden keine weiteren evdenzbasierten Leitlinien zu diesem Thema identifiziert.

4.2.2.2 In der S3-Leitlinie Mammakarzinom 2008 nicht enthaltene und diskrepante Empfehlungs-Inhalte

Die NZGG-Leitlinie enthält eine Empfehlung mit den **Inhalten, die vor einem genetischen Test mit der betreffenden Person zu besprechen sind** (LoE n.a., GoR C). Die S3-Leitlinie Mammakarzinom 2008 enthält dazu keine Empfehlung.

Weiterhin enthält die NZGG die Empfehlung, Frauen mit einer entsprechenden Familienanamnese („significant“) oder BRCA1/2-Mutationsträgerinnen eine **prophylaktische Mastektomie** anzubieten (LoE 1+, GoR C) und auch eine **prophylaktische Salpingo-Oophorektomie** zu diskutieren (LoE n.a., GoR C). In einer weiteren Empfehlung (LoE n.a., GoR C) wird die **bilaterale prophylaktische Salpingo-Oophorektomie** explizit **für prämenopausale Frauen** als Maßnahme genannt, mit der das Risiko,an Brustkrebs zu erkranken, gesenkt werden kann. Dabei wird empfohlen – als „good practice point“ – die Frauen, die eine prophylaktische Salpingo-Oophorektomie erwägen, darüber zu informieren, dass **Screening** für sie **keinen Nutzen** hat. Prophlayktische Maßnahmen bei (noch) gesunden Frauen werden in der S3-Leitlinie Mammakarzinom 2008 nicht empfohlen. Die Inhalte der übrigen Empfehlungen sind in ähnlicher bzw. abgewandelter Form in Kapitel A4 in den Empfehlungen oder im Hintergrundtext enthalten.

Tabelle 5: Familiäres Mammakarzinom

Leitlinie	Empfehlung	LoE[3]	GoR[1]	Referenzen
Familiäres Mammakarzinom				
NZGG 2009	All women from high risk families[4] should be offered referral to their regional genetics centre for information on genetic testing	+ n.a.	C	[Calderon-Margalit et al. 2004] [Christiaens et al. 2007]
NZGG 2009	Genetic counselling should be undertaken by a health practitioner with appropriate training (a certified genetic counsellor or medical geneticist)	n.a.	C	[Stopfer 2000]
NZGG 2009	Pre-test genetic counselling should include discussion of the following: ▪ aim of testing, inheritance, accuracy of the test (sensitivity and specificity) ▪ timeframe for providing results ▪ uncertainty of cancer risk estimates with a mutation ▪ possible test results (positive, negative, uninformative or variant of unknown clinical significance) ▪ implications for the individual and family including clinical management options, psychosocial impact of testing, potential risks of discrimination (eg, by life and health insurers); and ▪ alternative options to testing	n.a.	C	n.a.

[3] Für Erläuterungen des Level of Evidence (LoE) und Grade of Recommendation (GoR) siehe Anhang 5.6.
[4] Important risk factors include: early onset breast cancer, multiple affected family members, male breast cancer, bilateral breast cancer, ovarian cancer, Ashkenazi Jewish ancestry, or a known BRCA1 or BRCA2 mutation in the family

Leitlinie	Empfehlung	LoE[3]	GoR[1]	Referenzen
Familiäres Mammakarzinom				
NZGG 2009	Genetic testing aimed at identifying a mutation in a family should be offered to an affected family member. If a mutation is identified, predictive testing can then be offered to adult at-risk family members	n.a.	C	n.a.
NZGG 2009	Women or men with an estimated probability of 20% or greater of carrying a BRCA1 or BRCA2 mutation (probability estimated by use of models such as BRCAPRO or BOADICEA, and clinical judgment) should have access to genetic testing	n.a.	C	[National Institute for Clinical Excellence (NICE) 2004; Hopper et al. 2008; Parmigiani et al. 1998; Domchek et al. 2003; Antoniou et al. 2008]
NZGG 2009	Interpretation of test results and estimation of cancer risks for the family should take into account pedigree information, the analytical and clinical validity of the test methodology, and the penetrance and nature of the detected mutation	n.a.	C	n.a.
NZGG 2009	A woman with a significant family history of breast cancer or who is known to carry a BRCA1 or BRCA2 gene mutation should be offered the option of prophylactic mastectomy. Prophylactic salpingo-oophorectomy should also be discussed	1+	C	[Christiaens et al. 2007]
		+ / ~	n.a.	[Domchek et al. 2006]
		n.a.	n.a.	[Calderon-Margalit et al. 2004; Lostumbo et al. 2004; Bermejo-Perez et al. 2007; Evans et al. 2009]
NZGG 2009	A woman with a significant family history of breast cancer or who is known to carry a BRCA1 or BRCA2 gene mutation should have genetic counselling in a specialist cancer genetics clinic	n.a.	C	n.a.
NZGG 2009	For premenopausal women with a significant family history of breast cancer or who are known to carry a BRCA1 or BRCA2 mutation, information about bilateral salpingo-oophorectomy as a potential risk-	n.a.	C	[Kauff et al. 2008]

Leitlinie	Empfehlung	LoE[3]	GoR[1]	Referenzen
Familiäres Mammakarzinom				
	reducing strategy for breast cancer should be made available			
NZGG 2009	In women considering risk-reducing bilateral salpingo-oophorectomy, the lack of efficacy of screening should be discussed	n.a.	C	[van der Velde et al. 2009]
NZGG 2009	Breast conserving surgery should be used with caution in known BRCA gene carriers as it may result in high local recurrence rates	n.a.	GPP	n.a
Abkürzungen: GPP: good practice point; n.a. = nicht angegeben				

4.2.3 Empfehlungen zum Thema Diagnostik/Staging

4.2.3.1 Eingeschlossene Leitlinien

Zum Thema Diagnostik/Staging konnten drei Leitlinien der Gruppe 1 extrahiert werden [New Zealand Guidelines Group (NZGG) 2009; National Institute for Clinical Excellence (NICE) 2009; National Institute for Clinical Excellence (NICE) 2009]. Zwei Leitlinien wurden vom National Institute for Health and Clinical Excellence (NICE) aus Großbritannien in 2009 herausgegeben und adressieren die Diagnostik und Therapie der Primärerkrankung einschließlich lokal fortgeschrittener Tumore und die Therapie des fortgeschrittenen Mammakarzinoms. Für die Extraktion dieser Leitlinien (insbesondere der Evidenzklassifikationen [LoE]) wurden zusätzliche Hintergrund- bzw. Methodendokumente ausgewertet [National Institute for Clinical Excellence (NICE) 2009; National Institute for Clinical Excellence (NICE) 2009]. Zu den Empfehlungen haben die Autoren der NICE-Leitlinien sogenannte ‚Qualifying Statements' angeführt. Diese beschreiben zusammenfassend die zugrundeliegende Evidenz der Empfehlungen. Die ‚Qualifying Statements' wurden mit den Empfehlungen extrahiert, um als Ergänzung zu den berücksichtigten Referenzen auch die entsprechenden zusammenfassenden Einschätzungen der Autoren transparent zu machen

Eine Leitlinie wurde von der New Zealand Guidelines Group (NZGG) in 2009 herausgegeben. Diese Leitlinie adressiert umfassend die Diagnostik und Therapie der Primärerkrankung. Für die Extraktion dieser Leitlinie wurden keine weiteren Dokumente ausgewertet.

4.2.3.2 In der S3-Leitlinie Mammakarzinom 2008 nicht enthaltene oder diskrepante Empfehlungs-Inhalte

Die NICE 2009 early empfiehlt ebenso wie die S3-Leitlinie Mammakarzinom 2008 eine **Durchführung einer MRT nicht routinemäßig** (LoE 1++ bis 3, GoR n.a.). Als Indikationen werden – z.T. über die in der S3-Leitlinie Mammakarzinom 2008 aufgeführten genannt: Befunddiskrepanz zwischen klinischem Befund und/oder Ultraschall bzw. Mammographie für die weitere Behandlungsplanung, dichte Brust, die keine gut interpretierbare („accurat") Mammographie erlaubt sowie – diese Indikation entspricht der der S3-Leitlinie Mammakarzinom 2008 – Feststellung der Größenausdehnung bei lobulärem Karzinom. Die NZGG nennt in einer Empfehlung zur MRT (LoE ++ bis n.a., GoR A) neben der Indikation „lobuläres Mammakarzinom" und „dichte Brust" (entsprechend der NICE 2009 early) noch folgende weitere präoperative Indikationen: Verdacht auf multizentrisches Karzinom, klinisch oder mit sonstiger Bildgebung nicht darstellbares Karzinom (T0N+), hohes genetisches Risiko, Vorhandensein von Implantaten, Beurteilung nach neoadjuvanter Therapie und Alter unter 40 Jahren. In einem zusätzlichen „good practice point" (keine weiteren Angaben) wird darauf hingewiesen, dass eine MRT durchgeführt werden sollte, wenn eine nicht geringe („moderate") Wahrscheinlichkeit bestehe, dass das Ergebnis zur einer Änderung der therapeutischen Strategie führt. In den beiden genannten Leitlinien wird nicht darauf hingewiesen – wie dies in der S-3 Leitlinie

Mammakarzinom 2008 der Fall ist – , dass bei Durchführen einer MRT auch die Möglichkeit der MRT-gestützten Intervention vorhanden sein sollte.

Die NICE early 2009 empfiehlt im Rahmen der **Axillasonographie die Abklärung auffälliger Lymphknoten durch Feinnadelbiospie** (LoE 2+-3, GoT n.a.), da dies die Anzahl erforderlicher Sentinel Node Biopsien reduziere. Die Feinnadelbiopsie zur Abklärung auffälliger axillärer Befunde wird in der S3-Leitlinie Mammakarzinom 2008 nicht empfohlen.

Die NZGG führt aus, dass ein **Routinestaging bei PatientInnen mit T1-2 N0-1 nicht erforderlich** sei. Im (UICC-)Stadium I sei ein Röntgenthorax nicht erforderlich (LoE + bis n.a., GoR A). Als „good practice point" (keine weiteren Angaben) wird empfohlen, nach Erhalt der pathologischen Befunde ein Staging zu erwägen. Weiterhin empfiehlt die NZGG, das Durchführen einer Knochenszintigraphie, einer Lebersonographie und eines Röntgenthorax („thoracic imaging") bei fortgeschrittener operabler Erkrankung (T3 N1-2) in Betracht zu ziehen, wenn diese Befunde einen Einfluss auf die Behandlung haben (LoE ++ bis +/-, GoR n.a.). Die S3-Leitlinie Mammakarzinom 2008 empfiehlt ein Staging vor Beginn einer systemischen Primärtherapie. Grundsätzlich werden die genannten Staginguntersuchungen als sinnvoll zur Beurteilung der Ausgangssituation bei gesichertem Primärkarzinom angesehen, bei T1 N0 könne aber in der Regel darauf verzichtet werden.

Die NZGG nennt Ausnahmen, in denen eine klinische Indikation für die **Bestimmung präoperativer Serum-Biomarker** gesehen wird (good practice point, keine weiteren Angaben): u.a. bei Komorbidität, präoperativer Chemotherapie und fortgeschrittenerem Brustkrebs). In der S3-Leitlinie Mammakarzinom 2008 wird eine präoperative Bestimmung von Serum-Biomarkern als nicht erforderlich eingestuft, ohne Nennung von Ausnahmen.

Die NICE 2009 advanced spezifiziert **bildgebende Untersuchungsmethoden zur Diagnostik von Fernmetastasen** (viszerale und Knochenmetastasen). Diese Inhalte sind in der S3-Leitlinie Mammakarzinom 2008 im Kapitel zu Fernmetastasen adressiert.

Die übrigen Inhalte der übrigen Empfehlungen stimmen in ähnlicher bzw. leicht abgewandelter Form mit denen der S3-Leitlinie Mammakarzinom 2008 (Empfehlung oder Hintergrundtext) überein.

Zur diagnostischen Sicherung wurden keine Empfehlungen identifiziert.

Tabelle 6: Diagnostik/Staging

Leitlinie	Empfehlung	LoE[5]	GoR[1]	Referenzen
Diagnostik/Staging				
Primärdiagnostik				
NICE 2009 early	▪ The routine use of MRI of the breast is not recommended in the preoperative assessment of patients with biopsy-proven invasive breast cancer or DCIS. (Qualifying statement: There is insufficient evidence (a) to recommend the routine use of preoperative MRI in invasive breast cancer and no evidence that detection with MRI makes a difference to outcomes, and (b) on which to base any recommendation on the use of MRI in the assessment of the breast with a diagnosis of pure DCIS.) ▪ Offer MRI of the breast to patients with invasive breast cancer: o if there is discrepancy regarding the extent of disease from clinical examination, mammography and ultrasound assessment for planning treatment o if breast density precludes accurate mammographic assessment o to assess the tumour size if breast conserving surgery is being considered for invasive lobular cancer. (Qualifying statement: There is good quality evidence that MRI is effective at detecting size and multifocality. There is some published evidence and GDG consensus, based on the difficulties of assessing and treating lobular cancer, to support this recommendation. There is	1++ 2++ 2+ 3 n.a.	n.a. n.a. n.a. n.a. n.a.	[Blue Cross Blue Shield Association (BCBS) 2004] [Shiraishi et al. 2003; Schnall et al. 2005; Deurloo et al. 2006; Kvistad et al. 2000; Fischer et al. 2004] [Francescutti et al. 2002; Chung et al. 2005] [Menell et al. 2005; Boetes et al. 2004; Schelfout et al. 2004] [Bremner et al. 2007; Del Frate et al. 2007; Esserman et al. 1999]

[5] Für Erläuterungen des Level of Evidence (LoE) und Grade of Recommendation (GoR) siehe Anhang 5.6.

Leitlinie	Empfehlung	LoE[5]	GoR[1]	Referenzen
Diagnostik/Staging				
	no satisfactory health economic evidence to assist in this recommendation.)			
NICE 2009 early	▪ Pretreatment ultrasound evaluation of the axilla should be performed for all patients being investigated for early invasive breast cancer and, if morphologically abnormal lymph nodes are identified, ultrasound-guided needle sampling should be offered. (Qualifying statement: These recommendations are based on good evidence, including from a meta-analysis, of clinical effectiveness in reducing the number of patients who undergo SLNB and then need further axillary surgery, and reasonable evidence of cost effectiveness.)	2+	n.a.	[Alvarez et al. 2006]
		3	n.a.	[Altinyollar et al. 2005; Bartonkova et al. 2006; Brancato et al. 2004; Chandawarkar et al. 1997; Ciatto et al. 2007; Couto et al. 2004; Damera et al. 2003; de Kanter et al. 2006; Deurloo et al. 2003; Dixon et al. 1992; Esen et al. 2005; Hergan et al. 1996; Heusinger et al. 2005; Lee et al. 1996; Lemos et al. 2005; Nori et al. 2005; Perre et al. 1996; Podkrajsek et al. 2005; Sahoo et al. 2007; Sato et al. 2004; Somasundar et al. 2006; Stewart et al. 2006; van Rijk et al. 2006; Walsh et al. 1994]
		n.a.	n.a.	[Genta et al. 2007; Davies et al. 2006]
NZGG 2009	Magnetic resonance imaging (MRI) should be considered in specific clinical situations where other imaging modalities are not reliable, or have been inconclusive, and where there are indications that MRI is useful. These include: *Preoperative* ▪ Invasive lobular carcinoma	+ + +/- Quadas Score 10/14	A	[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Christiaens et al. 2007; Mann et al. 2008; Houssami et al. 2008; Solin et al. 2008] [Deurloo et al. 2006; Van Goethem M. et al. 2004]

Leitlinie	Empfehlung	LoE[5]	GoR[1]	Referenzen
Diagnostik/Staging				
	▪ Suspicion of multicentricity ▪ Lesions of the breast (ie, T0N+) not detectable on other clinical or imaging modalities ▪ Genetic high risk ▪ Women with breast implants ▪ Aged younger than 40 years ▪ Assessment following neoadjuvant treatment ▪ Women with dense breasts *Postoperative* ▪ Diagnosis of recurrence	n.a.		[Drew et al. 2008]
NZGG 2009	In a woman with early breast cancer magnetic resonance imaging should be considered where there is a moderate likelihood that it can lead to a change in management	n.a.	GPP	n.a.
NZGG 2009	Routine preoperative serum biomarkers are not recommended unless there are clinical indications (ie, comorbidity, preoperative chemotherapy, more advanced breast cancer)	n.a.	GPP	n.a.
NZGG 2009	Preoperative full blood count, renal function tests, liver function tests and calcium levels are recommended for assessment of fitness for surgery and adjuvant drug therapies	n.a.	GPP	n.a.

Leitlinie	Empfehlung	LoE[5]	GoR[1]	Referenzen
Diagnostik/Staging				
Diagnostik bei Fernmetastasen				
NICE 2009 advanced	▪ Assess the presence and extent of visceral metastases using a combination of plain radiography, ultrasound, computed tomograpy (CT) scans and magnetic resonance imaging (MRI).	1	n.a.	[Isasi et al. 2005; Shie et al. 2008]
	▪ Assess the presence and extent of metastases in the bones of the axial skeleton using bone windows on a CT scan or MRI or bone scintigraphy. ▪ Assess proximal limb bones for the risk of pathological fracture in patients with evidence of bone metastases elsewhere, using bone scintigraphy and/or plain radiography.	3	n.a.	[Abe et al. 2005; Altehoefer et al. 2001; Bradley et al. 2000; Bristow et al. 2008; Cook et al. 1998; Engelhard et al. 2004; Eubank et al. 2004; Fueger et al. 2005; Kamby et al. 1987; Nakai et al. 2005; Schirrmeister et al. 1999; Schmidt et al. 2008; Ternier et al. 2006]
	(Qualifying statement: There was insufficient evidence to support the choice of one imaging modality over another.)	3-	n.a.	[Eubank et al. 2001]
	▪ Use MRI to assess bony metastases if other imaging is equivocal for metastatic disease or if more information is needed (for example, if there are lytic metastases encroaching on the spinal canal). (Qualifying statement: There was GDG consensus that MRI should be used in these situations.)	n.a.	n.a.	[Haubold-Reuter et al. 1993]
	▪ Positron emission tomography fused with computed tomography (PET-CT) should only be used to make a new diagnosis of metastases for patients with breast cancer whose imaging is suspicious but not diagnostic of metastatic disease. (Qualifying statement: There was GDG consensus that PET-CT should be used in this situation.)			

Leitlinie	Empfehlung	LoE[5]	GoR[1]	Referenzen
Diagnostik/Staging				
Staging				
NZGG 2009	In asymptomatic women with early operable breast cancer (T1–2, N0–1), routine screening for metastatic disease is not required For women with stage I breast cancer, preoperative chest X-ray is not routinely indicated for staging purposes	+	A	[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Christiaens et al. 2007]
		n.a.		[National Breast Cancer Centre (NBCC) 2001; Myers et al. 2001; Zuiden 2005]
		Quadas Score 9/14		[Aslan et al. 2006]
NZGG 2009	Screening for metastatic disease should be reconsidered after pathology results are available	n.a.	GPP	n.a.
NZGG 2009	Bone scintigraphy, liver scans and thoracic imaging should be considered for patients with more advanced but operable disease (T3, N1–2) if it will affect treatment	+	n.a.	[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Christiaens et al. 2007]
		+ +/-	n.a.	[Shie et al. 2008]
NZGG 2009	Clinical staging based on history and physical examination should be routinely performed prior to treatment	n.a.	C	n.a.

Abkürzungen: DCIS = CT = computed tomography scan; Ductal carcinoma in situ; GDG = Guideline development group; GPP = Good practice point; MRI = magnetic resonance imaging; n.a. = nicht angegeben; PET-CT = Positron emission tomography fused with computed tomography

4.2.4 Empfehlungen zum Thema Pathomorphologische Untersuchungen und Prognosefaktoren

4.2.4.1 Eingeschlossene Leitlinien

Zum Thema Pathomorphologische Untersuchungen und Prognosefaktoren konnten drei Leitlinien der Gruppe 1 [New Zealand Guidelines Group (NZGG) 2009; National Institute for Clinical Excellence (NICE) 2009; National Institute for Clinical Excellence (NICE) 2009] und zwei Leitlinien der Gruppe 2 extrahiert werden [Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group 2009; Hammond et al. 2010]. Die Leitlinien der Gruppe 2 wurden zusätzlich extrahiert, da die beiden NICE und die NZGG Leitlinien nur wenige Empfehlungen zum Thema enthielten und einige der Aspekte der beiden zusätzlichen Leitlinien nicht enthalten waren.

Die beiden Leitlinien vom National Institute for Health and Clinical Excellence (NICE) aus Großbritannien wurden 2009 herausgegeben und adressieren die Diagnostik und Therapie der Primärerkrankung einschließlich lokal fortgeschrittener Tumore und die Therapie des fortgeschrittenen Mammakarzinoms. Für die Extraktion dieser Leitlinien (insbesondere der Evidenzklassifikationen [LoE]) wurden zusätzliche Hintergrund- bzw. Methodendokumente ausgewertet [National Institute for Clinical Excellence (NICE) 2009; National Institute for Clinical Excellence (NICE) 2009]. Zu den Empfehlungen haben die Autoren der NICE-Leitlinien sogenannte ‚Qualifying Statements' angeführt. Diese beschreiben zusammenfassend die zugrundeliegende Evidenz der Empfehlungen. Die ‚Qualifying Statements' wurden mit den Empfehlungen extrahiert, um als Ergänzung zu den berücksichtigten Referenzen auch die entsprechenden zusammenfassenden Einschätzungen der Autoren transparent zu machen. Eine Leitlinie wurde von der New Zealand Guideline Group (NZGG) 2009 herausgegeben, sie adressiert die Diagnostik und Therapie der Primärerkrankung.

Die von der American Society of Clinical Oncology (ASCO) 2010 herausgegebene Leitlinie enthält detaillierte Empfehlungen zur Durchführung und Interpretation von immunhistochemischen Tests zum Östrogen- und Progesteronrezeptorstatus beim Mammakarzinom. Für die Extraktion dieser Leitlinie wurden keine weiteren Dokumente ausgewertet. Die Leitlinie der „Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group" befasst sich ausschließlich mit dem Gen-Profiling von Mammakarzinomen.

Zu beachten ist, dass Anforderungen und Abläufe pathomorphologischer Untersuchungen in vielen Fällen rein konsensbasiert beschlossen werden. Hierzu wird in der S3-Leitlinie Mammakarzinom 2008 bereits auf mehrere anerkannte Dokumente verwiesen (u.a. z.B. die „Quality assurance guidelines for pathology" oder die „European guidelines for quality assurance in mammography screening"), die aufgrund fehlender Evidenzbasierung in die vorliegende Synopse nicht aufgenommen wurden. Diese Dokumente haben eine wichtige Bedeutung für eine verbesserte Standardisierung und Qualität der Befundung.

4.2.4.2 In der S3-Leitlinie Mammakarzinom 2008 nicht enthaltene und diskrepante Empfehlungs-Inhalte

Die EGAPP 2008 Leitlinie spricht wegen insuffizienter vorliegender Evidenz **keine Empfehlung zum Gen-Profiling** von Brustkarzinomen aus (LoR, GoR n.a.). Die S3-Leitlinie Mammakarzinom 2008 thematisiert das Gen-Profiling nicht.

Die NICE 2009 early empfiehlt im Gegensatz zur S3-Leitlinie Mammakarzinom 2008 beim invasiven Mammakarzinom **keine routinemäßige Bestimmung des Progesteronrezeptors** (LoE 2+, GoR n.a.) mit dem Hinweis, dass keine starke Evidenz für dessen Nutzen als prädiktiver Wert vorliege. Die ASCO 2010-Rezep und die NZGG empfiehlen dagegen wie die S3-Leitlinie Mammakarzinom 2008 die Bestimmung sowohl des Östrogen- als auch des Progesteronrezeptorstatus (LoE/GoR n.a.). Bezüglich des Östrogen- und HER-2-Status wird in der NICE 2009 early empfohlen, sicherzustellen, dass die **Ergebnisse verfügbar und dokumentiert** sind, wenn im Rahmen des multidisziplinären Treffens über die systemische Therapie beraten wird (LoE 3, GoR n.a.). Diese explizite Aufforderung findet sich in der S3-Leitlinie Mammakarzinom 2008 nicht, ggf. in den Anforderungen an Brustzentren.

Für die Interpretation des (immunhistochemisch bestimmten) Rezeptorstatus empfiehlt die ASCO 2010-Rezep als optimalen **Test-Algorithmus einen cut-off für Positivität von 1%** (LoE/GoR n.a.). Dabei wird betont, dass bei negativem Ergebnis (<1%) positive intrinsische Kontrollen vorliegen müssen („presence of evidence that the sample can express ER or PgR“) (LoE, GoR n.a.). Die S3-Leitlinie Mammakarzinom 2008 nennt als Grenze für Positivität >10% und weist Tumoren von 1-9% positiver Zellen ein unsicheres endokrines Ansprechen zu. Eine Unsicherheit bei der Grenzwertfestlegung wird explizit eingeräumt.
Die ASCO 2010-Rezep gibt auch eine Empfehlung dazu ab, wann ein **Gewebsstück** bezüglich Östrogen- oder Progesteronrezeptorstatus als **nicht interpretierbar** einzustufen ist (LoE/GoR n.a.). Diese Angabe ist in der S3-Leitlinie Mammakarzinom 2008 nicht enthalten. Weiterhin finden sich **Empfehlungen zu optimalen Test-Bedingungen und optimalen Voraussetzungen** für den Umgang mit dem verwendeten Gewebe (LoE/GoR n.a.), die in der S3-Leitlinie Mammakarzinom 2008 nicht enthalten sind. Ebenfalls nicht enthalten sind Empfehlungen der ASCO 2010-REZEP (ohne LoE, GoR) zur **initialen und fortlaufenden Personalschulung** (Laborpersonal/Pathologen) und Kompetenzbewertung sowie zur Spezifizierung des Zeitraums der (internen) **Überpüfung der Assays mindestens 2x pro Jahr** oder bei entsprechenden Veränderungen und die Empfehlung zur **jährlichen Akkreditierung des** mit der Untersuchung beauftragten **Labors**.

Die ASCO 2010-Rezep empfiehlt eine **externe Überprüfung mindestens 2x pro Jahr**, die S3-Leitlinie Mammakarzinom 2008 mindestens 1x pro Jahr. Bei der externen Überprüfung empiehlt die ASCO 2010-Rezep eine mind. 90% korrekte Performance als zufriedenstellend.

Die NICE 2009 advanced empfiehlt **bei Auftreten eines Rezidivs keine erneute Bestimmung des Östrogenrezeptor- oder HER-2-Status**, wenn diese bereits bei der Primärdiagnose bestimmt wurden (LoE 3, GoR n.a.). Dies wird in der S3-Leitlinie Mammakarzinom 2008 nicht thematisiert.

Die übrigen Empfehlungen finden sich in ähnlicher oder abgewandelter Form in der S3-Leitlinie Mammakarzinom 2008.

Tabelle 7: Pathomorphologische Untersuchungen und Prognosefaktoren

Leitlinie	Empfehlung	LoE[6]	GoR[1]	Referenzen
Pathomorphologische Untersuchungen und Prognosefaktoren				
EGAPP 2008	The EGAPP Working Group (EWG) found insufficient evidence to make a recommendation for or against the use of tumor gene expression profiles to improve outcomes in defined populations of women with breast cancer. For one test, the EWG found preliminary evidence of potential benefit of testing results to some women who face decisions about treatment options (reduced adverse events due to low risk women avoiding chemotherapy), but could not rule out the potential for harm for others (breast cancer recurrence that might have been prevented). The evidence is insufficient to assess the balance of benefits and harms of the proposed uses of the tests. The EWG encourages further development and evaluation of these technologies.	n.a.	n.a.	[Paik et al. 2004; Marchionni et al. 2008; Marchionni et al. 2008; Piper 2008; Food and Drug Administration 2008; Glas et al. 2006; Van de Vijver et al. 2002; Food and Drug Administration 2007; Ach et al. 2007; Buyse et al. 2006; Cronin et al. 2007; Habel et al. 2006; Chang et al. 2008; Cobleigh et al. 2005; Esteva et al. 2005; Gianni et al. 2005; Mina et al. 2007; Ma et al. 2006; Goetz et al. 2006; Jerevall et al. 2008; Paik et al. 2006; Van't Veer et al. 2002; European Organisation for Research and Treatment of Cancer (EORTC) 2011; National Cancer Institute 2011; Hornberger et al. 2005; Lyman et al. 2007; Oestreicher et al. 2005; Quest

[6] Für Erläuterungen des Level of Evidence (LoE) und Grade of Recommendation (GoR) siehe Anhang 5.6.

Leitlinie	Empfehlung	LoE[6]	GoR[1]	Referenzen
Pathomorphologische Untersuchungen und Prognosefaktoren				
				Diagnostics 2011]
NICE 2009 early	▪ Assess ER status of all invasive breast cancers, using immunohistochemistry with a standardised and qualitatively assured methodology, and report the results quantitatively.	2+	n.a.	[Dowsett et al. 2006; Stendahl et al. 2006]
	▪ Do not routinely assess progesterone receptor status of tumours in patients with invasive breast cancer. ▪ Test HER2 status of all invasive breast cancers, using a standardised and qualitatively assured methodology. ▪ Ensure that the results of ER and HER2 assessments are available and recorded at the multidisciplinary team meeting when guidance about systemic treatment is made. (Qualifying statement: These recommendations are based on evidence from observational studies that ER status is a useful predictor of survival and response to tamoxifen but that there is no strong evidence for the usefulness of measuring PR status.)	3	n.a.	[Ponzone et al. 2006; Dowsett et al. 2008]
NICE 2009 advanced	▪ Patients with tumours of known oestrogen receptor (ER) status whose disease recurs should not have a further biopsy just to reassess ER status. (Qualifying statement: Although there is some evidence from observational studies that ER status can change on recurrence, there was GDG consensus that there are few clinical situations in which re-biopsy can be justified.) ▪ Patients with tumours of known human epidermal growth factor receptor 2 (HER2) status whose disease recurs should not have a further biopsy just to reassess HER2 status. (Qualifying statement: The evidence about change in HER2 status was	3	n.a.	[Niehans et al. 1993; Shimizu et al. 2000; Gancberg et al. 2002; Carlsson et al. 2004; Regitnig et al. 2004; Gong et al. 2005; Zidan et al. 2005; Lorincz et al. 2006; Rom et al. 2006; Pectasides et al. 2006; Tapia et al. 2007; Santinelli et al. 2008; Spataro et al. 1992; Johnston et al. 1995; Lower et al. 2005; Brankovic-Magic et al. 1992]

Leitlinie	Empfehlung	LoE[6]	GoR[1]	Referenzen
Pathomorphologische Untersuchungen und Prognosefaktoren				
	poor and there was no evidence about how to manage patients in whom a change was detected.) ▪ Assess ER and HER2 status at the time of disease recurrence if receptor status was not assessed at the time of initial diagnosis. In the absence of tumour tissue from the primary tumour, and if feasible, obtain a biopsy of a metastasis to assess ER and HER2 status. (Qualifying statement: This recommendation is based on the GDG consensus that knowledge of receptor status will significantly affect management.)			
NZGG 2009	Every primary breast carcinoma should be submitted for oestrogen and progesterone receptor assay	n.a.	C	n.a.
	Pathology reports should formally state both the proportion of positive nuclei and intensity of staining for oestrogen receptor and progesterone receptor to which a simple scoring system (eg, Allred) can be applied	n.a.	C	[National Health Service Breast Screening Programme (NHSBSP) 2005; Goldhirsch et al. 2007; National Breast and Ovarian Cancer Centre (NBOCC) 2008]
		-		[Kurosumi 2007]
NZGG 2009	Participation in a quality assurance programme, such as the RCPA QAP or UK scheme, with an attainment of at least ‘satisfactory’ performance is recommended	n.a.	GPP	n.a.
NZGG 2009	Optimal tissue handling and prompt fixation of the sample preferably within one hour (or as soon as possible) from incision of the lesion is required	n.a.	GPP	n.a.

Leitlinie	Empfehlung	LoE[6]	GoR[1]	Referenzen
Pathomorphologische Untersuchungen und Prognosefaktoren				
ASCO 2010-Rezep	Optimal algorithm for ER/PgR testing: ▪ Positive for ER or PgR if finding of ≥ 1% of tumor cell nuclei are immunoreactive. ▪ Negative for ER or PgR if finding of < 1% of tumor cell nuclei are immunoreactive in the presence of evidence that the sample can express ER or PgR (positive intrinsic controls are seen). ▪ Uninterpretable for ER or PgR if finding that no tumor nuclei are immunoreactive and that internal epithelial elements present in the sample or separately submitted from the same sample lack any nuclear staining	n.a.	n.a.	[Paik et al. 2004; Stendahl et al. 2006; Barnes et al. 1996; Harvey et al. 1999; Elledge et al. 2000; Thomson et al. 2002; Regan et al. 2006; Mohsin et al. 2004; Badve et al. 2008; Viale et al. 2007; Viale et al. 2008; Cheang et al. 2006; McGuire et al. 1975; Osborne et al. 1980; Knight, III et al. 1980; Cowen et al. 1990; Lockwood 2010; Esteban et al. 1994; Yamashita et al. 2006; Dowsett et al. 2008; Phillips et al. 2007]
ASCO 2010- Rezep	Optimal testing conditions ▪ Large, preferably multiple core biopsies of tumor are preferred for testing if they are representative of the tumor (grade and type) at resection. ▪ Interpretation follows guideline recommendation. ▪ Accession slip and report must include guideline-detailed elements.	n.a.	n.a.	n.a.
ASCO 2010- Rezep	Optimal tissue handling requirements ▪ Time from tissue acquisition to fixation should be as short as possible. Samples for ER and PgR testing are fixed in 10% NBF for 6 to 72 hours. Samples should be sliced at 5-mm intervals after appropriate gross inspection and margins designation and placed in sufficient volume of NBF to allow adequate tissue penetration. If tumor comes from remote location, it should be bisected through the tumor on removal and sent to the laboratory immersed in a sufficient volume of NBF. Cold ischemia time, fixative type, and time the sample was placed in NBF must be recorded.	n.a.	n.a.	[Fitzgibbons et al. 2010; Yaziji et al. 2008; Gown 2004; Nenci et al. 1976; Diaz et al. 2005; Goldstein et al. 2003; Taylor et al. 2006]

Leitlinie	Empfehlung	LoE[6]	GoR[1]	Referenzen
Pathomorphologische Untersuchungen und Prognosefaktoren				
	▪ As in the ASCO/CAP HER2 guideline, storage of slides for more than 6 weeks before analysis is not recommended. ▪ Time tissue is removed from patient, time tissue is placed in fixative, duration of fixation, and fixative type must be recorded and noted on accession slip or in report.			
ASCO 2010- Rezep	Optimal internal validation procedure ▪ Validation of any test must be done before test is offered. See separate article on testing validation (Fitzgibbons et al 7). ▪ Validation must be done using a clinically validated ER or PgR test method. ▪ Revalidation should be done whenever there is a significant change to the test system, such as a change in the primary antibody clone or introduction of new antigen retrieval or detection systems.	n.a.	n.a.	[Fitzgibbons et al. 2010]
ASCO 2010- Rezep	Optimal internal QA procedures ▪ Initial test validation. See separate article on testing validation (Fitzgibbons et al [8]). ▪ Ongoing quality control and equipment maintenance. ▪ Initial and ongoing laboratory personnel training and competency assessment.	n.a.	n.a.	[Fitzgibbons et al. 2010]

7 Fitzgibbons PL, Murphy DA, Hammond MEH, et al: Recommendations for validating estrogen and progesterone receptor immunohistochemistry assays. Arch Pathol Lab Med (in press)

[8] Fitzgibbons PL, Murphy DA, Hammond MEH, et al: Recommendations for validating estrogen and progesterone receptor immunohistochemistry assays. Arch Pathol Lab Med (in press)

Leitlinie	Empfehlung	LoE[6]	GoR[1]	Referenzen
Pathomorphologische Untersuchungen und Prognosefaktoren				
	▪ Use of standardized operating procedures including routine use of external control materials with each batch of testing and routine evaluation of internal normal epithelial elements or the inclusion of normal breast sections on each tested slide, wherever possible. ▪ Regular, ongoing assay reassessment should be done at least semiannually (as described in Fitzgibbons et al [8]). Revalidation is needed whenever there is a significant change to the test system. ▪ Ongoing competency assessment and education of pathologists.			
ASCO 2010- Rezep	Optimal external proficiency assessment ▪ Mandatory participation in external proficiency testing program with at least two testing events (mailings) per year. ▪ Satisfactory performance requires at least 90% correct responses on graded challenges for either test.	n.a.	n.a.	[Yaziji et al. 2008; Wolff et al. 2007; Wolff et al. 2007]
ASCO 2010- Rezep	Optimal laboratory accreditation ▪ On-site inspection every other year with annual requirement for selfinspection.	n.a.	n.a.	n.a.
Abkürzungen: EGAPP = Evaluation of Genomic Applications in Practice and Prevention; ER = estrogen receptor; PgR = progesterone receptor; IHC = immunohistochemistry; QA = quality assurance; ; n.a. = nicht angegeben; NBF = neutral buffered formalin; ASCO = American Society of Clinical Oncology; CAP = College of American Pathologists; HER2 = human epidermal growth factor receptor 2.				

4.2.5 Empfehlungen zum Thema Operative Therapie

4.2.5.1 Eingeschlossene Leitlinien

Zum Thema Operative Therapie konnten zwei Leitlinien der Gruppe 1 [New Zealand Guidelines Group (NZGG) 2009; National Institute for Clinical Excellence (NICE) 2009] und eine Leitlinie der Gruppe 2 [National Institute for Clinical Excellence (NICE) 2009] extrahiert werden. Zwei Leitlinien wurden vom National Institute for Health and Clinical Excellence (NICE) aus Großbritannien in 2009 herausgegeben. Eine der Leitlinien adressiert die Diagnostik und Therapie der Primärerkrankung einschließlich lokal fortgeschrittener Tumore [National Institute for Clinical Excellence (NICE) 2009]. Die andere Leitlinie gibt Empfehlungen zur endoskopischen Mastektomie und „Wide Excision" (NICE Endoscopic mastectomy 2009). Für die Extraktion der umfassenden Leitlinie (insbesondere der Evidenzklassifikationen [LoE]) wurde zusätzlich ein Hintergrund- bzw. Methodendokument ausgewertet [National Institute for Clinical Excellence (NICE) 2009]. Zu den Empfehlungen haben die Autoren der umfassenden NICE-Leitlinie [National Institute for Clinical Excellence (NICE) 2009] sogenannte ‚Qualifying Statements' angeführt. Diese beschreiben zusammenfassend die zugrundeliegende Evidenz der Empfehlungen. Die ‚Qualifying Statements' wurden mit den Empfehlungen extrahiert, um als Ergänzung zu den berücksichtigten Referenzen auch die entsprechenden zusammenfassenden Einschätzungen der Autoren transparent zu machen. Die Leitlinien von NICE enthalten außerdem Empfehlungen für die weitere Erforschung bestimmter Aspekte (Research Recommendations). Diese Empfehlungen wurden extrahiert und entsprechend gekennzeichnet.

Eine Leitlinie wurde von der New Zealand Guidelines Group (NZGG) 2009 herausgegeben. Diese Leitlinie adressiert umfassend die Diagnostik und Therapie der Primärerkrankung. Für die Extraktion dieser Leitlinie wurden keine weiteren Dokumente ausgewertet.

4.2.5.2. In der S3-Leitlinie Mammakarzinom nicht enthaltene oder diskrepante Empfehlungs-Inhalte

Im Gegensatz zur S3-Leitlinie Mammakarzinom 2008 empfiehlt die NZGG einen **tumorfreien Randsaum von 2mm** (LoE + bis n.a., GoR C). Falls dieser nicht erreicht werden kann, werden Aspekte genannt, die im Hinblick auf eine **Nachresektion** zu bedenken sind, wie z.B. Alter oder histologischer Befund (LoE + bis n.a., GoR C). Nachresektionen werden in der S3-Leitlinie Mammakarzinom 2008 nicht thematisiert. Ebenso wird die Quadrantektomie, die in der NZGG wegen ungünstiger kosmetischer Ergebnisse nicht routinemäßig empfohlen wird (LoE + bis n.a., GoR B) nicht thematisiert.

Die NICE 2009 early empfiehlt, die **brusterhaltende Operation (BET**) mit Entfernung des Nippel-Areola-Komplexes bei vorliegendem **Morbus Paget** (der Mamille) als lokale Therapie zu werten. Zu onkoplastischen Eingriffen zur Verbesserung des kosmetischen

Ergebnisses wird geraten (LoE 3, GoR n.a.). Die operative Behandlung von Morbus Paget wird in der S3-Leitlinie Mammakarzinom 2008 nicht thematisiert.

Die NZGG empfiehlt weiterhin, eine BET für Patientinnen mit zentralem Tumor zu erwägen, auch wenn dies die Exzision des Nippel-Areola-Komplexes erfordern sollte und das kosmetische Ergebnis beeinträchtigen könnte (LoE + bis n.a., GoR A). Dies wird in der S3-Leitlinie Mammakarzinom 2008 nicht explizit thematisiert.

Bei den **Indikationen zur Mastektomie** nennt die NZGG entsprechend der S3-Leitlinie Mammakarzinom 2008 ausgedehnte Kalzifikationen vom malignen Typ bzw. Multizentrizität, allerdings verbunden mit dem Hinweis, dass die Mastektomie dann indiziert sei, wenn bei brusterhaltender Therapie kein akzeptables kosmetisches Ergebnis erreicht werden könne (LoE n.a., GoR A). Dieser Hinweis fehlt in der S3-Leitlinie Mammakarzinom 2008. Im Hintergrundtext zur BET wird dagegen explizit ausgeführt, dass von einer brusterhaltenden Therapie bei Vorliegen von Multizentrizität Abstand genommen werden sollte. Die NZGG nennt auch „fitness for surgery“ als einen zu bedenkenden Aspekt für eine Mastektomie (LoE n.a., GoR A), der in der S3-Leitlinie Mammakarzinom nicht genannt wird.

Die NZGG empfiehlt, Patientinnen mit „early stage breast cancer“ über Nutzen und möglichen Schaden einer Bestrahlung zu informieren, bevor sie sich zwischen einer BET und einer Mastektomie entscheiden (LoE + bis n.a., GoR A). Dies wird in der S3-Leitlinie Mammakarzinom 2008 ggf. implizit vorausgesetzt, d.h. nicht explizit thematisiert.

Wie die S3-Leitlinie Mammakarzinom 2008 empfiehlt die NZGG eine auf die individuelle Patientin zugeschnittene lokale Therapie. Allerdings wird dies mit dem Erreichen eines möglichst geringen lokalen Rezidivrisikos begründet („good practice point“), nicht wie in der S3-Leitlinie Mammakarzinom 2008 mit dem Wunsch der Patientin.

Die NZGG empfiehlt, die **operative Therapie innerhalb 20 Werktagen** nach Diagnoststellung durchzuführen und gibt dafür auch Ausnahmen an. Dies wird in der S3-Leitlinie Mammakarzinom 2008 nicht thematisiert.

Die NICE 2009 Endoscopic empfiehlt die **endoskopisch durchgeführte „Wide Excision“ oder Mastektomie** nur im Kontext von Studien durchzuführen aufgrund zu weniger vorliegender Studien zu Sicherheit und Wirksamkeit. Weitere Forschung wird empfohlen (LoE, GoR n.a.). Endoskopisch durchgeführte operative Eingriffe werden in der S3-Leitlinie Mammakarzinom nicht thematisiert.

Die Indikation für eine **Sentinel Node Biospie** (SNP) wird in der NICE 2009 early und in der NZGG auch vom Vorliegen einer negativen axillären Axillasonographie bzw. eines negativen Feinnadelbiopsie-Ergebnisses abhängig gemacht (LoE 2 bis 3, GoR n.a., LoE+ bis n.a., GoR B) bzw. bei positivem Feinnadelergebnis wird in der NICE 2009 early die Durchführung einer weiteren axillären Therapie, v.a. Axilladissektion, empfohlen (LoE 2-3, GoR n.a.). Die S3-Leitlinie Mammakarzinom 2008 nennt keine Bildgebung, sondern nur den klinischen Verdacht auf fortgeschrittene Lymphknotenbeteiligung als Kontraindiaktion für eine Sentinel Node Biopsie. Die NZGG nennt als

Indikation für die SNP Tumoren bis 3 cm (LoE + bis n.a., GoR B). Die S3-Leitlinie Mammakarzinom 2008 führt aus, dass bei entsprechender Erfahrung auch SNP bei Tumoren größer als 3 cm durchgeführt werden können.

Weiterhin enthalten die NICE 2009 early und vor allem die NZGG viele Empfehlungen zur Durchführungs- und Strukturqualität bzw. Qualitätssicherung der SNP, die in der S3-Leitlinie nicht enhalten sind.

Im Hinblick auf die **Durchführung der Axilladissektion** enthält die NZGG detaillierte Empfehlungen, die in der S3-Leitlinie Mammakarzinom 2008 nicht enthalten sind, u.a. dass bei einzelnen Tumorzellen auf eine Axilladissektion verzichtet werden kann. Die NICE 2009 early empfiehlt PatientInnen bei positivem Sentinel eine Studienteilnahme mit Randomisierung zwischen axillärer Strahlentherapie und Axilladissektion (LoE n.a. „research recommendation“). Dies wird in der S3-Leitlinie Mammakarzinom nicht thematisiert.

Es finden sich weiterhin in der NZGG detaillierte Empfehlungen zu **Risikofaktoren für ein Lymphödem und Prävention des Lymphödems**, nach axillären Eingriffen, die im entsprechenden Abschnitt D.5.4.1 der S3-Leitlinie Mammakarzinom 2008 nicht abgebildet sind.

Für die Exzision **supraklavikulärer Lymphknoten** oder **Lymphknoten entlang der Arteria mammaria interna** gibt die NZGG aufgrund ungenügender Evidenz keine Empfehlung (LoE n.a., GoR I). Diese Lymphknotenregionen werden in der S3-LL Mammakarzinom 2008 nicht thematisiert.

Die übrigen Empfehlungen finden sich in ähnlicher Form in der S3-Leitlinie Mammakarzinom 2008.

Tabelle 8: Operative Therapie

Leitlinie	Empfehlung	LoE[9]	GoR[1]	Referenzen
Operative Therapie				

[9] Für Erläuterungen des Level of Evidence (LoE) und Grade of Recommendation (GoR) siehe Anhang 5.6.

Leitlinie	Empfehlung	LoE[9]	GoR[1]	Referenzen
Operative Therapie				
Brusterhaltende Therapie und Mastektomie				
NICE 2009 Endoscopie	1.1 Current evidence on the safety and efficacy of endoscopic mastectomy and endoscopic wide local excision for breast cancer is inadequate in quantity. Therefore, these procedures should only be used in the context of research. The research should include adequacy of resection margins, survival, recurrence or reoperation rates, tumour size and location, patient breast size, quality of life, and cosmesis. 1.2 Research should be conducted only in units specialising in the management of breast cancer, by surgeons trained in both breast cancer surgery and endoscopy. 1.3 NICE may review the procedure on publication of further evidence.	n.a.	n.a.	[Kitamura et al. 2002; Yamashita et al. 2008; Yamashita et al. 2006; Tamaki et al. 1998; Yamashita et al. 2008; Yamashita et al. 2006; Tamaki et al. 1998; Tamaki et al. 2001; Owaki et al. 2005; Lee et al. 2006; Ho et al. 2002] [Nakajima et al. 2009; Ito et al. 2008; Nakajima et al. 2002; Tamaki et al. 2002; Yamaguchi et al. 2008; Yamashita et al. 2006; Yamashita et al. 2008; Yamashita et al. 2008]
NICE 2009 early	▪ Offer breast conserving surgery with removal of the nipple-areolar complex as an alternative to mastectomy for patients with Paget's disease of the nipple that has been assessed as localised. Offer oncoplastic repair techniques to maximise cosmesis. (Qualifying statement: This recommendation was based on observational studies which provided no strong evidence that survival of these patients would be adversely affected by having breast conserving surgery rather than mastectomy.)	3	n.a.	[Singh et al. 1999; Bijker et al. 2001; Dixon et al. 1991; Duff et al. 1998; Howard et al. 1989; Nicolosi et al. 1996; Polgar et al. 2002; Zurrida et al. 1993; Estabrook et al. 1996; Marshall et al. 2003; Chen et al. 2006]
NICE 2009 early	▪ Offer local treatment by mastectomy (or in exceptional cases, breast conserving surgery) followed by radiotherapy to patients with locally advanced or inflammatory breast cancer who have been treated with chemotherapy,. (Qualifying statement: This recommendation is based on evidence from a	1++	n.a.	[Mieog et al. 2007]
		1+		[Mauri et al. 2005; Veyret et al. 2006]
		1-		[Buchholz et al. 2006]

Leitlinie	Empfehlung	LoE[9]	GoR[1]	Referenzen
Operative Therapie				
	RCT and retrospective studies and GDG consensus.)	2+		[Shenkier et al. 2004]
		3		[Huang et al. 2004; McGuire et al. 2007]
NZGG 2009	All women with early stage invasive breast cancer who are candidates for breast conserving surgery should be offered the choice of breast conserving surgery or mastectomy	+		[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Christiaens et al. 2007; Rodger et al. 2006]
		n.a.	A	[National Breast Cancer Centre (NBCC) 2001; Wright et al. 2003; McCready et al. 2005; Jatoi et al. 2005; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 1995; Veronesi et al. 1990; Blichert-Toft et al. 1992; Fisher 1995; Fallowfield et al. 1990; Turner et al. 1998; Moyer 1997; Sacchini et al. 1991; Clarke et al. 2005]
NZGG 2009	The choice of surgery should be tailored to the individual, who should be fully informed of the options, and who should be made aware that radiotherapy is required following breast conserving surgery and that further surgery may be required if the margins are positive or close	+		[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Christiaens et al. 2007; Rodger et al. 2006]
		n.a.	A	[National Breast Cancer Centre (NBCC) 2001; Wright et al. 2003; McCready et al. 2005; Jatoi et al. 2005; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 1995; Veronesi et al. 1990; Blichert-Toft et al. 1992; Fisher 1995; Fallowfield et al. 1990; Turner et al.

Leitlinie	Empfehlung	LoE[9]	GoR[1]	Referenzen
Operative Therapie				
				1998; Moyer 1997; Sacchini et al. 1991; Clarke et al. 2005]
NZGG 2009	A woman with early stage invasive breast cancer should be informed of the benefits and harms of radiotherapy prior to making a decision regarding breast conserving surgery or mastectomy	+		[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Christiaens et al. 2007; Rodger et al. 2006]
		n.a.	A	[National Breast Cancer Centre (NBCC) 2001; Wright et al. 2003; McCready et al. 2005; Jatoi et al. 2005; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 1995; Veronesi et al. 1990; Blichert-Toft et al. 1992; Fisher 1995; Fallowfield et al. 1990; Turner et al. 1998; Moyer 1997; Sacchini et al. 1991; Clarke et al. 2005]
NZGG 2009	Mastectomy rather than breast conserving surgery should be considered if: ▪ the ratio of the size of the tumour to the size of the breast, and	+	A	[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Christiaens et al. 2007; Rodger et al. 2006]

Leitlinie	Empfehlung	LoE[9]	GoR[1]	Referenzen
Operative Therapie				
	location of the tumour would not result in acceptable cosmesis ▪ there is multifocal/multicentric disease or extensive malignant microcalcification on mammogram which can not be adequately cleared with an acceptable cosmetic result with breast conserving surgery ▪ there is a contraindication to local radiotherapy (eg, previous radiotherapy at this site, connective tissue disease, severe heart and lung disease, pregnancy) ▪ fitness for surgery is an issue ▪ patient choice	n.a.		[National Breast Cancer Centre (NBCC) 2001; Wright et al. 2003; McCready et al. 2005; Jatoi et al. 2005; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 1995; Veronesi et al. 1990; Blichert-Toft et al. 1992; Fisher 1995; Fallowfield et al. 1990; Turner et al. 1998; Moyer 1997; Sacchini et al. 1991; Clarke et al. 2005]
NZGG 2009	Breast conserving surgery can be considered for a woman with a centrally located tumour, although it may require excision of the nipple and areola, which may compromise cosmesis	+		[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Christiaens et al. 2007; Rodger et al. 2006]
		n.a.	A	[National Breast Cancer Centre (NBCC) 2001; Wright et al. 2003; McCready et al. 2005; Jatoi et al. 2005; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 1995; Veronesi et al. 1990; Blichert-Toft et al. 1992; Fisher 1995; Fallowfield et al. 1990; Turner et al. 1998; Moyer 1997; Sacchini et al. 1991; Clarke et al. 2005]
NZGG 2009	Breast conserving surgery should be used with caution in known BRCA gene carriers as it may result in high local recurrence rates	n.a.	GPP	n.a
NZGG 2009	A woman with early breast cancer should be informed that local recurrence	n.a.	GPP	n.a

Leitlinie	Empfehlung	LoE[9]	GoR[1]	Referenzen
Operative Therapie				
	can occur with either breast conserving surgery or mastectomy			
NZGG 2009	Women should undergo surgery within 20 working days of receiving the final diagnostic result. There may be specific instances where very complex decisions need to be made and/or where women require longer: ▪ women receiving neoadjuvant treatment ▪ women undergoing non-surgical treatment (eg, women unfit for surgery) ▪ women at high risk requiring further staging investigations ▪ women at high genetic risk ▪ women considering breast reconstruction ▪ patient choice	n.a.	GPP	n.a
NZGG 2009	Local therapy should be tailored to the individual to reasonably minimise the risk of local recurrence	n.a.	GPP	n.a
NZGG 2009	Breast conserving surgery requires the complete excision of the tumour with clear margins and an acceptable cosmetic result following excision and radiotherapy	+	C	[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Rodger et al. 2006]
		n.a.		[National Breast Cancer Centre (NBCC) 2001; Smitt et al. 1995], [Bleicher et al. 2007], expert opinion
NZGG 2009	Detailed pathological assessment of the distance of the invasive carcinoma from all margins should be made	+	C	[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Rodger et al. 2006]

Leitlinie	Empfehlung	LoE[9]	GoR[1]	Referenzen
Operative Therapie				
		n.a.		[National Breast Cancer Centre (NBCC) 2001; Smitt et al. 1995], [Bleicher et al. 2007], expert opinion
NZGG 2009	A circumferential or radial margin of greater than or equal to 2 mm should be achieved where possible	+	C	[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Rodger et al. 2006]
		n.a.		[National Breast Cancer Centre (NBCC) 2001; Smitt et al. 1995], [Bleicher et al. 2007], expert opinion
NZGG 2009	For women with margin widths of less than 2 mm several factors should be considered in determining whether re-excision is required. These include: ▪ age ▪ tumour histology (lymphovascular invasion, grade, extensive in situ component, tumour type, eg, lobular carcinoma) ▪ which margin is approximated by tumour (smaller margins may be acceptable for deep and superficial margins) ▪ extent of cancer approaching the margin	+	C	[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Rodger et al. 2006]
		n.a.		[National Breast Cancer Centre (NBCC) 2001; Smitt et al. 1995], [Bleicher et al. 2007], expert opinion
NZGG 2009	Quadrantectomy is not routinely recommended as breast conserving surgery due to adverse cosmetic results. In most cases quadrantectomy is not required to achieve complete excision	+	B	[Rodger et al. 2006]
		n.a.		[Smitt et al. 1995; Mariani et al. 1998]

Leitlinie	Empfehlung	LoE[9]	GoR[1]	Referenzen
Operative Therapie				
Brustrekonstruktion				
NICE 2009 early	▪ Discuss immediate breast reconstruction with all patients who are being advised to have a mastectomy, and offer it except where significant comorbidity or (the need for) adjuvant therapy may preclude this option. All appropriate breast reconstruction options should be offered and discussed with patients, irrespective of whether they are all available locally. (Qualifying statement: These recommendations are based on limited clinical evidence from observational studies and on GDG consensus that immediate reconstruction is an acceptable procedure that does not disadvantage patients compared to delayed reconstruction.)	2-	n.a.	[Fischbacher 2002; Javaid et al. 2006]
		3	n.a.	[Drucker-Zertuche et al. 2007; Gendy et al. 2003; Anderson et al. 2004; Cordeiro et al. 2004; Vandeweyer et al. 2003; Knottenbelt et al. 2004; Woerdeman et al. 2006; Taylor et al. 2005; Gouy et al. 2005; Wilson et al. 2004; Rey et al. 2005; Tykka et al. 2002; Ascherman et al. 2006]
		4	n.a.	[Taylor et al. 2005]
NZGG 2009	A woman being prepared for a mastectomy should be informed of the option of breast reconstruction and, if appropriate, should discuss the option with a surgeon trained in reconstructive techniques prior to the surgery.	n.a.	C	n.a.
NZGG 2009	The use of immediate or delayed breast reconstruction is an important means of enhancing body image and self-confidence after mastectomy and both options should be available to women in the public and private sectors in New Zealand.	n.a.	C	n.a.
NZGG 2009	Breast reconstruction may be immediate or delayed. If it is immediate, discussion of breast reconstruction should include the fact that a complication may occasionally delay adjuvant chemotherapy or	n.a.	GPP	n.a.

Leitlinie	Empfehlung	LoE[9]	GoR[1]	Referenzen
Operative Therapie				
	radiotherapy			
NZGG 2009	Neo-adjuvant chemotherapy may avoid the possibility that a complication of immediate breast reconstruction delays postoperative chemotherapy	n.a.	GPP	n.a.
NZGG 2009	A woman should be provided with information on the advantages and disadvantages of breast reconstruction	n.a.	GPP	n.a.
NZGG 2009	A woman who chooses to have a mastectomy with or without reconstruction should be supported in that decision	n.a.	GPP	n.a.
NZGG 2009	If post-mastectomy radiotherapy is likely women should be aware that this may impact on the cosmetic outcome of breast reconstruction	n.a.	GPP	n.a.
Operative Eingriffe an der Axilla (Sentinel Node Biopsie/Axialldissektion) und weiteren Lymphknotenregionen				
NICE 2009 early	▪ Minimal surgery, rather than lymph node clearance, should be performed to stage the axilla for patients with early invasive breast cancer and no evidence of lymph node involvement on ultrasound or a negative ultrasound-guided needle biopsy. SLNB is the preferred technique. ▪ SLNB should only be performed by a team that is validated in the use of the technique, as identified in the New Start training programme1. ▪ Perform SLNB using the dual technique with isotope and blue dye.	1++	n.a.	[Fleissig et al. 2006; Mansel et al. 2006]
		1+	n.a.	[Purushotham et al. 2005; Veronesi et al. 2006; Krag et al. 2007; Veronesi et al. 2003; Zavagno et al. 2008; Chetty et al. 2000; Forrest et al. 1995]
		1	n.a.	[Julian et al. 2004; Lucci et al. 2007]
		2++	n.a.	[Kim et al. 2006]

Leitlinie	Empfehlung	LoE[9]	GoR[1]	Referenzen
Operative Therapie				
	▪ Breast units should audit their axillary recurrence rates. (Qualifying statement: These recommendations are based on evidence from a metaanalysis of the results of observational studies and RCTs confirming the accuracy of SLNB in staging the axilla, RCT evidence of less morbidity with SLNB compared to axillary clearance and limited evidence that SLNB does not result in poorer overall or disease-free survival. Published health economic evidence is difficult to interpret in the UK context.)	2-	n.a.	[Cox et al. 2000; Leidenius et al. 2004]
		3	n.a.	[Agarwal et al. 2005; Blanchard et al. 2003; Carlo et al. 2005; Clarke et al. 2004; Cody, III et al. 1999; Cserni et al. 2002; Giuliano et al. 1997; Haid et al. 2002; Imoto et al. 2004; Katz et al. 2006; Kokke et al. 2005; Krag et al. 2001; Langer et al. 2004; Langer et al. 2005; Naik et al. 2004; Reitsamer et al. 2004; Rietman et al. 2003; Ung 2004; Zavagno et al. 2005; Zavagno et al. 2005; Hadjiminas et al. 1994; Rampaul et al. 2004; Tanaka et al. 2006; Thompson et al. 1995; Mathew et al. 2006; Sato et al. 2001; Ishikawa et al. 2005; Narreddy et al. 2006; Macmillan et al. 2001; Hoar et al. 2003; Gui et al. 2005; Cserni 1999; Kingsmore et al. 2003; Anan et al. 2000; Barth et al. 1997; Brenin et al. 2001; Cao et al. 2005; Chen et al. 2002; Cutuli et al. 2001; Giuliano et al. 1996; Grube et al. 2002; Houvenaeghel et al. 2003; Katz et al. 2006; Peters-Engl et al. 2004; Rivadeneira et al. 2000; Specht et al. 2005; Tan et al. 2005; Tan et al. 2005; Velanovich et al. 1998]
		n.a.	n.a.	[BMJ Clinical Evidence 2005]

Leitlinie	Empfehlung	LoE[9]	GoR[1]	Referenzen
Operative Therapie				
NICE 2009 early	▪ Offer further axillary treatment to patients with early invasive breast cancer who: o have macrometastases or micrometastases shown in a sentinel lymph node o have a preoperative ultrasound-guided needle biopsy with histologically proven metastatic cancer. The preferred technique is ALND because it gives additional staging information. ▪ Do not offer further axillary treatment to patients found to have only isolated tumour cells in their sentinel lymph nodes. These patients should be regarded as lymph node-negative. (Qualifying statement: These recommendations are based on a large body of mainly observational evidence showing that increasing size of metastasis in the sentinel lymph node is associated with increasing likelihood of further, non- sentinel lymph node, metastases.)	1+	n.a.	[Chetty et al. 2000; Forrest et al. 1995; Veronesi et al. 2003]
		2-	n.a.	[Cserni et al. 2004; Degnim et al. 2003]
		3	n.a.	[Ganaraj et al. 2003; Giard et al. 2004; Gipponi et al. 2006; Guenther et al. 2003; Katz et al. 2006; Langer et al. 2005; Naik et al. 2004; Park et al. 2007; Pinkney et al. 2007; Viale et al. 2001; de Widt-Levert et al. 2003; Calhoun et al. 2005; Bolster et al. 2007; Ternier et al. 2006; Katz et al. 2006; van Rijk et al. 2006; Viale et al. 2005; Degnim et al. 2005]
		n.a.	n.a.	[Goyal et al. 2004; Samoilova et al. 2007; Chagpar et al. 2006; EORTC Intergroup Study 2007; Lyman et al. 2005]
NICE 2009 early	«Research recommendation» ▪ In the absence of good data about differences in clinical outcome between axillary radiotherapy and completion ALND, entry into appropriate clinical trials, e.g. AMAROS, is recommended for early breast cancer patients when the axilla has been found by SLNB to contain metastasis.	n.a.	n.a.	n.a.
NZGG 2009	Assessment of axillary lymph node status should be undertaken for most early invasive breast cancers in order to stage the disease, to minimise the	+	A	[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Christiaens et al.

Leitlinie	Empfehlung	LoE[9]	GoR[1]	Referenzen
Operative Therapie				
	risk of loco-regional recurrence and assist in the planning of adjuvant therapy			2007; Stebbing et al. 2007; Wildiers et al. 2007; International Breast Cancer Study Group (IBCSG) 2006; Forrest et al. 1995]
		n.a.		[National Breast Cancer Centre (NBCC) 2001; National Breast Cancer Centre (NBCC) 2001; Myers et al. 2001; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 1995; Dutch Institute for Healthcare Improvement (CBO) 2005; Lyman et al. 2005; Browning et al. 1998; Chetty et al. 2000; Fisher et al. 2002; Louis-Sylvestre et al. 2004; Orr 1999; National Breast and Ovarian Cancer Centre (NBOCC) 2008; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2000]
NZGG 2009	Axillary node dissection is normally recommended in a woman with clinically involved nodes or breast cancer greater than 3 cm or multifocal disease. These criteria and the role of sentinel node-based management in this setting are currently the subject of ongoing clinical trials (SNAC2, and limited data from NSABP B32 and ALMANAC trials)	+	A	[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Christiaens et al. 2007; Stebbing et al. 2007; Wildiers et al. 2007; International Breast Cancer Study Group (IBCSG) 2006; Forrest et al. 1995]
		n.a.		[National Breast Cancer Centre (NBCC) 2001; National Breast Cancer Centre (NBCC) 2001; Myers et al. 2001; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 1995; Dutch Institute

Leitlinie	Empfehlung	LoE[9]	GoR[1]	Referenzen
Operative Therapie				
				for Healthcare Improvement (CBO) 2005; Lyman et al. 2005; Browning et al. 1998; Chetty et al. 2000; Fisher et al. 2002; Louis-Sylvestre et al. 2004; Orr 1999; National Breast and Ovarian Cancer Centre (NBOCC) 2008; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2000]
NZGG 2009	Sentinel lymph node biopsy should be offered as a suitable alternative to axillary dissection in a woman with: ▪ a unifocal tumour of diameter less than or equal to 3 cm; and ▪ a clinically negative axilla, including consideration of imaging findings	+		[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Christiaens et al. 2007; Stebbing et al. 2007; Wildiers et al. 2007; International Breast Cancer Study Group (IBCSG) 2006; Forrest et al. 1995]
		n.a.	B	[National Breast Cancer Centre (NBCC) 2001; National Breast Cancer Centre (NBCC) 2001; Myers et al. 2001; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 1995; Dutch Institute for Healthcare Improvement (CBO) 2005; Lyman et al. 2005; Browning et al. 1998; Chetty et al. 2000; Fisher et al. 2002; Louis-Sylvestre et al. 2004; Orr 1999; National Breast and Ovarian Cancer Centre (NBOCC) 2008; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2000]
NZGG 2009	Women should be informed regarding side effects of axillary node	+	A	[Scottish Intercollegiate Guidelines

Leitlinie	Empfehlung	LoE[9]	GoR[1]	Referenzen
Operative Therapie				
	dissection, including seroma formation, altered sensation in the arm, lymphoedema and possible reduced shoulder movement long term			Network (SIGN) 2005; Christiaens et al. 2007; Stebbing et al. 2007; Wildiers et al. 2007; International Breast Cancer Study Group (IBCSG) 2006; Forrest et al. 1995]
		n.a.		[National Breast Cancer Centre (NBCC) 2001; National Breast Cancer Centre (NBCC) 2001; Myers et al. 2001; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 1995; Dutch Institute for Healthcare Improvement (CBO) 2005; Lyman et al. 2005; Browning et al. 1998; Chetty et al. 2000; Fisher et al. 2002; Louis-Sylvestre et al. 2004; Orr 1999; National Breast and Ovarian Cancer Centre (NBOCC) 2008; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2000]
NZGG 2009	Axillary node dissection levels I and II (and level III nodes where indicated) should be undertaken in all women with clinically node-positive disease	+	A	[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Christiaens et al. 2007; Stebbing et al. 2007; Wildiers et al. 2007; International Breast Cancer Study Group (IBCSG) 2006; Forrest et al. 1995]
		n.a.		[National Breast Cancer Centre (NBCC) 2001; National Breast Cancer Centre (NBCC) 2001; Myers et al. 2001; Early Breast Cancer Trialists' Collaborative

Leitlinie	Empfehlung	LoE[9]	GoR[1]	Referenzen
Operative Therapie				
				Group (EBCTCG) 1995; Dutch Institute for Healthcare Improvement (CBO) 2005; Lyman et al. 2005; Browning et al. 1998; Chetty et al. 2000; Fisher et al. 2002; Louis-Sylvestre et al. 2004; Orr 1999; National Breast and Ovarian Cancer Centre (NBOCC) 2008; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2000]
NZGG 2009	Due to lack of evidence no recommendations were made for the effectiveness of excising the supraclavicular and internal mammary chain nodes versus no excision	n.a.	I	n.a.
NZGG 2009	The results of axillary surgery, and any unusual or difficult cases, should be discussed at a multidisciplinary team meeting	n.a.	GPP	n.a.
NZGG 2009	Radiotherapy to the axilla may be considered as an alternative to surgery for a woman who is unfit for or who declines axillary surgery	n.a.	GPP	n.a.
NZGG 2009	For women undergoing axillary dissection, the intercostobrachial nerve should be preserved where this does not compromise cancer clearance	n.a.	GPP	n.a.
NZGG 2009	Sentinel lymph node biopsy should be offered as a suitable alternative to axillary dissection in a woman with: ▪ a unifocal tumour of diameter less than or equal to 3 cm; and ▪ a clinically negative axilla, including consideration of imaging findings	++ +	B	[Krag et al. 2007] [Veronesi et al. 2003; Veronesi et al. 2006; Cox et al. 2000; Fraile et al. 2000; Miltenburg et al. 1999; Martin et al. 2005; Tafra et al. 2001; Bergkvist et al. 2001; McMasters et al. 2000]

Leitlinie	Empfehlung	LoE[9]	GoR[1]	Referenzen
Operative Therapie				
		n.a.		[Fleissig et al. 2006; Wetzig et al. 2005; Gill et al. 2006; Ung 2004; Julian et al. 2004; Harlow et al. 2005; Purushotham et al. 2005; Del Bianco et al. 2008; Zavagno et al. 2008; Mansel et al. 2006]
NZGG 2009	A woman should be informed of the potential risks and benefits of the sentinel lymph node biopsy technique and procedure	++	C	[Krag et al. 2007]
		+		[Veronesi et al. 2003; Veronesi et al. 2006; Cox et al. 2000] [Fraile et al. 2000; Miltenburg et al. 1999; Martin et al. 2005; Tafra et al. 2001; Bergkvist et al. 2001; McMasters et al. 2000]
		n.a.		[Fleissig et al. 2006; Wetzig et al. 2005; Gill et al. 2006; Ung 2004; Julian et al. 2004; Harlow et al. 2005; Purushotham et al. 2005; Del Bianco et al. 2008; Zavagno et al. 2008; Mansel et al. 2006]
NZGG 2009	A woman should be informed of the potential for an unsuccessful sentinel lymph node biopsy or a false negative result	++	C	[Krag et al. 2007]
		+		[Veronesi et al. 2003; Veronesi et al. 2006; Cox et al. 2000; Fraile et al. 2000; Miltenburg et al. 1999; Martin et al. 2005; Tafra et al. 2001; Bergkvist et al. 2001; McMasters et al. 2000]

Leitlinie	Empfehlung	LoE[9]	GoR[1]	Referenzen
Operative Therapie				
		n.a.		[Fleissig et al. 2006; Wetzig et al. 2005; Gill et al. 2006; Ung 2004; Julian et al. 2004; Harlow et al. 2005; Purushotham et al. 2005; Del Bianco et al. 2008; Zavagno et al. 2008; Mansel et al. 2006]
NZGG 2009	The team performing the sentinel lymph node biopsy should comprise a surgeon, nuclear physician (where available), pathologist, anaesthetist and appropriate nursing support	n.a	C	[National Breast and Ovarian Cancer Centre (NBOCC) 2008]
NZGG 2009	The surgeon performing sentinel lymph node biopsy should be appropriately trained and experienced in the technique	++	B	[Kim et al. 2005] (Studies supporting recommendation)
		+		[Tafra et al. 2001] (Studies supporting recommendation)
		n.a.		[National Breast and Ovarian Cancer Centre (NBOCC) 2008; Gill et al. 2006; Ung 2004] (Studies supporting recommendation) [Del Bianco et al. 2008; Zavagno et al. 2008] (Study contradicting recommendation)
NZGG 2009	Where possible lymphatic mapping with preoperative lymphoscintigraphy in combination with intraoperative use of the gamma probe and blue dye should be used to locate the sentinel node	++	B	[Kim et al. 2005]
		+		[Bergkvist et al. 2001; McMasters et al. 2000]
		n.a.		[National Breast and Ovarian Cancer

Leitlinie	Empfehlung	LoE[9]	GoR[1]	Referenzen
Operative Therapie				
				Centre (NBOCC) 2008]
NZGG 2009	Where a combination technique for the sentinel lymph node biopsy procedure is unavailable, use of blue dye or radioisotopes alone is appropriate	++	B	[Kim et al. 2005]
		+		[Bergkvist et al. 2001; McMasters et al. 2000]
		n.a.		[National Breast and Ovarian Cancer Centre (NBOCC) 2008]
NZGG 2009	Detailed, definitive histological assessment of the sentinel node is recommended to detect metastatic disease	n.a.	C	[National Breast and Ovarian Cancer Centre (NBOCC) 2008]
				[National Breast and Ovarian Cancer Centre (NBOCC) 2008; National Breast and Ovarian Cancer Centre (NBOCC) 2008; Julian et al. 2004; Harlow et al. 2005; Del Bianco et al. 2008; Zavagno et al. 2008]
NZGG 2009	Intraoperative assessment of the sentinel node should be confirmed with a definitive histological assessment to reduce the risk of a false negative result	++	B	[Krag et al. 2007]
		n..a.		[National Breast and Ovarian Cancer Centre (NBOCC) 2008; Julian et al. 2004; Harlow et al. 2005; Del Bianco et al. 2008; Zavagno et al. 2008]
NZGG 2009	For definitive assessment of a sentinel node (if the initial haematoxylin and eosin-stained section is negative) four sections at 500 microns through each	n.a.	C	[National Breast and Ovarian Cancer Centre (NBOCC) 2008]

Leitlinie	Empfehlung	LoE[9]	GoR[1]	Referenzen
Operative Therapie				
	2 mm slice should be cut and three sections should be stained with haematoxylin and eosin with one randomly chosen section submitted for cytokeratin immunohistochemistry.			
NZGG 2009	If the sentinel node is not identified at the time of sentinel lymph node biopsy, axillary dissection should be performed.	n.a.	B	n.a.
NZGG 2009	If a positive sentinel node is identified, axillary dissection is recommended with due consideration of the risks and benefits to the individual.	n.a.	B	n.a.
NZGG 2009	If a negative sentinel node is identified, clinical follow-up of the axilla is recommended.	n.a.	B	n.a.
NZGG 2009	Surgeons and anaesthetists should be aware of the possibility of adverse reactions in some patients during the sentinel lymph node biopsy procedure.	n.a.	C	n.a.
NZGG 2009	For a woman with a positive non-axillary node (eg, internal mammary, supraclavicular or infraclavicular nodes) radiotherapy to those nodes should be considered.	n.a.	C	n.a.
NZGG 2009	Axillary lymph node dissection is recommended where positive nodes are identified on sentinel lymph node biopsy in a woman with early breast cancer. Even if micrometastases only are found, because there is a significant incidence of positive non-sentinel nodes, axillary lymph node dissection should normally be performed unless the patient is entered into a randomised trial Note: The data from the IBCSG 23-01 trial is awaited. This trial compares axillary node dissection with no axillary node dissection in patients with micrometases ≤2 mm/tumour ≤5 cm / tumour (International Breast Cancer	n.a.	GPP	n.a.

Leitlinie	Empfehlung	LoE[9]	GoR[1]	Referenzen
Operative Therapie				
	Study Group)			
NZGG 2009	In a woman who has undergone axillary surgery and/or radiotherapy health practitioners should avoid, if possible: ▪ taking blood from the associated arm ▪ obtaining blood pressure readings from the associated arm ▪ insertion of cannula, injection or vaccination in the associated arm	n.a.	GPP	n.a.
NZGG 2009	There are a number of risk factors associated with lymphoedema to consider: ▪ a woman having undergone axillary surgery and/or radiotherapy ▪ infection in the arm ▪ high body mass index ▪ having any other injury to the arm, including insect bites and sunburn ▪ increased age ▪ undertaking air travel ▪ positive axillary node status	n.a.	GPP	n.a.
NZGG 2009	A woman should be advised about lymphoedema prevention and support services available nationally and locally	n.a.	GPP	n.a.
Abkürzungen: ; ALND = axillary lymph node dissection; BRCA = breast cancer; GDG = guideline development group; n.a. = nicht angegeben; SLNB = sentinel lymph node biopsy				

4.2.6 Empfehlungen zum Thema Strahlentherapie – adjuvant

4.2.6.1 Eingeschlossene Leitlinien

Zum Thema adjuvante Strahlentherapie wurden drei Leitlinien der Gruppe 1 [National Institute for Clinical Excellence (NICE) 2009; New Zealand Guidelines Group (NZGG) 2009; Belkacemi et al. 2010] extrahiert werden. Eine Leitlinie wurde vom National Institute for Health and Clinical Excellence (NICE) aus Großbritannien 2009 herausgegeben. Diese Leitlinien adressiert umfassend die Diagnostik und Therapie der Primärerkrankung einschließlich lokal fortgeschrittener Tumore [National Institute for Clinical Excellence (NICE) 2009]. Für die Extraktion der Leitlinie (insbesondere der Evidenzklassifikationen [LoE]) wurde zusätzlich ein Hintergrund- bzw. Methodendokument ausgewertet [National Institute for Clinical Excellence (NICE) 2009]. Zu den Empfehlungen haben die Autoren der NICE-Leitlinie [National Institute for Clinical Excellence (NICE) 2009] sogenannte ‚Qualifying Statements' angeführt. Diese beschreiben zusammenfassend die zugrundeliegende Evidenz der Empfehlungen. Die ‚Qualifying Statements' wurden mit den Empfehlungen extrahiert, um als Ergänzung zu den berücksichtigten Referenzen auch die entsprechenden zusammenfassenden Einschätzungen der Autoren wiederzugeben. Die Leitlinie von NICE enthält außerdem Empfehlungen für die weitere Erforschung bestimmter Aspekte (Research Recommendations). Diese Empfehlungen wurden extrahiert und entsprechend gekennzeichnet.

Eine Leitlinie wurde von der New Zealand Guidelines Group (NZGG) in 2009 herausgegeben. Diese Leitlinie adressiert umfassend die Diagnostik und Therapie der Primärerkrankung. Für die Extraktion dieser Leitlinie wurden keine weiteren Dokumente ausgewertet.

Die dritte Leitlinie wurde von einem französischen Expertenkreis (French expert review board of Nice/Saint-Paul de Vence = Belkacemi 2010) erstellt und 2010 veröffentlicht. Diese Leitlinie gibt Empfehlungen zur Strahlentherapie bei invasivem Mammakarzinom. Für die Extraktion dieser Leitlinie wurden keine weiteren Dokumente ausgewertet.

4.2.6.2 In der S3-Leitlinie Mammakarzinom nicht enthaltene und diskrepante Empfehlungs-Inhalte

Alle drei eingeschlossenen Leitlinien (Belkacemi 2010, Nice 2009 early, NZGG) weisen **Empfehlungen zur maximalen Zeitspanne zwischen Operation und Strahlentherapie** auf (Angabe unterschiedl. LoE, GoR) (2x 8 Wochen, 1x31 Tage nach Abschluss der operativen Therapie). Die S3-Leitlinie Mammakarzinom nennt 4-6 Wochen.

Bei Belkacemi 2010 wird empfohlen, mindestens **3 Clips zur Markierung des Tumorbetts** zu platzieren (Expertenkonsens), dies wird in der S3-Leitlinie Mammakarzinom nicht thematisiert. Auch wird nicht thematisiert, dass die **Entscheidung zur Bestrahlung nach einem**

ersten Kontakt mit der Patientin im Rahmen eines multidisziplinären Treffens stattfinden soll. Das Letztere ist in den Strukturanforderungen von Brustzentren geregelt.

Im Gegensatz zu Belkacemi 2010 und der S3-Leitlinie Mammakarzinom 2008 nennt die NICE 2009 early für die **Bestrahlung nach BET** eine **Gesamtdosis** von 40 Gy (in 15 Fraktionen) und die NZGG empfiehlt verschiedene Regimes (40-50 Gy über 3-5 Wochen), dabei wird nur 50 Gy in 25 Fraktionen mit dem GoR A empfohlen (LoE + bis n.a.).

In Bezug auf den **lokalen Boost nach BET** nennen Belkacemi 2010 - als Expertenkonsens - das **Alter von >70J als Grenze**, bei der der Nutzen diskutiert werden soll, im Gegensatz zur S3-Leitlinie Mammakarzinom 2008, die ein Alter > 60J nennt, die NZGG empfiehlt den Boost allen Patientinnen (LoE+, GOR A). Die NZGG empfiehlt für PatientInnen mit großen oder sehr indurierten Brüsten das Erwägen kleinerer täglicher Strahlendosen („extended fractionation with smaller daily dose over 5-6 weeks“, „good practice point“).

Im Hinblick auf **eine partielle oder akzelerierte Teilbrustbestrahlung** gibt die NZGG wegen mangelnder Evidenz (GoR I) wie die S3-Leitlinie Mammakarzinom 2008 keine Empfehlung ab, als „good practice point“ wird angeführt, dass eine Indikation bestehen könne, wenn eine Bestrahlung der ganzen Brust nicht durchführbar („unsuitable“) sei.

Belkacemi 2010 nennen als **Indikation für eine Bestrahlung nach Mastektomie** grundsätzlich PatientInnen mit positiven Lymphknoten (LoE 1, GoR A), die NICE 2009 early empfiehlt die Bestrahlung ab 4 befallenen Lymphknoten (LoE 1++, GoR n.a.) wie die NZGG (LoE +, GoR A) und die S3-Leitlinie Mammakarzinom 2008 jeweils explizit mit dem Hinweis auf das **hohe (Lokal-)Rezidivrisiko**. Als Risikofaktor für eine Indikation zur Bestrahlung nach Mastektomie nennen Belkacemi 2010 - als Expertenkonsens- u.a. auch Multifokalität und ein Grading von III, dies wird in der S3-Leitlinie Mammakarzinom nicht thematisiert. Die NICE early empfiehlt die Aufnahme von PatientInnen mit **mittlerem Rezidivrisiko** (u.a.1-3 befallene Lymphknoten, Grading von III, Alter <40J.) in eine laufende Studie, die NZGG empfiehlt bei diesen PatientInnen die Diskussion bezüglich der Bestrahlung in einem multidisziplinären Team (LoE +, GoR B). Dies empfiehlt die NZGG auch bei **niedrigem Rezidivrisiko**, mit dem expliziten Hinweis, dass keine Evidenz für eine routinemäßige Bestrahlung in dieser Gruppe vorliege (LoE n.a., GoR B). Patientinnen ohne erhöhtes Rezidivrisiko wird in der NICE 2009 early explizit keine Bestrahlung empfohlen (LoE 1+, GoR n.a.). Die S3-Leitlinie Mammakarzinom empfiehlt hier ein sorgfältiges Abwägen der Indikation mit Hinweis auf schlechteres Gesamtüberleben in einem RCT. Wegen Mangel an Evidenz gibt die NZGG keine Empfehlung zum Boost nach Mastektomie und Strahlentherapie (LoE n.a., GoR I).

Zur **Bestrahlung nach Brustrekonstruktion** empfehlen Belkacemi 2010 das gleiche Vorgehen wie nach BET, aber keinen Boost („expert agreement“).

Im Hinblick auf die **Bestrahlung der Lymphabflusswege** weisen Belkacemi 2010 und NZGG im Vergleich zur S3-Leitlinie Mammakarzinom 2008 diskrepante Empfehlungen im Hinblick auf eine Ausweitung der Indikation zur Bestrahlung auf.

Tabelle 9: Strahlentherapie

Leitlinie	Empfehlung	LoE[10]	GoR[1]	Referenzen
Strahlentherapie				
Zeitpunkt der Strahlentherapie/Strahlentherapie und Systemtherapie				
Belkacemi 2010	Optimal delay from surgery to radiotherapy: □ Absence of indication for CT: A maximum delay of 8 weeks is recommended between surgery and loco-regional RT particularly for patients with high risk of recurrence. □ Indication for CT: Standard fractionated RT should start after the end of chemotherapy. However, the maximum delay between surgery and RT should be between 20 and 24 weeks.	3	C	[Bellon et al. 2005; Hershman et al. 2006; Huang et al. 2003; Mikeljevic et al. 2004; Hebert-Croteau et al. 2004]
NICE 2009 early	□ Start adjuvant chemotherapy or radiotherapy as soon as clinically possible within 31 days of completion of surgery[11] in patients with early breast cancer having these treatments. (Qualifying Statement: This recommendation is based on GDG consensus in the absence of good quality evidence.)	1. Concurrent adjuvant chemotherapy/radiotherapy versus chemotherapy followed by radiotherapy:		
		1+	n.a.	[Hickey et al. 2006; Calais et al. 2005; Toledano et al. 2007]
		2. Radiotherapy followed by chemotherapy versus chemotherapy followed by radiotherapy:		

[10] Für Erläuterungen des Level of Evidence (LoE) und Grade of Recommendation (GoR) siehe Anhang 5.6.
[11] Department of Health (2007). Cancer reform strategy. London: Department of Health. (At present no equivalent target has been set by the Welsh Assembly Government.)

Leitlinie	Empfehlung	LoE[10]	GoR[1]	Referenzen
Strahlentherapie				
		1+	n.a.	[Hickey et al. 2006]
		2-		[Huang et al. 2003]
		3. Early versus late chemotherapy:		
		1+	n.a.	[International Breast Cancer Study Group (IBCSG) 1997]
		4. Interval from surgery to radiotherapy:		
		2+	n.a.	[Mikeljevic et al. 2004]
		2-		[Huang et al. 2003; Whelan et al. 2003; Hershman et al. 2006; Jobsen et al. 2006]
		3		[Benchalal et al. 2005]
		5. Interval from surgery to chemotherapy:		
		2-	n.a.	[Hershman et al. 2006; Sanchez C.J. et al. 2007]
		3		[Cold et al. 2005; Colleoni et al. 2000]
NZGG 2009	Radiotherapy should ideally commence within 8 weeks of completion of surgery or chemotherapy	n.a.	GPP	n.a.

Leitlinie	Empfehlung	LoE[10]	GoR[1]	Referenzen
Strahlentherapie				
Belkacemi 2010	In clinical practice, given the absence of difference in carcinologic efficiency between a concomitant and sequential administration, the group of experts has recommended the start of TAM at the end of RT.	3	C	[Pierce et al. 2005; Ahn et al. 2005; Harris et al. 2005]
Belkacemi 2010	In the absence of other mature data on these molecules, the group of experts concluded that AI may be delivered either concomitantly or sequentially.	2	B	[Azria et al. 2010]
Belkacemi 2010	Finally, the group of experts does not recommend the practice of any concomitant CT-RT schemes outside trials.	expert agreement	n.a.	[Arcangeli et al. 2006; Rouesse et al. 2006; Toledano et al. 2007; Burstein et al. 2006; Taghian et al. 2001]
Belkacemi 2010	In clinical practice, given the efficacy demonstrated with adjuvant trastuzumab in HER2-positive BC patients [29–31] and the absence of severe toxicity when nodal RT is limited, it is recommended to continue trastuzumab (every 3 weeks) during irradiation on condition that the cardiac volume is as limited as possible. This occurs with the absence of systematic irradiation of the IMC or the optimisation of the technique if indicated. In addition, given the relatively long half-life of trastuzumab (of the order of 4–6 weeks), the interruption may be considered as insignificant.	expert agreement	n.a.	[Joensuu et al. 2006; Romond et al. 2005; Piccart-Gebhart et al. 2005]
Bestrahlung nach neoadjuvanter Therapie				
Belkacemi 2010	Whatever the type of surgery and the response to neoadjuvant CT, the RT indication should be taken into consideration by considering the initial tumour criteria. The indications are identical to those described in the adjuvant situation. There is no exception to the rule for RT after conservative surgery	expert agreement	n.a.	n.a.

Leitlinie	Empfehlung	LoE[10]	GoR[1]	Referenzen
Strahlentherapie				
Belkacemi 2010	RT to the nodal areas should be systematic for N+ patients and for tumours located in the central or internal quadrants. For patients that have node negative status after CT, the initial nodal and tumour status must be taken into consideration, and the risk/benefit relationship of a more or less extended irradiation must be considered	expert agreement	n.a.	n.a.
Bestrahlung nach brusterhaltender Therapie				
Belkacemi 2010	RT indications and modalities after breast conservation • Whole breast RT should be systematic after breast conserving surgery. The total dose should be equal or equivalent to 50 Gy in 25 fractions over 5 weeks.	1	A	[Overgaard et al. 1999]
Belkacemi 2010	In the elderly population, certain particular cases presenting comorbidities associated with a limited life expectancy, RT indication (even hypofractioned) may be unnecessary in the light of an unfavourable risk/benefit ratio.	expert agreement	n.a.	n.a.
Belkacemi 2010	Following whole breast irradiation, it is recommended to deliver a boost of 10–16 Gy to the tumour bed. Three randomized trials have shown the importance of an increase in the dose to the tumour bed in order to improve local control.	1	A	[Romestaing et al. 1997; Romestaing et al. 2009; Bartelink et al. 2001; Bartelink et al. 2007; Polgar et al. 2002]
Belkacemi 2010	For older patients (>70 years) the decision to deliver the boost should be discussed taking in consideration the tumour size, extent of surgical margins and a possible presence of a large extensive in situ component and grade.	expert agreement	n.a.	n.a.

Leitlinie	Empfehlung	LoE[10]	GoR[1]	Referenzen
Strahlentherapie				
Belkacemi 2010	The surgical clips marking the original tumour bed should indicate the borders of the excision particularly in the case of remodelling. The number of surgical clips can vary, but a minimum of three is recommended.	expert agreement	n.a.	n.a.
Belkacemi 2010	The quality of RT begins with the methodology adopted for establishing its indication. In spite of the formal character of the indication of RT, after a conservative surgery, the decision should be endorsed within the framework of a multidisciplinary consultation meeting (MCM). A pre-treatment consultation prior to a decision on the management of the patient forms part of "Good Clinical Practice". The radiation-oncologist should ensure the definition of volumes to be treated and dose prescription. The RT quality should, in all cases, match certain strict technical criteria. The treatment modality, as well as the possible secondary side effects, should be clearly explained to the patient and recorded during and after RT.	expert agreement	n.a.	n.a.
NICE 2009 early	□ Patients with early invasive breast cancer who have had breast conserving surgery with clear margins should have breast radiotherapy. ▪ Offer adjuvant radiotherapy to patients with DCIS following adequate breast conserving surgery3 and discuss with them the potential benefits and risks. (Qualifying statement: There is good quality randomised controlled trial evidence that radiotherapy reduces absolute risk of further recurrence. There was GDG consensus that there may be a subgroup of patients with DCIS who have a lowrisk of recurrence and thus for whom the addition)	1++	n.a.	[Clarke et al. 2005; Vinh-Hung et al. 2004; Ford et al. 2006; Johansen et al. 2002; Rayan et al. 2003; Whelan et al. 2000] DCIS: [Bijker et al. 2006; Emdin et al. 2006; Holmberg et al. 2008]
		1+		[Liljegren 2002; Lee et al. 2008] DCIS: [Fisher et al. 1998]
		1-		[Rutqvist et al. 2003; Mul et al. 2007; Cuncins-Hearn et al. 2004; Sarin 2005]

Leitlinie	Empfehlung	LoE[10]	GoR[1]	Referenzen
Strahlentherapie				
				DCIS: [Houghton et al. 2003]
		2+		[Vinh-Hung et al. 2003] DCIS: [Shelley et al. 2006]
		2-		[Deutsch et al. 2003]
		3		[Back et al. 2005] DCIS: [Omlin et al. 2006; Boyages et al. 1999; Fonseca et al. 1997; Baxter et al. 2005; Smith et al. 2006]
		4		[Kuerer et al. 2004; Shelley et al. 2002; Whelan et al. 2003; Morrow et al. 2002; Sautter-Bihl et al. 2007]
		n.a.	n.a.	[Kunkler et al. 2006]
NICE 2009 early	▪ Use external beam radiotherapy giving 40 Gy in 15 fractions as standard practice for patients with early invasive breast cancer after breast conserving surgery or mastectomy. (Qualifying statement: This recommendation is based on RCT evidence of clinical effectiveness and the GDG agreeing that a regimen using fewer fractions would probably be cost effective.)	1++	n.a.	[Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2002; Gebski et al. 2006; Owen et al. 2006; Bentzen et al. 2008; Bentzen et al. 2008; Whelan et al. 2002; Yarnold et al. 2005]
		1+		[Bates 1988]

Leitlinie	Empfehlung	LoE[10]	GoR[1]	Referenzen
Strahlentherapie				
		1-		[Goel et al. 2000; Taher et al. 2004]
		2+		[Olivotto et al. 1996; Marhin et al. 2007]
		3		[Marcenaro et al. 2004; Mladenovic 2001; Wallace et al. 1993; Yamada et al. 1999]
		4		[Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) 2002; Whelan et al. 2003]
		n.a.		[Dewar et al. 2007]
NICE 2009 early	▪ Offer an external beam boost to the site of local excision to patients with early invasive breast cancer and a high risk of local recurrence, following breast conserving surgery with clear margins and whole breast radiotherapy.	1++	n.a.	EORTC 22881-10882-Trial: [Antonini et al. 2007; Poortmans et al. 2004; Bartelink et al. 2007]
	▪ If an external beam boost to the site of local excision following breast conserving surgery is being considered in patients with early invasive breast cancer, inform the patient of the side effects associated with this intervention, including poor cosmesis, particularly in women with larger breasts. (Qualifying statement: These recommendations are based on good RCT evidence and GDG consensus.)	1+ n.a.		[Vrieling et al. 1999; Romestaing et al. 1997] [Prescott et al. 2007; Hayman et al. 1998; Liljegren et al. 1997; Alvegard et al. 2005; Persson et al. 2005; Hayman et al. 2000]
NICE 2009 early	«Research recommendation» ▪ What is the effectiveness in patients with early invasive breast	n.a.	n.a.	n.a.

Leitlinie	Empfehlung	LoE[10]	GoR[1]	Referenzen
Strahlentherapie				
	cancer of: (a) different hypofractionation radiotherapy regimens (b) partial breast radiotherapy and (c) newer radiotherapy techniques (including intensity modulated radiotherapy), in terms of long term outcomes such as, quality of life, side effects, disease recurrence rates, disease-free survival and overall survival?			
NZGG 2009	A woman should be offered radiotherapy following breast conserving surgery for early invasive breast cancer unless there is a particular contraindication	+	A	[Schnaper et al. 2011; Rodger et al. 2006; Prescott et al. 2007; Scottish Intercollegiate Guidelines Network (SIGN) 2005]
		n.a.		[Clarke et al. 2005]
NZGG 2009	A boost radiotherapy dose should be considered for all women with early invasive breast cancer treated with radiotherapy and breast conserving surgery, in particular: ▪ women younger than 50 years of age	+	A	[Bartelink et al. 2007]
NZGG 2009	Consideration should be given to adverse events (eg, fibrosis) caused by additional radiation when planning treatment	+	A	[Bartelink et al. 2007]
NZGG 2009	A boost radiotherapy dose should be considered for women with positive margins	n.a.	GPP	n.a.
NZGG 2009	Due to a lack of evidence no recommendations were made for the routine use of partial or accelerated partial breast radiotherapy for women following breast conserving surgery	n.a.	I	Insufficient information

Leitlinie	Empfehlung	LoE[10]	GoR[1]	Referenzen
Strahlentherapie				
NZGG 2009	Partial breast radiotherapy for women after breast conserving surgery may be undertaken as part of a well conducted clinical trial	n.a.	GPP	n.a.
NZGG 2009	Partial breast radiotherapy may be offered for individual women after breast conserving surgery where whole breast radiotherapy is deemed unsuitable	n.a.	GPP	n.a.
NZGG 2009	Radiotherapy treatment for early invasive breast cancer should use an accepted regimen such as: ▪ 50 Gy in 25 fractions over 5 weeks	+ n.a.	A	[Owen et al. 2006; Bentzen et al. 2008] [Yamada et al. 1999; Whelan et al. 2002]
	▪ 45 Gy in 20 fractions over 5 weeks ▪ 42.5 Gy in 16 fractions over 3.5 weeks for those with small or medium breasts, not requiring boost or nodal radiation ▪ 40 Gy in 15 fractions over 3 weeks	+ n.a.	B	[Owen et al. 2006; Bentzen et al. 2008] [Yamada et al. 1999; Whelan et al. 2002]
NZGG 2009	If boost radiotherapy is used after a hypofractionated regimen it should be at the standard 2 Gy per fraction	n.a.	GPP	n.a.
NZGG 2009	Women with large breasts and those with significant postoperative induration, oedema, erythema, haematoma or infection should be considered for extended fractionation, with smaller daily doses over 5–6 weeks	n.a.	GPP	n.a.
Bestrahlung nach Mastektomie				

Leitlinie	Empfehlung	LoE[10]	GoR[1]	Referenzen
Strahlentherapie				
Belkacemi 2010	RT indications and modalities after total mastectomy Post-mastectomy radiotherapy (PMRT) has shown an absolute overall survival benefit of about 10% in pre- or postmenopausal node positive (N+) patients. Thus, the indications for PMRT are clearly established for the T3–T4 patients and for those presenting with nodal involvement	1	A	[Clarke et al. 2005; Overgaard et al. 1997; Overgaard et al. 1999; Ragaz et al. 2005]
Belkacemi 2010	RT indications and modalities after total mastectomy In node negative patients, RT should be indicated on the basis of the existence of one or more risk factors for local relapse, described by the working group as: age less than 40 years, size ≥pT3, grade III, multifocality, lymphovascular and/or muscular and/or cutaneous invasion These factors have been also reported as independent factors in retrospective studies [17,18]. In clinical practice, notwithstanding associated comorbidities, the tumour volume (≥T3) and/or nodal involvement (≥4 positive nodes) are generally situations where the indication is clear. RT will include the chest wall, internal mammary chain (IMC) and ipsilateral supra clavicular areas. Apart from cases with insuf-ficient lymph node dissection, irradiation of the axilla should not be carried out systematically.	expert agreement	n.a.	[Wallgren et al. 1996; Jagsi et al. 2005]
NICE 2009 early	▪ Offer adjuvant chest wall radiotherapy to patients with early invasive breast cancer who have had a mastectomy and are at a high risk of local recurrence. Patients at a high risk of local recurrence include those with four or more positive axillary lymph nodes or involved resection margins. ▪ Consider entering patients who have had a mastectomy for early invasive breast cancer and who are at an intermediate risk of local recurrence into the current UK trial (SUPREMO) assessing the value of postoperative radiotherapy. Patients at an	1++	n.a.	[Clarke et al. 2005; Gebski et al. 2006; Whelan et al. 2000; Fisher et al. 2002; Gustavsson et al. 1999; Hojris et al. 2000; Hojris et al. 1999]

Leitlinie	Empfehlung	LoE[10]	GoR[1]	Referenzen
Strahlentherapie				
	intermediate risk of local recurrence include those with one to three lymph nodes involved, lymphovascular invasion, histological grade 3 tumours, ER-negative tumours, and those aged under 40 years.	1+		[Kyndi et al. 2008; Nielsen et al. 2006; Overgaard et al. 2007; Van de et al. 2000; Nielsen et al. 2006]
	▪ Do not offer radiotherapy following mastectomy to patients with early invasive breast cancer who are at low risk of local recurrence (for example, most patients who are lymph node-negative).	1-		[Killander et al. 2007]
		2+		[Smith et al. 2006]
	(Qualifying statement: These recommendations are based on strong evidence from RCTs.)	n.a.		[Bartelink 2000; Bellon et al. 2006; Recht et al. 2001; Truong et al. 2004]
NZGG 2009	A woman at high risk of loco-regional recurrence post-mastectomy (ie, 4 or more nodes positive in axilla, tumour size greater than 5 cm, close margins) should have their case discussed at a multidisciplinary meeting with a radiation oncologist present, or discussed with a radiation oncologist, and should receive radiotherapy unless there is a particular contraindication	+	A	[Rodger et al. 2006; Nielsen et al. 2006; Overgaard et al. 2007]
	(Definition of high risk by GDT)	n.a.		[National Health and Medical Research Council (NHMRC) 2001]
NZGG 2009	A woman at moderate risk of loco-regional recurrence (1–3 nodes positive in axilla, high grade tumours, lymphovascular invasion or young age) should have their case discussed at a multidisciplinary meeting with a radiation oncologist present, or discussed with a radiation oncologist, and the woman should be referred for a discussion regarding radiotherapy (Definition of moderate risk by GDT)	+	B	[Rodger et al. 2006]
		n.a.		[National Health and Medical Research Council (NHMRC) 2001]
NZGG 2009	There is no evidence for the routine use of radiotherapy for women at lower risk of local recurrence post-mastectomy. These women should	n.a.	B	n.a.

Leitlinie	Empfehlung	LoE[10]	GoR[1]	Referenzen
Strahlentherapie				
	have their case discussed at a multidisciplinary meeting with a radiation oncologist present, or discussed with a radiation oncologist			
NZGG 2009	Due to lack of evidence no recommendations were made for the routine use of boost dose radiotherapy after mastectomy and radiotherapy	n.a.	I	Insufficient information
Bestrahlung nach Brustrekonstruktion				
Belkacemi 2010	The RT indications and technique are similar to those of RT after standard conservative surgery. All decisions should be endorsed within the framework of an MCM. The dose delivered to the reconstructed breast (whatever the type of reconstruction) should be between 45 and 50.4 Gy in 28 fractions (1.8–2 Gy/fraction). The techniques and constraints are those defined previously. However, there is no indication for a boost dose due to the fact that in most cases it is impossible to locate the initial tumour site	expert agreement	n.a.	n.a.
Bestrahlung der Axilla und der weiteren Lymphabflusswege				
Belkacemi 2010	Recommendations for N+ patients: The supra- and subclavicular and the IMC nodes should be systematically irradiated to a dose of 46–50 Gy using conventional fractionation (2 Gy per fraction) through an alternate mixed photon–electron beams. IMC RT is particularly indicated in patients with internal-central node positive patients and those with >4N+.	expert agreement	n.a.	n.a.
Belkacemi 2010	Recommendations for isolated cells and axillary micrometastases: In tumours located in the external quadrants, systematic irradiation of the	expert agreement	n.a.	n.a.

Leitlinie	Empfehlung	LoE[10]	GoR[1]	Referenzen
Strahlentherapie				
	nodal areas is not recommended. In tumours located in the internal and central quadrants, indications are identical to those for node negative cases.			
Belkacemi 2010	Recommendations for N− patients: ▪ The indication for nodal RT is discussed in the section for tumours of the internal and central quadrants. In this case, the indication should be modulated according to the tumour size, patient's age and associated comorbidities as well as consideration to the risk/benefit ratio. ▪ When supra clavicular and IMC RT is to be given, then it should be performed according to the same modalities as for node positive cases. ▪ For tumours in the external quadrants, nodal RT should not be given.	expert agreement	n.a.	n.a.
Belkacemi 2010	Recommendations for RT to the axilla: In the N− patients irradiation of the axilla is not justified. The other cases should be discussed in the MCM on a case by case basis: ▪ Positive sentinel node without axillary dissection. ▪ Sufficient axillary dissection (≥7 nodes removed): in case of massive invasion with consideration of the nodal ratio (number of positive nodes/total number of nodes removed). ▪ Insufficient axillary dissection (<7 nodes removed): o N+: take into account the nodal ratio of positive nodes/total number of nodes removed. The number of nodes with extra-capsular extension should not count in the decision-making process. o N−: take into account the total number of nodes	expert agreement	n.a.	n.a.

Leitlinie	Empfehlung	LoE[10]	GoR[1]	Referenzen
Strahlentherapie				
	dissected and other local and general prognostic factors.			
NICE 2009 early	▪ Do not offer adjuvant radiotherapy to the axilla or supraclavicular fossa to patients with early breast cancer who have been shown to be histologically lymph node-negative.	1++	n.a.	[Fisher et al. 2002; Overgaard et al. 1999; Ragaz et al. 2005]
	▪ Do not offer adjuvant radiotherapy to the axilla after ALND for early breast cancer. ▪ If ALND is not possible following a positive axillary SLNB or four-node sample, offer adjuvant radiotherapy to the axilla to patients with early breast cancer (see recommendations in Chapter 3.).	1+		[Wallgren et al. 1986; Louis-Sylvestre et al. 2004; Veronesi et al. 2005; Vinod et al. 1999; Kaija et al. 1995]
	▪ Offer adjuvant radiotherapy to the supraclavicular fossa in patients with early breast cancer and four or more involved axillary lymph nodes.	3		[Pejavar et al. 2006; Arriagada et al. 1988; Obedian et al. 1999; Livi et al. 2006; Grills et al. 2003; Fortin et al. 2006; Tai et al. 2007]
	▪ Offer adjuvant radiotherapy to the supraclavicular fossa to patients with early breast cancer and one to three positive lymph nodes if they have other poor prognostic factors (for example, T3 and/or histological grade 3 tumours) and good performance status. ▪ Do not offer adjuvant radiotherapy to the internal mammary chain to patients with early breast cancer who have had breast surgery. (Qualifying statement: These recommendations are based on evidence from randomised control trials and GDG consensus.)	4		[Grabenbauer 2004]
NZGG 2009	Radiotherapy to the ipsilateral supraclavicular fossa should be given in a woman who is at high risk (4 or more positive axillary nodes)	+	B	[McArdle et al. 1986; Ragaz et al. 2005; Scottish Intercollegiate Guidelines Network (SIGN) 2005]

Leitlinie	Empfehlung	LoE[10]	GoR[1]	Referenzen
Strahlentherapie				
NZGG 2009	Radiotherapy to the axilla should be considered when: ▪ no axillary dissection has occurred ▪ there has been inadequate surgery, although this may add to morbidity ▪ a high number or percentage of nodes are involved, or where there are positive margins or major extra-nodal spread or it is considered likely that residual breast cancer has been left in the axilla	+	B	[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Christiaens et al. 2007]
		n.a.	n.a.	[Veronesi et al. 2005; Louis-Sylvestre et al. 2004]
NZGG 2009	Radiotherapy to the internal mammary chain should be considered for women who have a positive internal mammary node on sentinel node biopsy Routine use of radiotherapy to the internal mammary chain is not recommended	+	C	[Scottish Intercollegiate Guidelines Network (SIGN) 2005]
		n.a.		[Arriagada et al. 1988; Veronesi et al. 2008]
NZGG 2009	It is reasonable to offer radiation to the internal mammary chain to those with inner half tumours particularly if the axilla is positive or lymphoscintigraphy shows drainage to internal mammary nodes	n.a.	GPP	n.a.
NZGG 2009	Other indications for radiotherapy to nodal areas may be considered and the benefits and risks balanced	n.a.	GPP	n.a.

Abkürzungen: DCIS = ductal carcinoma in situ; GDG = guideline development group; RCT = randomized controlled trial; ALND = axillary lymph node dissection; SLNB = sentinel lymph node biopsy; GPP = Good Practice Point; GDT = guideline development team; Gy = Gray (unit); CT = computed tomography; RT = radiotherapy; n.a. = nicht angegeben; MCM = multidisciplinary consultation meeting; PMRT = post-mastectomy radiotherapy; IMC = internal mammary chain; TAM = tumor-associated macrophage; HER2 = human epidermal growth factor receptor 2; BC = breast cancer

4.2.7 Empfehlungen zum Thema Systemische Therapie/Chemotherapie – adjuvant

4.2.7.1 Eingeschlossene Leitlinien

Zum Thema adjuvante Chemotherapie wurden drei Leitlinien der Gruppe 1 [National Institute for Clinical Excellence (NICE) 2009; New Zealand Guidelines Group (NZGG) 2009; National Breast and Ovarian Cancer Centre (NBOCC) 2008] extrahiert.

Eine Leitlinie wurde vom National Institute for Health and Clinical Excellence (NICE) aus Großbritannien in 2009 herausgegeben. Diese Leitlinien adressiert die Therapie der Primärerkrankung einschließlich lokal fortgeschrittener Tumore [National Institute for Clinical Excellence (NICE) 2009]. Für die Extraktion (insbesondere der Evidenzklassifikationen [LoE]) wurde zusätzlich ein Hintergrund- bzw. Methodendokument ausgewertet [National Institute for Clinical Excellence (NICE) 2009]. Zu den Empfehlungen haben die Autoren der NICE-Leitlinie [National Institute for Clinical Excellence (NICE) 2009] sogenannte ‚Qualifying Statements' angeführt. Diese beschreiben zusammenfassend die zugrundeliegende Evidenz der Empfehlungen. Die ‚Qualifying Statements' wurden mit den Empfehlungen extrahiert, um als Ergänzung zu den berücksichtigten Referenzen auch die entsprechenden zusammenfassenden Einschätzungen der Autoren wiederzugeben.

Eine Leitlinie wurde von der New Zealand Guidelines Group (NZGG) in 2009 herausgegeben. Diese Leitlinie adressiert umfassend die Diagnostik und Therapie der Primärerkrankung. Für die Extraktion dieser Leitlinie wurden keine weiteren Dokumente ausgewertet.

Die dritte Leitlinie wurde vom National Breast and Ovarian Cancer Centre (NBOCC) aus Australien in 2008 herausgegeben. Diese Leitlinie gibt Empfehlungen zur Therapie mit Taxanen bei operablem Mammakarzinom. Für die Extraktion dieser Leitlinie wurden keine weiteren Dokumente ausgewertet. Die Leitlinie des NBOCC enthält Statements, in denen evidenzbasierte Aussagen zusammengefasst werden und Empfehlungen, die eine Handlungsanweisung enthalten, beide wurden extrahiert. Einer Empfehlung können mitunter mehrere Statements thematisch zugeordnet werden.

4.2.7.2 In der S3-Leitlinie Mammakarzinom 2008 nicht enthaltene oder diskrepante Empfehlungs-Inhalte

Im Gegensatz zur S3-Leitlinie Mammakarzinom 2008 empfiehlt die NBOCC 2008-Tax **grundsätzlich die Gabe eines Taxans** als Bestandteil des Chemotherapie-Regimes **bei Patientinnen mit mittlerem oder hohem Rezidivrisiko** (LoE I, GoR n.a), **unabhängig vom Rezeptorstatus** („there was no level I evidence"), gleichwertig entweder Paclitaxel oder Docitaxel. Mit LoE II wird empfohlen, **bei Nicht-Veträglichkeit von Anthrazyklin ein Taxan** einzusetzen. Die NICE 2009 empfiehlt Paclitaxel und nicht Docitaxel bei PatientInnen mit befallenen Lymphknoten (LoE 1++, GoR n.a.). Die NZGG empfiehlt grundsätzlich ein Anthrazyklin-basiertes Regime (entsprechend

der S3-Leitlinie Mammakarzinom 2008) (LoE + bis n.a., GoR A) und mit einem schwächeren Empfehlungsgrad (GoR B) das Erwägen eines Taxan-haltigen Regimes.

Die NBOCC 2008-Tax enthält spezifische Statements in Bezug auf die **Evidenz zu Taxanen** und Empfehlungen zur **Aufklärung der PatientInnen über Neben- und (fehlende) Langzeitwirkungen** (LoE I), die in der S3-Leitlinie Mammakarzinom 2008 nicht enthalten sind.

Tabelle 10: Systemische Therapie/Chemotherapie – adjuvant

Leitlinie	Empfehlung	LoE[12]	GoR[1]	Referenzen
Systemische Therapie/Chemotherapie – adjuvant				
Indikationsstellung/Zeitpunkt der Chemotherapie				
NICE 2009 early	▪ Consider adjuvant therapy for all patients with early invasive breast cancer after surgery at the multidisciplinary team meeting and ensure that decisions are recorded. ▪ Decisions about adjuvant therapy should be made based on assessment of the prognostic and predictive factors, the potential benefits and side effects of the treatment. Decisions should be made following discussion of these factors with the patient. ▪ Consider using Adjuvant! Online5 to support estimations of individual prognosis and the absolute benefit of adjuvant treatment for patients with early invasive breast cancer. (Qualifying statement: These recommendations are based on GDG consensus and an expert position paper on Adjuvant! Online.)	n.a.	n.a.	position paper on Adjuvant! Online siehe Evidence Review zur Leitlinie (S. 700 ff.)

[12] Für Erläuterungen des Level of Evidence (LoE) und Grade of Recommendation (GoR) siehe Anhang 5.6.

Leitlinie	Empfehlung	LoE[12]	GoR[1]	Referenzen
Systemische Therapie/Chemotherapie – adjuvant				
NICE 2009 early	▪ Start adjuvant chemotherapy or radiotherapy as soon as clinically possible within 31 days of completion of surgery13 in patients with early breast cancer having these treatments. (Qualifying Statement: This recommendation is based on GDG consensus in the absence of good quality evidence.)	1. Concurrent adjuvant chemotherapy/radiotherapy versus chemotherapy followed by radiotherapy:		
		1+	n.a.	[Hickey et al. 2006; Calais et al. 2005; Toledano et al. 2007]
		2. Radiotherapy followed by chemotherapy versus chemotherapy followed by radiotherapy:		
		1+	n.a.	[Hickey et al. 2006]
		2-		[Huang et al. 2003]
		3. Early versus late chemotherapy:		
		1+	n.a.	[International Breast Cancer Study Group (IBCSG) 1997]
		4. Interval from surgery to radiotherapy:		
		2+	n.a.	[Mikeljevic et al. 2004]
		2-		[Huang et al. 2003; Whelan et al. 2003; Hershman et al. 2006; Jobsen et al.

[13] Department of Health (2007). Cancer reform strategy. London: Department of Health. (At present no equivalent target has been set by the Welsh Assembly Government.)

Leitlinie	Empfehlung	LoE[12]	GoR[1]	Referenzen
Systemische Therapie/Chemotherapie – adjuvant				
				2006]
		3		[Benchalal et al. 2005]
		5. Interval from surgery to chemotherapy:		
		2-	n.a.	[Hershman et al. 2006; Sanchez C.J. et al. 2007]
		3		[Cold et al. 2005; Colleoni et al. 2000]
NZGG 2009	Adjuvant therapy should be considered for all women with early invasive breast cancer who have undergone surgery	n.a.	GPP	n.a.
NZGG 2009	Adjuvant therapy for an individual woman should be considered within the confines of a multidisciplinary team and the decision recorded	n.a.	GPP	n.a.
NZGG 2009	Adjuvant chemotherapy should ideally commence within 6 weeks of completion of surgery	n.a.	GPP	n.a.
Chemotherapie-Substanzen/Regime				
NBOCC 2008-Tax	Statement: Inclusion of a taxane in adjuvant chemotherapy regimens improves disease-free and overall survival compared to non-taxane containing regimens	I	n.a.	[Ferguson et al. 2007]
NBOCC 2008-Tax	Statement: There are similar benefits for disease-free and overall survival for taxane regimens containing either paclitaxel or docetaxel	I	n.a.	[Ferguson et al. 2007]

Leitlinie	Empfehlung	LoE[12]	GoR[1]	Referenzen
Systemische Therapie/Chemotherapie – adjuvant				
NBOCC 2008-Tax	Statement: There are similar benefits for disease-free survival and overall survival for women treated with a taxane-containing regimen regardless of whether the anthracycline is administered sequentially or concurrently with the taxane	I	n.a.	[Ferguson et al. 2007]
NBOCC 2008-Tax	Statement: There are similar benefits for disease-free and overall survival for women treated with a taxane-containing regimen when adding or substituting a taxane as part of a chemotherapy regimen	I	n.a.	[Ferguson et al. 2007]
NBOCC 2008-Tax	Statement: There are similar benefits for disease-free and overall survival for women treated with a taxane-containing regimen: ▪ which is of the same duration as the non-taxane containing regimen, or ▪ which is of longer duration than the non-taxane containing regimen	I	n.a.	[Ferguson et al. 2007]
NBOCC 2008-Tax	Statement: There was no level I evidence reporting efficacy of taxanes according to hormone receptor status Results from individual randomised controlled phase III studies are conflicting and no recommendation can be made according to hormone receptor status	n.a.	n.a.	n.a.
NBOCC 2008-Tax	Statement: Taxane-containing regimens are associated with an increased incidence of febrile neutropenia compared with non-taxane-containing chemotherapy regimens The increase in febrile neutropenia is most pronounced in concurrent anthracycline and taxane regimens	I		[Ferguson et al. 2007]
NBOCC 2008-Tax	Statement: Taxane-containing chemotherapy regimens are associated with decreased incidence of nausea and vomiting compared with a non-taxane containing chemotherapy regimens The decrease in nausea and vomiting is most pronounced where the	I		[Ferguson et al. 2007]

Leitlinie	Empfehlung	LoE[12]	GoR[1]	Referenzen
Systemische Therapie/Chemotherapie – adjuvant				
	inclusion of a taxane has resulted in lower doses of anthracycline			
NBOCC 2008-Tax	Statement: Taxane-containing regimens may be associated with a reduction in cardiac toxicity compared with non taxane-containing chemotherapy regimens, where the inclusion of a taxane has resulted in lower cumulative anthracycline exposure	I		[Ferguson et al. 2007]
NBOCC 2008-Tax	Statement: There are similar benefits for disease-free survival and overall survival between studies that include women with node positive disease only and studies that include women with node positive or node negative disease No studies have reported results on the use of taxane-containing regimens in women with node negative disease only	I	n.a.	[Ferguson et al. 2007]
NBOCC 2008-Tax	Recommendation: A taxane-containing regimen should be considered for women at intermediate-to-high risk of breast cancer recurrence	I	n.a.	[Ferguson et al. 2007]
NBOCC 2008-Tax	Recommendation: The risks and benefits of using a taxane-containing regimen should be discussed with the woman, taking into consideration her individual risk profile and co-morbidities	I	n.a.	[National Health and Medical Research Council (NHMRC) 2003]i
NBOCC 2008-Tax	Recommendation: The optimal scheduling and dosing of taxanes in adjuvant chemotherapy regimens for survival benefits is unknown Decisions on scheduling and dosing of taxane-containing regimens should be based on factors other than survival outcomes, and take into consideration the woman's individual risk profile and co-morbidities—consideration of toxicity effects should guide dosing and scheduling decisions	n.a.	n.a.	n.a.

Leitlinie	Empfehlung	LoE[12]	GoR[1]	Referenzen
Systemische Therapie/Chemotherapie – adjuvant				
NBOCC 2008-Tax	Recommendation: Taxane-containing regimens should be considered as an option regardless of tumour hormone-receptor status	I	n.a.	[Ferguson et al. 2007]
NBOCC 2008-Tax	Recommendation: Women should be informed of the increased risk of febrile neutropenia associated with taxane-containing regimens For women at significant risk of febrile neutropenia, primary prophylaxis with growth factor support should be considered	n.a.	n.a.	n.a.
NBOCC 2008-Tax	Recommendation: Women should be informed of the potential adverse effects of a taxane-containing regimen and any uncertainties about long-term effects	I	n.a.	[Ferguson et al. 2007]
NBOCC 2008-Tax	Recommendation: If a woman is not suitable to receive an anthracycline-containing regimen, a taxane-containing non-anthracycline regimen can be considered	II	n.a.	[Jones et al. 2006]
NICE 2009 early	▪ Offer docetaxel to patients with lymph node-positive breast cancer as part of an adjuvant chemotherapy regimen. ▪ Do not offer paclitaxel as an adjuvant treatment for lymph node-positive breast cancer. (Qualifying statement: These recommendations were based on a systematic review which found no new evidence to change the health economic analysis carried out for TA 108 (NICE 2006b). The GDG considered the data from the TACT trial but, because it had not been fully published and it was at variance with a large body of other RCT evidence showing that the addition of docetaxel improved outcomes, they did not believe it should change the recommendation. They were also aware of the data from Sparano et al. (2008) showing that in terms of overall survival weekly paclitaxel was more effective than 3 weekly paclitaxel. This trial also showed no difference in overall survival between 3 weekly docetaxel and 3	1++ 1+ 1 n.a.	n.a.	[Ferguson et al. 2007; De Laurentiis et al. 2008; Ward et al. 2007] [Kummel et al. 2006; Piedbois et al. 2007] [Bria et al. 2006] [Sparano et al. 2008; Wolowacz et al. 2008; Ellis et al. 2001; Limwattananon et al. 2006]

Leitlinie	Empfehlung	LoE[12]	GoR[1]	Referenzen
Systemische Therapie/Chemotherapie – adjuvant				
	weekly paclitaxel. Because this trial was only found when updating the evidence searches, it was not possible to start a de novo health economic analysis. Given the current significantly reduced acquisition cost of pacitaxel for the NHS, it is possible that a regimen including paclitaxel may be appropriate.)			
NZGG 2009	Anthracycline-based regimens should be considered for adjuvant chemotherapy as they are more effective than standard cyclophosphamide, methotrexate and fluorouracil (CMF) regimens	n.a. +	A	[Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2005; Levine et al. 2005; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 1998] [Ejlertsen et al. 2007; Scottish Intercollegiate Guidelines Network (SIGN) 2005; Christiaens et al. 2007; Stebbing et al. 2007]
NZGG 2009	The absolute benefits of anthracycline-based regimens should be balanced against the side effects on an individual basis when planning management	n.a. +	B	[Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2005; Levine et al. 2005; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 1998] [Ejlertsen et al. 2007; Scottish Intercollegiate Guidelines Network (SIGN) 2005; Christiaens et al. 2007; Stebbing et al. 2007]

Leitlinie	Empfehlung	LoE[12]	GoR[1]	Referenzen
Systemische Therapie/Chemotherapie – adjuvant				
NZGG 2009	Inclusion of a taxane as part of adjuvant chemotherapy should be considered in all cases where chemotherapy is contemplated	n.a.		[Henderson et al. 2003; Martin et al. 2005]
		+	A	[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Christiaens et al. 2007; De Laurentiis et al. 2008; National Institute for Clinical Excellence (NICE) 2006; Ward et al. 2007; Ferguson et al. 2007; Bria et al. 2006; Trudeau et al. 2006; Estevez et al. 2007]
NZGG 2009	A woman with early breast cancer should be informed about the benefits of adding a taxane to adjuvant chemotherapy and known side effects of taxanes. Information should be made available to assist in making an informed choice	n.a.	GPP	n.a.

Abkürzungen: n.a. = nicht angegeben; HER2 = human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction; ECG = electrocardiograph; CMF = cyclophosphamide, methotrexate and fluorouracil regimens; GPP = Good Practice Point; MUGA = Multi Gated Acquisition scans

4.2.8 Empfehlungen zum Thema Systemische Therapie/Endokrine Therapie – adjuvant

4.2.8.1 Eingeschlossene Leitlinien

Zum Thema adjuvante endokrine Therapie wurden zwei Leitlinien der Gruppe 1 ([National Institute for Clinical Excellence (NICE) 2009; New Zealand Guidelines Group (NZGG) 2009] und vier Leitlinien der Gruppe 2 [Burstein et al. 2010; Eisen et al. 2010; Eisen et al. 2006; Flemming et al. 2008] extrahiert.

Eine Leitlinie wurde vom National Institute for Health and Clinical Excellence (NICE) aus Großbritannien in 2009 herausgegeben. Diese Leitlinie adressiert die Diagnostik und Therapie der Primärerkrankung einschließlich lokal fortgeschrittener Tumore [National Institute for Clinical Excellence (NICE) 2009]. Für die Extraktion dieser Leitlinie (insbesondere der Evidenzklassifikationen [LoE]) wurde zusätzlich ein Hintergrund- bzw. Methodendokument ausgewertet [National Institute for Clinical Excellence (NICE) 2009]. Zu den Empfehlungen haben die Autoren der NICE-Leitlinie [National Institute for Clinical Excellence (NICE) 2009] sogenannte ‚Qualifying Statements' angeführt. Diese beschreiben zusammenfassend die zugrundeliegende Evidenz der Empfehlungen. Die ‚Qualifying Statements' wurden mit den Empfehlungen extrahiert, um als Ergänzung zu den berücksichtigten Referenzen auch die entsprechenden zusammenfassenden Einschätzungen der Autoren wiederzugeben. Eine Leitlinie wurde von der New Zealand Guidelines Group (NZGG) in 2009 herausgegeben. Diese Leitlinie adressiert umfassend die Diagnostik und Therapie der Primärerkrankung. Für die Extraktion dieser Leitlinie wurden keine weiteren Dokumente ausgewertet.

Drei Leitlinien der Gruppe 2 wurden von der kanadischen Institution Cancer Care Ontario (CCO) in den Jahren 2008 bzw. 2010 herausgegeben. Diese Leitlinien enthalten Empfehlungen zu den Themen: Aromatasehemmer bei postmenopausalen hormonrezeptorpositiven Frauen (2008), ovarielle Suppression bei prämenopausalen Frauen (2010), Fulvestrant bei postmenopausalen Frauen mit lokal fortgeschrittenem oder metastasiertem Brustkrebs (2008) und Aromatasehemmer. Für die CCO-Leitlinien wurden zusätzlich Hintergrund- bzw. Methodendokument ausgewertet. Extrahiert wurde außerdem die Leitlinie der American Society of Clinical Oncology (ASCO) von 2010 zur endokrinen Therapie bei hormonrezeptorpositiven Frauen (ASCO 2010) [Burstein et al. 2010].

4.2.8.2 In der S3-Leitlinie Mammakarzinom 2008 nicht enthaltene oder diskrepante Empfehlungs-Inhalte

Die NICE 2009 early empfiehlt zur unterstützenden Schätzung der individuellen Prognose und des adjuvanten Therapiebenefits den **Einsatz von Adjuvant!Online**, (auch für Chemotherapie) dies wird in der S3-Leitlinie Mammakarzinom 2008 nicht thematisiert. Diskrepant zu der S3-Leitlinie Mammakarzinom 2008 (= „…eine adjuvante endokrine Therapie sollte im Allgemeinen …erfolgen") lautet

eine Empfehlung der NZGG (good practice point), bei **PatientInnen mit niedrigem Rezidivrisiko** zu erwägen, auf eine endokrine Therapie zu verzichten. Die NICE 2009 early empfiehlt für alle Patientinnen das Erwägen („consider“) einer adjuvanten Therapie (LoE, GoR n.a.), formuliert aber die spezifische Empfehlung zur endokrinen Therapie ebenfalls mit Ausnahme der Patientinnen mit niedrigem Rezidivrisiko (LoE 1++, GoR n.a.). Die anderen eingeschlossenen Leitlinien thematisieren in ihren Empfehlungen die Indikationsstellung abhängig vom Rezidivrisiko nicht, sondern die Empfehlungen gelten für alle (prä- und/oder postmenopausale) PatientInnen mit positiven Hormonrezeptoren entsprechend der S3-Leitlinie Mammakarzinom 2008.

In Bezug auf die einzusetzenden Substanzen und Therapiestrategien wie „switch“ oder „extented“ nennen alle eingeschlossenen Leitinien die **gleichen Optionen für postmenopauseale Patientinnen** mit unterschiedlicher Gewichtung der **Tamoxifentherapie** als gleichrangige (CCO-A-2008, „mature RCT“) oder **im Vergleich zu Aromatasehemmern der 3. Generation sekundäre Option** (ASCO 2010 LoE n.a., NICE 2009 early LoE 1++, NZGG 2009 LoE ++, GoR A). Bei PatientInnen mit lokal fortgeschrittenem Mammakarzinom wird **Fulvestrant** von der CCO-F-2008 explizit **nicht** (als Alternative zu Tamoxifen) als **Therapie erster Wahl** empfohlen (LoE, GoR n.a.).

Die ASCO 2010 empfiehlt bei **Aromatasehemmertherapie unter 5 Jahre** und einer später erneut begonnenen endokrinen Therapie mit Tamoxifen, dies für 5 komplette Jahre einzunehmen (LoE, GoR n.a.). Die S3-Leitlinie Mammakarzinom 2008 thematisiert dies nur nach kürzer als 5 Jahre erfolgter Tamoxifentherapie und späterer Wiederaufnahme derselben.

Für Männer empfiehlt die ASCO 2010 **Tamoxifen** als endokrine Therapie der ersten Wahl (LoE, GoR n.a.). Die spezifische endokrine Behandlung von männlichen Brustkrebspatienten wird in der S3-Leitlinie Mammakarzinom 2008 nicht thematisiert.
Die ASCO 2010 stellt ausdrücklich fest, dass es **keine spezifischen Marker oder klinischen Auswahlkriterien zur Festlegung einer endokrinen Strategie** gibt (LoE, GoR n.a) und spricht sich insbesondere gegen den Genotyp CYP2D6 als Kriterium aus. Die CCO-A-2008 stellt fest, dass es **keine Evidenz für eine Indikation von Aromatasehemmern abhängig vom HER-2-Status** gibt. Diese Inhalte finden sich in der S3-Leitlinie Mammakarzinom 2008 nicht.

In Bezug auf die Aufklärung der PatientInnen wird in der ASCO 2010 explizit erwähnt, dass die **Nebenwirkungsprofile auch Bestandteil der Diskussion mit der PatientIn bei der Entscheidung über die (endokrinen) Therapieoptionen** sein soll (LoE, GoR n.a.). Dieser Aspekt wird in der S3-Leitlinie Mammakarzinom 2008 nicht explizit ausgeführt (auch nicht im Abschnitt Aufklärung A 2.2).

Die NZGG empfiehlt **für jüngere Patientinnen die Bestimmung von Gonadotropin und Östrogenspiegel vor Beginn einer Aromatasehemmertherapie** zur Überprüfung des Menopausenstatus z.B. bei chemotherapieinduzierter Amenorrhoe (LoE n.a., GoR A). Dies wird in der S3-Leitlinie Mammakarzinom 2008 nicht explizit thematisiert.

Die CCO 2010-OA empfiehlt im Gegensatz zur S3-Leitlinie Mammakarzinom 2008 die **ovarielle Ablation nur, wenn die betreffenden Patientinnen keine andere adjuvante Therapie erhalten wollen oder können** (Empfehlung beruht auf einer Metaanalyse von RCTs,

GoR n.a.). Die NZGG stuft die **Oophorektomie** als akzeptable Option mit hoher Morbidität und ungünstigen Langzeitfolgen ein (LoE +, GoR A). Die NICE 2009 early rät explizit von einer **Ausschaltung der Ovarialfunktion gleichzeitig zu einer Tamoxifentherapie oder Chemotherapie** ab (LoE 1++ bis 1-, GoRn.a.). Die NZGG empfiehlt einen **LHRH-Agonisten gleichzeitig zu Tamoxifen** bei Patientinnen mit hohem Rezidivrisiko, die nach Chemotherapie nicht postmenopausal sind (LoE +, GoR B). Die Ausschaltung der Ovarialfunktion bei Gabe von Aromatasehemmern wird bei fehlender vorliegender Evidenz nur in Studien empfohlen. Die Ausschaltung der Ovarialfunktion nach Chemotherapie (alleine und in Kombination mit Tamoxifen) wird in der S3-Leitlinie Mammakarzinom 2008 als ungewiss in ihrer Wirksamkeit eingestuft.

Die Leitlinien CCO-A-2008, NICE 2009 early und NZGG enthalten **Empfehlungen zur Überwachung der Knochendichte unter Aromatasehemmern** (LoE jew. n.a., GoR n.a., n.a. und A) unter Nennung von Methoden und Cut-Off-Werten (NICE; NZGG). Ebenso finden sich Empfehlungen von NICE 2009 early und NZGG zur **Therapie mit Bisphosphonaten** (LoE 1++, ++, +) und **Aufklärung der PatientInnen in Bezug auf die Lebensführung**, die so spezifisch in der S3-Leitlinie Mamakarzinom 2008 nicht enthalten sind (auch nicht in Abschnitt D 5.4).

Tabelle 11: Systemische Therapie/Endokrine Therapie - adjuvant

Leitlinie	Empfehlung	LoE[14]	GoR[1]	Referenzen
Systemische Therapie/Endokrine Therapie – adjuvant				
Endokrine Therapie – Indikationsstellung				
NICE 2009 early	▪ Consider adjuvant therapy for all patients with early invasive breast cancer after surgery at the multidisciplinary team meeting and ensure that decisions are recorded. ▪ Decisions about adjuvant therapy should be made based on assessment of the prognostic and predictive factors, the potential	n.a.	n.a.	position paper on Adjuvant! Online siehe Evidence Review zur Leitlinie (S. 700 ff.)

[14] Für Erläuterungen des Level of Evidence (LoE) und Grade of Recommendation (GoR) siehe Anhang 5.6.

Leitlinie	Empfehlung	LoE[14]	GoR[1]	Referenzen
Systemische Therapie/Endokrine Therapie – adjuvant				
	benefits and side effects of the treatment. Decisions should be made following discussion of these factors with the patient. ▪ Consider using Adjuvant! Online5 to support estimations of individual prognosis and the absolute benefit of adjuvant treatment for patients with early invasive breast cancer. (Qualifying statement: These recommendations are based on GDG consensus and an expert position paper on Adjuvant! Online.)			
NZGG 2009	In hormone receptor negative breast cancer, endocrine therapy offers no benefit and should be avoided due to the risk of side effects	+	A	[Early Breast Cancer Trialists' Collaborative Group (EBCTCG) et al. 2008; Kaufmann et al. 2007; Bernhard et al. 2007; Cuzick et al. 2007]
NZGG 2009	For a woman with a low risk of recurrence the option not to use endocrine or chemotherapy treatment may be considered	n.a.	GPP	n.a.
Endokrine Therapie für postmenopausale Patientinnen				
ASCO 2010-Endo	«Gilt für: Women With Hormone Receptor–Positive Breast Cancer» Postmenopausal women should consider taking an AI during the course of adjuvant treatment to lower recurrence risk, either as primary therapy or after 2 to 3 years of tamoxifen. Duration of AI therapy should not exceed 5 years.	n.a.	n.a.	[Hind et al. 2007; Aihara et al. 2008; Boccardo et al. 2006; Coombes et al. 2007; Forbes et al. 2008; Gnant et al. 2009; Goss et al. 2007; Ingle et al. 2008; Jakesz et al. 2007; Jones et al. 2007; Jakesz et al. 2008; Jones et al. 2008; Kaufmann et al. 2007; Mamounas et al. 2008; Mouridsen et al. 2009; Rea et al. 2009; Jakesz et al. 2005; Mouridsen et al. 2008; Baum et al. 2002; Boccardo et al. 2003; Coombes et al. 2004; Jakesz et al. 2005; Goss et al. 2003; Jakesz et al. 2005;

Leitlinie	Empfehlung	LoE[14]	GoR[1]	Referenzen
Systemische Therapie/Endokrine Therapie – adjuvant				
				Mamounas et al. 2006]
ASCO 2010- Endo	«Gilt für: Women With Hormone Receptor–Positive Breast Cancer» Therapy with an AI should not extend beyond 5 years in either the primary or extended adjuvant settings outside the clinical trials setting. In the sequential setting, patients should receive an AI after 2 or 3 years of tamoxifen for a total of 5 years of adjuvant endocrine therapy. Patients initially treated with an AI but who discontinue treatment before 5 years of therapy should consider incorporating tamoxifen for a total of 5 years of adjuvant endocrine therapy.	n.a.	n.a.	n.a.
ASCO 2010- Endo	«Gilt für: Women With Hormone Receptor–Positive Breast Cancer» Patients who initially receive tamoxifen as adjuvant therapy may be offered an AI after 2 to 3 years (sequential) or after 5 years (extended) of therapy. The best time to switch from an AI to tamoxifen (or the converse) is not known. Switching at 2 to 3 years is recommended, but switching at 5 years is also supported by available data.	n.a.	n.a.	[Hind et al. 2007; Aihara et al. 2008; Boccardo et al. 2006; Crivellari et al. 2008; Forbes et al. 2008; Gnant et al. 2009; Goss et al. 2007; Ingle et al. 2008; Jakesz et al. 2007; Jones et al. 2007; Jakesz et al. 2008; Jones et al. 2008; Kaufmann et al. 2007; Mamounas et al. 2008; Mouridsen et al. 2009; Rea et al. 2009; Thürlimann et al. 2005; Jakesz et al. 2005; Dowsett et al. 2010; Mouridsen et al. 2008; Baum et al. 2002; Boccardo et al. 2003; Coombes et al. 2004; Jakesz et al. 2005; Goss et al. 2003; Jakesz et al. 2005; Mamounas et al. 2006]
ASCO 2010- Endo	«Gilt für: Men With Hormone Receptor–Positive Breast Cancer» A specific marker or clinical subset that predicts which adjuvant treatment strategy (tamoxifen alone, AI alone, or AI and tamoxifen-based) is best has not been identified. Among men with breast cancer,	n.a.	n.a.	[Coombes et al. 2007; Forbes et al. 2008; Goss et al. 2007; Mamounas et al. 2008; Mauriac et al. 2007; Rasmussen et al. 2008; Viale et al.

Leitlinie	Empfehlung	LoE[14]	GoR[1]	Referenzen
Systemische Therapie/Endokrine Therapie – adjuvant				
	tamoxifen remains the standard adjuvant endocrine treatment. The CYP2D6 genotype is not recommended to select adjuvant endocrine therapy. Caution with concurrent use of CYP2D6 inhibitors (such as bupropion, paroxetine, or fluoxetine) and tamoxifen is recommended because of drug-drug interactions.			2008; Dowsett et al. 2010; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2005; Fisher et al. 2001; Paik et al. 2004; Giordano et al. 2005; Borges et al. 2006; Goetz et al. 2007; Goetz et al. 2005; Mouridsen et al. 2008; Dowsett et al. 2008; Viale et al. 2009; Blue Cross Blue Shield Association (BCBS) 2008; Albain et al. 2007; Gonzalez-Santiago et al. 2007; Schroth et al. 2009; Goss 2006]
ASCO 2010- Endo	«Gilt für: Women With Hormone Receptor–Positive Breast Cancer» Clinicians should consider adverse effect profiles, patient preferences, and preexisting conditions when discussing adjuvant endocrine strategies. Adverse effect profiles should be discussed with patients when presenting available treatment options. Clinicians may recommend that patients change treatments if adverse effects are intolerable or patients are persistently noncompliant with therapy.	n.a.	n.a.	[Fallowfield et al. 2007; Mamounas et al. 2008; Ohsumi et al. 2008; van Nes et al. 2008; Cella et al. 2006; Whelan et al. 2005; Osborne 1998; Mouridsen et al. 2007; Cuppone et al. 2008; Eastell et al. 2008; Rabaglio et al. 2009; Coleman 2008; Forbes et al. 2007; Gnant et al. 2008; Brufsky et al. 2007; Bundred et al. 2008; Hillner et al. 2003; Burstein et al. 2007; Crew et al. 2007; Henry et al. 2008; Sestak et al. 2009; Sestak et al. 2008; Cella et al. 2006; Whelan et al. 2005; Fallowfield et al. 2007; Jones et al. 2007; Rea et al. 2009; Fallowfield et al. 2004; Fallowfield et al. 2006]
ASCO 2010- Endo	Meaningful clinical differences between the commercially available third-generation AIs have not been demonstrated to date. The Update Committee believes that postmenopausal patients intolerant of one AI may be advised to consider tamoxifen or a different AI.	n.a.	n.a.	[Crivellari et al. 2008; Koeberle et al. 2007; Mouridsen et al. 2009; Jakesz et al. 2008; Boccardo et al. 2006; Rea et al. 2009; Coombes et al. 2007;

Leitlinie	Empfehlung	LoE[14]	GoR[1]	Referenzen
Systemische Therapie/Endokrine Therapie – adjuvant				
				Kaufmann et al. 2007; Aihara et al. 2008; Goss 2007; Baum et al. 2002; Mouridsen et al. 2009; Gnant et al. 2009; Jakesz et al. 2005; Boccardo et al. 2003; Jones et al. 2007; Coombes et al. 2004; Aihara et al. 2008; Jakesz et al. 2005; Goss et al. 2003; Jakesz et al. 2005; Mamounas et al. 2006; Boccardo et al. 2005; Howell et al. 2005; Buzdar et al. 2006]
CCO-A-2008	Adjuvant tamoxifen (20 mg daily for five years) remains an acceptable option for the treatment of women with hormone receptor-psoitive, early stage breast cancer	"The body of evidence in this review is primarily comprised of mature randomized controlled trial data."	n.a.	[Baum et al. 2002; Howell et al. 2005; Thürlimann et al. 2005; Coates et al. 2007; Coombes et al. 2004; Coombes et al. 2007; Boccardo et al. 2005; Jakesz et al. 2005; Mamounas et al. 2006; Jakesz et al. 2005; Jakesz et al. 2005; Jonat et al. 2006]
CCO-A-2008	Adjuvant anastrozole (1.0 mg daily for five years) or letrozole (2.5mg daily for five years) is an acceptable alternative for five years of tamoxifen therapy.		n.a.	
CCO-A-2008	Adjuvant tamoxifen (20 mg for two to three years) followed by switching to either adjuvant exemestane (25 mg daily, to a total of five years of hormone therapy) or adjuvant anastrozole (1 mg daily, to a total of five years) therapy is also an acceptable alternative to five years of tamoxifen.		n.a.	
CCO-A-2008	Adjuvant letrozole (2.5mg daily for five years) should be considered for women who have completed five years of adjvuant tamoxifen therapy.		n.a.	[Goss et al. 2003]
CCO-A-2008	Due of the lack of evidence, no recommendation for the use of aromatase inhibitors based on HER2/*neu*-Status can be made at this time.	n.a.	n.a.	[Dowsett et al. 2006; Eiermann et al. 2001; Ellis et al. 2001; Smith et al. 2005; Lipton et al. 2003]

Leitlinie	Empfehlung	LoE[14]	GoR[1]	Referenzen
Systemische Therapie/Endokrine Therapie – adjuvant				
				(Evidenz aus anderem Setting: neoadjuvant oder bei metastasiertem Brustkrebs)
NICE 2009 early	▪ Postmenopausal women with ER-positive early invasive breast cancer who are not considered to be at low risk[15] should be offered an aromatase inhibitor, either anastrozole or letrozole, as their initial adjuvant therapy. Offer tamoxifen if an aromatase inhibitor is not tolerated or contraindicated.	1++	n.a.	[Buzdar et al. 2006; Buzdar et al. 2006; Howell et al. 2005; Hind et al. 2007; Coates et al. 2007; Thurlimann 2005; Goss et al. 2005; Ingle et al. 2006; Coombes et al. 2004]
	▪ Offer an aromatase inhibitor, either exemestane or anastrozole instead of tamoxifen to postmenopausal women with ER-positive early invasive breast cancer who are not low-risk and who have been treated with tamoxifen for 2−3 years.	1+	n.a.	[Dowsett et al. 2005; Boccardo et al. 2005; Forbes et al. 2008; Jakesz et al. 2005; Goss et al. 2007; Rasmussen et al. 2008; Muss et al. 2008]
	▪ Offer additional treatment with the aromatase inhibitor letrozole for 2−3 years to postmenopausal women with lymph node-positive ER-positive early invasive breast cancer who have been treated with tamoxifen for 5 years.	2+	n.a.	[Goss et al. 2008]
	(Qualifying statement: These recommendations are based on high-quality RCTs.)	n.a.	n.a.	[Crivellari et al. 2008; Eisen et al. 2008]
NICE 2009 early	▪ The aromatase inhibitors anastrozole, exemestane and letrozole, within their licensed indications, are recommended as options for the adjuvant treatment of early ER-positive invasive breast cancer in postmenopausal women.	n.a.	n.a.	[National Institute for Clinical Excellence (NICE) 2006]

[15] Low-risk patients are those in the EPG or GPG groups in the Nottingham Prognostic Index (NPI) who have a 10 year predictive survival of 96% and 93% respectively. They would have a similar prediction using Adjuvant! Online. High-risk patients are those in groups PPG with 53% or VPG with 39%

Leitlinie	Empfehlung	LoE[14]	GoR[1]	Referenzen
Systemische Therapie/Endokrine Therapie – adjuvant				
	▪ The choice of treatment should be made after discussion between the responsible clinician and the woman about the risks and benefits of each option. Factors to consider when making the choice include whether the woman has received tamoxifen before, the licensed indications and side-effect profiles of the individual drugs and, in particular, the assessed risk of recurrence.			
NZGG 2009	For a postmenopausal woman with hormone receptor positive breast cancer the use of chemotherapy in addition to endocrine therapy should be considered, taking into account the overall benefits and risks of treatment* * Benefits in those aged over 70 years are uncertain	+ n.a.	A	[Christiaens et al. 2007; Namer et al. 2006; Poole et al. 2007] [Albain et al. 2004; Love et al. 2002; Goldhirsch et al. 2001; Adjuvant Breast Cancer Trials Collaborative Group 2007]
NZGG 2009	Aromatase inhibitors should form at least part of the treatment regimen when adjuvant endocrine therapy is prescribed to postmenopausal women with hormone receptor positive early breast cancer, unless contraindications to their use exist Adjuvant endocrine therapy for postmenopausal women with hormone receptor positive early breast cancer should comprise treatment for 5 years with either an aromatase inhibitor alone or with a sequence of an aromatase inhibitor and tamoxifen. Women already on tamoxifen for 2–3 years should switch to an aromatase inhibitor	++ + n.a.	A	[Eisen et al. 2008] [Christiaens et al. 2007; Stebbing et al. 2007; Poole et al. 2007; Jonat et al. 2006; Howell et al. 2005; Boccardo et al. 2007] [Mamounas et al. 2005; Jakesz et al. 2005; Forbes et al. 2008; Coombes et al. 2007; Ingle et al. 2008; Coates et al. 2007; Thurlimann 2005; Coombes et al. 2004; Coleman et al. 2007; Goss et al. 2003; Goss et al. 2005; Mouridsen et al. 2008]

Leitlinie	Empfehlung	LoE[14]	GoR[1]	Referenzen
Systemische Therapie/Endokrine Therapie – adjuvant				
NZGG 2009	Adjuvant endocrine therapy should be given for a duration of at least 5 years	++	A	[Eisen et al. 2008]
		+		[Christiaens et al. 2007; Stebbing et al. 2007; Poole et al. 2007; Jonat et al. 2006; Howell et al. 2005; Boccardo et al. 2007]
		n.a.		[Mamounas et al. 2005; Jakesz et al. 2005; Forbes et al. 2008; Coombes et al. 2007; Ingle et al. 2008; Coates et al. 2007; Thurlimann 2005; Coombes et al. 2004; Coleman et al. 2007; Goss et al. 2003; Goss et al. 2005; Mouridsen et al. 2008]
NZGG 2009	The use of tamoxifen alone as adjuvant therapy for postmenopausal women is recommended only when an aromatase inhibitor is contraindicated or has been tried and was not tolerated. Tamoxifen for 5 years remains the standard of care in premenopausal women with hormone receptor positive breast cancer	++	A	[Eisen et al. 2008]
		+		[Christiaens et al. 2007; Stebbing et al. 2007; Poole et al. 2007; Jonat et al. 2006; Howell et al. 2005; Boccardo et al. 2007]
		n.a.		[Mamounas et al. 2005; Jakesz et al. 2005; Forbes et al. 2008; Coombes et al. 2007; Ingle et al. 2008; Coates et al. 2007; Thurlimann 2005; Coombes et al. 2004; Coleman et al. 2007; Goss et al. 2003; Goss et al. 2005; Mouridsen et al. 2008]

Leitlinie	Empfehlung	LoE[14]	GoR[1]	Referenzen
Systemische Therapie/Endokrine Therapie – adjuvant				
NZGG 2009	Premenopausal women who have completed 5 years of tamoxifen and have become menopausal should be given the option of extended therapy with an aromatase inhibitor	++	A	[Eisen et al. 2008]
		+.		[Christiaens et al. 2007; Stebbing et al. 2007; Poole et al. 2007; Jonat et al. 2006; Howell et al. 2005; Boccardo et al. 2007]
	Extended (or 'late') use of an aromatase inhibitor after 5 years of tamoxifen is recommended only for those women with hormone receptor positive breast cancer who have completed a 5-year course of tamoxifen and become suitable for treatment with an aromatase inhibitor late in that course (eg, having become reliably menopausal after the time when a switch policy would have been considered)	n.a.		[Mamounas et al. 2005; Jakesz et al. 2005; Forbes et al. 2008; Coombes et al. 2007; Ingle et al. 2008; Coates et al. 2007; Thurlimann 2005; Coombes et al. 2004; Coleman et al. 2007; Goss et al. 2003; Goss et al. 2005; Mouridsen et al. 2008]
NZGG 2009	Measurement of oestrogen and gonadotrophin levels is recommended before initiating treatment with an aromatase inhibitor where there is a chance that the woman is still premenopausal Note: Particular care is required for younger women just post chemotherapy or on tamoxifen, as amenorrhoea can occur when normal premenopausal ovarian oestrogen production is present. Tamoxifen leads to elevated gonadotrophin levels even in the presence of normal premenopausal ovarian endocrine function	n.a.	A	n.a.
NZGG 2009	Aromatase inhibitors should be prescribed with caution for women in their forties with chemotherapy-induced premature ovarian failure	n.a.	B	n.a.
NZGG 2009	The side effects of aromatase inhibitors and tamoxifen should be considered against the absolute benefit in breast cancer relapse	n.a.	GPP	n.a.

Leitlinie	Empfehlung	LoE[14]	GoR[1]	Referenzen
Systemische Therapie/Endokrine Therapie – adjuvant				
Fulvestrant bei lokal fortgeschrittenem Mammakarzinom postmenopausaler Patientinnen				
CCO-F-2008	▪ Fulvestrant is NOT recommended as an alternative to tamoxifen for first-line therapy of locally advanced or metastastic breast cancer in postmenopausal women who had no prior endocrine or cytotoxic therapy for advanced disease and no recent endocrine therapy (within previous twelve months)	n.a.	n.a.	[Howell et al. 2004]
Endokrine Therapie für prämenopausale Patientinnen				
ASCO 2010- Endo	«Gilt für: Women With Hormone Receptor–Positive Breast Cancer» Women who are pre- or perimenopausal at diagnosis should be treated with 5 years of tamoxifen.	n.a.	n.a.	[Gnant et al. 2009; Goss et al. 2009; Burstein et al. 2006; Smith et al. 2006]
CCO 2010-OA	▪ OA (ovarian ablation) should not be routinely added to systemic therapy with chemotherapy, tamoxifen, or the combination of tamoxifen and chemotherapy. ▪ OA alone is not recommended as an alternative to any other form of systemic therapy, except in the specific case of patients who are candidates for other forms of systemic therapy but who for some reason will not receive any other systemic therapy (e.g., patients who cannot tolerate other forms of systemic therapy or patients who choose no other form of systemic therapy).	n.a.	n.a.	[Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2005; Cuzick et al. 2007; Soreide et al. 2002; Adjuvant Breast Cancer Trials Collaborative Group 2007; Robert et al. 2003; Robert et al. 2005; Baum et al. 2006] + Metanalyyse der LL-Gruppe mit folgenden Studien [Thomson et al. 2002; Schmid et al. 2007; Kaufmann et al. 2003; Jonat et al. 2002; Castiglione-Gertsch et al. 2003; von Minckwitz et al. 2006; Ejlertsen et al. 2006; Schmid et al. 2002; Scottish Cancer Trials Breast Group et al. 1993; Salvadori et al. 2000] (siehe Evidence Review zur

Leitlinie	Empfehlung	LoE[14]	GoR[1]	Referenzen
Systemische Therapie/Endokrine Therapie – adjuvant				
				Leitlinie)
CCO 2010-OA	▪ When chemical suppression using LHRH agonists is the chosen method of OA, in the opinion of the Breast Cancer DSG monthly injection is the recommended mode of administration.	n.a.	n.a.	"The mode of administration in nearly all of the available trials has been monthly administration."
NICE 2009 early	▪ Do not offer adjuvant ovarian ablation/suppression to premenopausal women with ER-positive early invasive breast cancer who are being treated with tamoxifen and, if indicated, chemotherapy. ▪ Offer adjuvant ovarian ablation/suppression in addition to tamoxifen to premenopausal women with ER-positive early invasive breast cancer who have been offered chemotherapy but have chosen not to have it. (Qualifying statement: There is conflicting evidence and GDG consensus to support these recommendations.)	1++	n.a.	[Sharma et al. 2007]
		1+	n.a.	[Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2005; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 1998; Thomson et al. 2002; Kaufmann et al. 2007; Cuzick et al. 2007; Love et al. 1999; Love et al. 2008; Schmid et al. 2007]
		1-	n.a.	[Brunt et al. 2004; Groenvold et al. 2006; Celio et al. 2011] (In der LL wird Celio 2002 zitiert. Hier Version mit gleichem Titel von 2011 berücksichtigt)
NZGG 2009	In premenopausal women with hormone receptor positive breast cancer, endocrine therapy should be considered	+	A	[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Stebbing et al. 2007; Christiaens et al. 2007; Morales et al. 2007; Cuzick et al. 2007]
		n.a.		[Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2005; Love et al. 2002; Goldhirsch et al.

Leitlinie	Empfehlung	LoE[14]	GoR[1]	Referenzen
Systemische Therapie/Endokrine Therapie – adjuvant				
				2001]
NZGG 2009	At the time of this review there was no randomised controlled trial evidence to support the use of ovarian function suppression (LHRH agonists or oophorectomy) in conjunction with an aromatase inhibitor in premenopausal women. This is not recommended outside the remit of a clinical trial	n.a.	A	n.a.
NZGG 2009	When both endocrine therapy and chemotherapy are to be administered the chemotherapy should be administered first	n.a.	C	n.a.
NZGG 2009	In women considering oophorectomy a trial of at least one month of a LHRH agonist is recommended to allow an assessment of the tolerability of such treatment before committing to an irreversible procedure	n.a.	C	n.a.
NZGG 2009	«Addition of chemotherapy to endocrine therapy ± surgery ± radiotherapy» For a woman with hormone receptor negative breast cancer adjuvant chemotherapy should be considered	n.a.	A	[Early Breast Cancer Trialists' Collaborative Group (EBCTCG) et al. 2008]
NZGG 2009	«Addition of chemotherapy to endocrine therapy ± surgery ± radiotherapy» For a premenopausal woman with hormone receptor positive breast cancer, chemotherapy (including an anthracycline and/or a taxane) followed by tamoxifen should be considered	+ n.a.	A	[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Christiaens et al. 2007; Wildiers et al. 2007; Namer et al. 2006; Viale et al. 2008; Aebi 2006] [Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2005]
NZGG 2009	Oophorectomy is an acceptable treatment option but is associated with high morbidity and long-term adverse effects	+	A	[Stebbing et al. 2007; Early Breast Cancer Trialists' Collaborative Group

Leitlinie	Empfehlung	LoE[14]	GoR[1]	Referenzen
Systemische Therapie/Endokrine Therapie – adjuvant				
				(EBCTCG) et al. 2008]
NZGG 2009	A LHRH agonist in addition to tamoxifen should be considered for a woman at high risk of recurrence (age <40 years), who is not postmenopausal (at least 3 months of amenorrhoea) after chemotherapy	+	B	[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Christiaens et al. 2007; Cuzick et al. 2007; Baum et al. 2006]
		n.a.		[Adjuvant Breast Cancer Trials Collaborative Group 2007]
		n.a.		[Mamounas et al. 2005; Jakesz et al. 2005; Forbes et al. 2008; Coombes et al. 2007; Ingle et al. 2008; Coates et al. 2007; Thurlimann 2005; Coombes et al. 2004; Coleman et al. 2007; Goss et al. 2003; Goss et al. 2005; Mouridsen et al. 2008]
Überwachung der Knochendichte unter adjuvanter endokriner Therapie/Behandlung mit Bisphosphonaten				
CCO-A-2008	Women receiving aromatase inhibitors should be monitored for changes in bone mineral density.	n.a.	n.a.	[Howell et al. 2005; Boccardo et al. 2005; Jakesz et al. 2005; Goss et al. 2003; Mamounas et al. 2006; Howell et al. 2006; Coleman et al. 2007; Jones et al. 2005; Jones et al. 2005; Asmar et al. 2006]

Leitlinie	Empfehlung	LoE[14]	GoR[1]	Referenzen
Systemische Therapie/Endokrine Therapie – adjuvant				
NICE 2009 early	▪ Patients with early invasive breast cancer should have a baseline dual energy X-ray absorptiometry (DEXA) scan to assess bone mineral density if they: o are starting adjuvant aromatase inhibitor treatment o have treatment-induced menopause o are starting ovarian ablation/suppression therapy. ▪ Do not offer a DEXA scan to patients with early invasive breast cancer who are receiving tamoxifen alone, regardless of pretreatment menopausal status. (Qualifying Statement: These recommendations are based on guidance produced by Reid et al. (2008) and GDG consensus.)	n.a.[16]	n.a.	[Reid et al. 2008]
NICE 2009 early	▪ Offer bisphosphonates to patients identified by algorithms 1 and 2 in 'Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK expert group' (2008) (see Appendix 2). (Qualifying statement: This recommendation is based on evidence from RCTs and guidance produced by Reid et al. (2008)).	1++	n.a.	[Pavlakis et al. 2005; Wu et al. 2007]
		1+		[Brufsky 2006; Fuleihan et al. 2005; Gnant et al. 2007; Greenspan et al. 2007; Ha et al. 2007; Saarto et al. 2004; Vehmanen et al. 2004]
		1-		[Bundred et al. 2008]
		n.a.[16]		[Mystakidou et al. 2005; Reid et al. 2008]

[16] Der Evidence Review zu dieser Leitlinie enthält eine Bewertung der Leitlinie von Reid et al. 2008 mit dem AGREE-Instrument

Leitlinie	Empfehlung	LoE[14]	GoR[1]	Referenzen
Systemische Therapie/Endokrine Therapie – adjuvant				
NZGG 2009	For women receiving aromatase inhibitors, baseline assessment of bone density should be completed and ongoing monitoring of bone density planned depending on the initial measurement	n.a.	GPP	n.a.
NZGG 2009	Due to the lack of consistent evidence no recommendations were made regarding use of oral bisphosphonates for the reduction of osseous metastases in early breast cancer	n.a.	I	n.a.
NZGG 2009	Women who are osteoporotic and on adjuvant endocrine therapy that enhances loss of bone density or who have undergone premature treatment-induced menopause should receive a bisphosphonate	++	A	[Greenspan et al. 2008; Brufsky et al. 2008]
		+		[Reid et al. 2008; Kristensen et al. 2008; Gnant et al. 2007]
NZGG 2009	Women who are osteopenic and on adjuvant therapy which enhances loss of bone density, or who have undergone premature treatment-induced menopause should be considered for a bisphosphonate, especially in the presence of other risk factors: prior non-traumatic fracture, aged over 65 years, family history, tobacco use, low body weight	+	C	[Reid et al. 2008]
NZGG 2009	Postmenopausal women taking aromatase inhibitors are recommended to commence treatment with bisphosphonates if the T-score is <-2.0, or <-1.0 in the presence of a vertebral fracture. Secondary causes of osteoporosis should be excluded and standard lifestyle advice on smoking and exercise, calcium supplementation and adequacy of vitamin D intake should also be provided	+	C	[Reid et al. 2008]

Leitlinie	Empfehlung	LoE[14]	GoR[1]		Referenzen
Systemische Therapie/Endokrine Therapie – adjuvant					
NZGG 2009	Women with premature menopause due to chemotherapy, ovarian function suppression or oophorectomy and postmenopausal women receiving adjuvant therapy with an aromatase inhibitor should have bone density monitored at least every 2 years following a baseline DEXA (dual energy X-ray absorptiometry) scan of the spine and hip	n.a.	C	n.a.	
NZGG 2009	Frequency of bone mineral density monitoring should be tailored to the individual. If baseline T-score >-1.0 further monitoring of bone density may not be necessary	n.a.	C	n.a.	
NZGG 2009	A woman with early breast cancer at risk of bone mineral loss should be provided with appropriate advice for good bone health. This includes, but is not limited to: o a healthy diet o cessation or continuing abstinence from smoking o maintenance of a healthy body mass index o regular exercise o calcium o adequate vitamin D levels	n.a.	C	n.a.	
Abkürzungen: AI = aromatase inhibitor; CYP2D6 = Cytochrome P450 2D6; ER = estrogen receptor; DEXA = dual energy X-ray absorptiometry; GDG = guideline development group; LHRH = luteinising hormon releasing-hormon; n.a. = nicht angegeben; OA = ovarian ablation; RCPA QAP = Royal College of Pathologists of Australasia Quality Assurance Programme					

4.2.9 Empfehlungen zum Thema Systemische Therapie/Antikörpertherapie – adjuvant

4.2.9.1 Eingeschlossene Leitlinien

Zum Thema adjuvante Antikörpertherapie wurden zwei Leitlinien der Gruppe 1 [National Institute for Clinical Excellence (NICE) 2009; New Zealand Guidelines Group (NZGG) 2009] und eine Leitlinie der Gruppe 2 [Dhesy-Thind et al. 2006] extrahiert.

Eine Leitlinie wurde vom National Institute for Health and Clinical Excellence (NICE) aus Großbritannien 2009 herausgegeben. Diese Leitlinie adressiert umfassend die Diagnostik und Therapie der Primärerkrankung einschließlich lokal fortgeschrittener Tumore [National Institute for Clinical Excellence (NICE) 2009]. Für die Extraktion dieser Leitlinie (insbesondere der Evidenzklassifikationen [LoE]) wurde zusätzlich ein Hintergrund- bzw. Methodendokument ausgewertet [National Institute for Clinical Excellence (NICE) 2009]. Zu den Empfehlungen haben die Autoren der NICE-Leitlinie [National Institute for Clinical Excellence (NICE) 2009] sogenannte ‚Qualifying Statements' angeführt. Diese beschreiben zusammenfassend die zugrundeliegende Evidenz der Empfehlungen. Die ‚Qualifying Statements' wurden mit den Empfehlungen extrahiert, um als Ergänzung zu den berücksichtigten Referenzen auch die entsprechenden zusammenfassenden Einschätzungen der Autoren wiederzugeben.

Eine Leitlinie wurde von der New Zealand Guidelines Group (NZGG) 2009 herausgegeben. Diese Leitlinie adressiert umfassend die Therapie der Primärerkrankung. Für die Extraktion dieser Leitlinie wurden keine weiteren Dokumente ausgewertet.

Die Leitlinie der Gruppe 2 wurde von der kanadischen Institution Cancer Care Ontario (CCO) in 2006 herausgegeben. Diese Leitlinie gibt Empfehlungen zur adjuvanten und neoadjuvanten Therapie mit Trastuzumab bei Frauen mit Brustkrebs und HER-2-Überexpression. Für die CCO-Leitlinie wurde zusätzlich ein Hintergrund- bzw. Methodendokument ausgewertet.

4.2.9.2 In der S3-Leitlinie Mammakarzinom 2008 nicht enthaltene und diskrepante Empfehlungs-Inhalte

Die CCO 2006 und die NICE early empfehlen die **Therapie mit Trastuzumab nach abgeschlossener Chemotherapie,** (LoE, GoR jeweils n.a.) die NZGG empfiehlt die sequentielle Verabreichung nur bei „borderline cardiac function" (good practice point). Die S3-Leitlinie Mammakarzinom 2008 weist die Optionen aus, Trastuzumab simultan zu einem Taxan oder sequentiell zu einer Antrazyklin-(Taxan-)haltigen Chemotherapie zu verabreichen.

Die NICE 2009 early weist **kardiale Kontraindikationen für die Gabe von Trastuzumab** aus (LoE, GoR n.a). Diese sind in der S3-Leitlinie Mammakarzinom 2008 nicht spezifiziert. Im Hinblick auf das erforderliche kardiale **Monitoring** empfiehlt die NZGG eine

Überprüfung alle 3 Monate und spezifiziert die Untersuchungsmethode (LoE n.a., GoR B). Beides beinhaltet die S3-Leitlinie Mammakarzinom 2008 nicht. Die Inhalte der übrigen Empfehlungen stimmen mit der S3-Leitlinie Mammakarzinom 2008 überein.

Tabelle 12: Systemische Therapie/Antikörpertherapie – adjuvant

Leitlinie	Empfehlung	LoE[17]	GoR[1]	Referenzen
Systemische Therapie/Antikörpertherapie – adjuvant				
CCO 2006	Trastuzumab should be offered for one year to all patients with HER2-positive node-positive or node-negative, tumour greater than 1 cm in size, and primary breast cancer and who are receiving or have received (neo)adjuvant chemotherapy. Trastuzumab should be offered after chemotherapy.	n.a.	n.a.	[Piccart-Gebhart et al. 2005; Romond et al. 2005; Slamon et al. 2006; Tan-Chiu et al. 2005; Joensuu et al. 2006]
NICE 2009 early	▪ Offer trastuzumab, given at 3-week intervals for 1 year or until disease recurrence (whichever is the shorter period), as an adjuvant treatment to women with HER2- positive early invasive breast cancer following surgery, chemotherapy, and radiotherapy when applicable. ▪ Assess cardiac function before starting treatment with trastuzumab. Do not offer trastuzumab treatment to women who have any of the following: o a left ventricular ejection fraction (LVEF) of 55% or less o a history of documented congestive heart failure o high-risk uncontrolled arrhythmias o angina pectoris requiring medication o clinically significant valvular disease o evidence of transmural infarction on electrocardiograph	n.a.	n.a.	[Smith et al. 2007; Shiroiwa et al. 2008; Suter et al. 2007; Romond et al. 2005; Tan-Chiu et al. 2005; Perez et al. 2008; Bria et al. 2008; Joensuu et al. 2006; Buzdar et al. 2007; Garrison, Jr. et al. 2007; Kurian et al. 2007; Liberato et al. 2007; Millar et al. 2007; Dedes et al. 2007; Neyt et al. 2008; Norum et al. 2007]

[17] Für Erläuterungen des Level of Evidence (LoE) und Grade of Recommendation (GoR) siehe Anhang 5.6.

Leitlinie	Empfehlung	LoE[17]	GoR[1]	Referenzen
Systemische Therapie/Antikörpertherapie – adjuvant				
	(ECG) ○ poorly controlled hypertension. ▪ Repeat cardiac functional assessments every 3 months during trastuzumab treatment. If the LVEF drops by 10 percentage (ejection) points or more from baseline and to below 50% then trastuzumab treatment should be suspended. Restart trastuzumab therapy only after further cardiac assessment and a fully informed discussion of the risks and benefits with the woman. (Qualifying statement: These recommendations are based on good clinical evidence and cost effective analysis.)			
NICE 2009 early	«Research Recommendation» How effective is trastuzumab in patients with invasive breast cancer: (a) as adjuvant therapy without chemotherapy, (b) in terms of scheduling and duration of treatment in patients who are also receiving or who have completed chemotherapy, and (c) as primary systemic treatment in terms of quality of life, side effects, disease recurrence rates, disease-free survival and overall survival?	n.a.	n.a.	n.a.
NZGG 2009	An improvement in overall survival is confirmed only by trials where the duration of trastuzumab was one year. This duration of treatment is considered the standard of care (Based on the current evidence for clinical effectiveness) and should be offered to all women receiving adjuvant trastuzumab for HER2-positive breast cancer	++	A	[Trudeau et al. 2007]
		+		[Smith et al. 2007; Viani et al. 2007; Huybrechts et al. 2006]
		-		[Buzdar et al. 2007]

Leitlinie	Empfehlung	LoE[17]	GoR[1]	Referenzen
Systemische Therapie/Antikörpertherapie – adjuvant				
		n.a.		[National Institute for Clinical Excellence (NICE) 2006; National Breast Cancer Centre (NBCC) 2007; Romond et al. 2005; Piccart-Gebhart et al. 2005; Joensuu et al. 2006; Slamon et al. 2006; Bria et al. 2008; Perez et al. 2007; Sledge et al. 2006; Spielmann et al. 2007; Madarnas et al. 2008]
NZGG 2009	A woman prescribed trastuzumab should have their cardiac function monitored regularly (eg, 3-monthly) using Multi Gated Acquisition (MUGA) scans or echocardiography** ** Left ventricular ejection fraction (LVEF) is a good clinical indicator of left ventricular systolic function. Damage to the heart muscle during myocardial infarction or as a result of cardiotoxicity from chemotherapy impairs the heart's ability to eject blood and results in a decreased ejection fraction. The ejection fraction is an important prognostic indicator with a significantly reduced LVEF typically resulting in poorer prognosis	++	B	[Trudeau et al. 2007]
		+		[Smith et al. 2007; Viani et al. 2007; Huybrechts et al. 2006]
		-		[Buzdar et al. 2007]
		n.a.		[National Institute for Clinical Excellence (NICE) 2006; National Breast Cancer Centre (NBCC) 2007; Romond et al. 2005; Piccart-Gebhart et al. 2005; Joensuu et al. 2006; Slamon et al. 2006; Bria et al. 2008; Perez et al. 2007; Sledge et al. 2006; Spielmann et

Leitlinie	Empfehlung	LoE[17]	GoR[1]	Referenzen
Systemische Therapie/Antikörpertherapie – adjuvant				
				al. 2007; Madarnas et al. 2008]
NZGG 2009	In women with borderline cardiac function, it may be preferable to administer trastuzumab after the completion of chemotherapy. Whether there is any difference in the effectiveness of trastuzumab used sequentially or concurrently with chemotherapy is uncertain	n.a.	GPP	n.a.

Abkürzungen: ECG = electrocardiograph; GPP = Good Practice Point; HER2 = human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction; MUGA = Multi Gated Acquisition scans; n.a. = nicht angegeben

4.2.10 Empfehlungen zum Thema Systemische Therapie– neoadjuvant (primär systemische Therapie)

4.2.10.1 Eingeschlossene Leitlinien

Zum Thema neoadjuvante Systemtherapie wurden drei Leitlinien der Gruppe 1 ([National Institute for Clinical Excellence (NICE) 2009; New Zealand Guidelines Group (NZGG) 2009; National Breast and Ovarian Cancer Centre (NBOCC) 2008]) extrahiert.

Eine Leitlinie wurde vom National Institute for Health and Clinical Excellence (NICE) aus Großbritannien in 2009 herausgegeben. Diese Leitlinien adressiert umfassend die Therapie der Primärerkrankung einschließlich lokal fortgeschrittener Tumore [National Institute for Clinical Excellence (NICE) 2009]. Für die Extraktion dieser Leitlinie (insbesondere der Evidenzklassifikationen [LoE]) wurde zusätzlich ein Hintergrund- bzw. Methodendokument ausgewertet [National Institute for Clinical Excellence (NICE) 2009]. Zu den Empfehlungen haben die Autoren der NICE-Leitlinie [National Institute for Clinical Excellence (NICE) 2009] sogenannte ‚Qualifying Statements' angeführt. Diese beschreiben zusammenfassend die zugrundeliegende Evidenz der Empfehlungen. Die ‚Qualifying Statements' wurden mit den Empfehlungen extrahiert, um als Ergänzung zu den berücksichtigten Referenzen auch die entsprechenden zusammenfassenden Einschätzungen der Autoren wiederzugeben.

Eine Leitlinie wurde von der New Zealand Guidelines Group (NZGG) in 2009 herausgegeben. Diese Leitlinie adressiert umfassend die Therapie der Primärerkrankung. Für die Extraktion dieser Leitlinie wurden keine weiteren Dokumente ausgewertet.

Die dritte Leitlinie wurde vom National Breast and Ovarian Cancer Centre (NBOCC) aus Australien in 2008 herausgegeben. Diese Leitlinie enthält Empfehlungen zur Therapie mit Taxanen bei operablem Mammakarzinom. Für die Extraktion dieser Leitlinie wurde kein weiteres Dokumente ausgewertet. Zum Thema primär systemische Therapie enthält die NBOCC-Leitlinie ein Statement.

4.2.10.2 In der S3-Leitlinie Mammakarzinom 2008 nicht enthaltene oder diskrepante Empfehlungs-Inhalte

Sowohl die NICE early als auch die NZGG thematisieren in Empfehlungen das ggf. **erhöhte (Lokal-)Rezidivrisiko bei brusterhaltender Therapie**, die aufgrund einer neoadjuvante Systemtherapie ermöglich wurde (LoE 1, good practice point). Die erhöhte Lokalrezidivrate wird in der S3-Leitlinie Mammakarzinom 2008 nicht als sicher belegt eingestuft.

Tabelle 13: Systemische Therapie– neoadjuvant (primär systemische Therapie)

Leitlinie	Empfehlung	LoE[18]	GoR[1]	Referenzen
Systemische Therapie– neoadjuvant (primär systemische Therapie)				
NBOCC 2008 taxane	«neoadjuvant chemotherapy in women with early [operable] breast cancer» Statement: One study reported that the inclusion of a taxane in a neoadjuvant chemotherapy regimen significantly increased pathological and clinical complete response rates compared to a non-taxane-containing chemotherapy regimen There is currently insufficient evidence to determine the optimal role of taxane-containing regimens in neoadjuvant chemotherapy treatment	II	n.a.	[Bear et al. 2006]
NICE 2009 early	▪ Treat patients with early invasive breast cancer, irrespective of age, with surgery and appropriate systemic therapy, rather than endocrine therapy alone, unless significant comorbidity precludes surgery. (Qualifying statement: This recommendation is based on a Cochrane review of RCTs with small patient numbers.)	1+	n.a.	[Hind et al. 2006]
NICE 2009 early	▪ Preoperative systemic therapy can be offered to patients with early invasive breast cancer who are considering breast conserving surgery that is not advisable at presentation. However, the increased risk of local recurrence with breast conserving surgery and radiotherapy rather than mastectomy after systemic therapy should be discussed with the patient. (Qualifying statement: This recommendation is based on the results of a Cochrane review of RCTs of good quality.)	1++ n.a. 1-	n.a.	[Mieog et al. 2007], [Rastogi et al. 2008] [Trudeau et al. 2005]

[18] Für Erläuterungen des Level of Evidence (LoE) und Grade of Recommendation (GoR) siehe Anhang 5.6.

Leitlinie	Empfehlung	LoE[18]	GoR[1]	Referenzen
Systemische Therapie– neoadjuvant (primär systemische Therapie)				
NZGG 2009	Preoperative chemotherapy may be considered where a woman with a large breast tumour has a preference for breast conserving surgery	n.a.	A	[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Christiaens et al. 2007; National Breast Cancer Centre (NBCC) 2001; Stebbing et al. 2007; Mieog et al. 2007; Rastogi et al. 2008; van Nes et al. 2009; Boughey et al. 2006; Wolmark et al. 2001]
NZGG 2009	Preoperative chemotherapy is recommended for a woman with inflammatory or inoperable locally advanced breast cancer without evidence of systemic spread	n.a.	A	[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Christiaens et al. 2007; National Breast Cancer Centre (NBCC) 2001; Boughey et al. 2006; Mieog et al. 2007; Rastogi et al. 2008; Stebbing et al. 2007; van Nes et al. 2009; Wolmark et al. 2001]
NZGG 2009	Practitioners should be aware that conversion from mastectomy to breast conserving surgery by preoperative chemotherapy may be associated with a higher risk of loco-regional recurrence	n.a.	GPP	n.a.
Abbkürzungen: GPP = Good Practice Point				

4.2.11 Empfehlungen zum Thema Sonderformen (DCIS, inflammatorisches Mammakarzinom, inoperables Mammakarzinom)

4.2.11.1 Eingeschlossene Leitlinien

Zum Thema Sonderformen (DCIS, inflammatorisches Mammakarzinom, inoperables Mammakarzinom) wurden zwei Leitlinien der Gruppe 1 ([National Institute for Clinical Excellence (NICE) 2009; New Zealand Guidelines Group (NZGG) 2009] extrahiert. Weitere Leitlinien mit Empfehlungen zu diesem Thema konnten nicht identifiziert werden.

Eine Leitlinie wurde vom National Institute for Health and Clinical Excellence (NICE) aus Großbritannien in 2009 herausgegeben. Diese Leitlinie adressiert umfassend die Therapie der Primärerkrankung einschließlich lokal fortgeschrittener Tumore [National Institute for Clinical Excellence (NICE) 2009]. Für die Extraktion dieser Leitlinie (insbesondere der Evidenzklassifikationen [LoE]) wurde zusätzlich ein Hintergrund- bzw. Methodendokument ausgewertet. Zu den Empfehlungen haben die Autoren der NICE-Leitlinie [National Institute for Clinical Excellence (NICE) 2009] sogenannte ‚Qualifying Statements' angeführt. Diese beschreiben zusammenfassend die zugrundeliegende Evidenz der Empfehlungen. Die ‚Qualifying Statements' wurden mit den Empfehlungen extrahiert, um als Ergänzung zu den berücksichtigten Referenzen auch die entsprechenden zusammenfassenden Einschätzungen der Autoren wiederzugeben. Die Leitlinie von NICE enthält außerdem Empfehlungen für die weitere Erforschung bestimmter Aspekte (Research Recommendations). Diese Empfehlungen wurden extrahiert und entsprechend gekennzeichnet.

Eine Leitlinie wurde von der New Zealand Guidelines Group (NZGG) in 2009 herausgegeben. Diese Leitlinie adressiert umfassend die Daignostik und Therapie der Primärerkrankung. Für die Extraktion dieser Leitlinie wurden keine weiteren Dokumente ausgewertet. In der Synopse (Tabelle 14) sind Empfehlungen zu den Themen DCIS und inflammatorisches Mammakarzinom getrennt aufgeführt. Spezifische Empfehlungen zum inoperablen Mammakarzinom allein konnten nicht identifiziert werden.

4.2.11.1 In der S3-Leitlinie Mammakarzinom 2008 nicht enthaltene oder diskrepante Empfehlungs-Inhalte

Die NICE 2009 early empfiehlt die **präoperative MRT nicht routinemäßig bei DCIS** mit dem Hinweis auf insuffiziente vorliegende Evidenz. Die S3-Leitlinie Mammakarzinom 2008 enthält keine gesonderte Empfehlung zur präoperativen MRT bei DCIS.

In Bezug auf die Entscheidung **BET versus Mastektomie bei DCIS** nennt die NZGG Kriterien, die in der S3-Leitlinie Mammakarzinom 2008 nicht alle genannt werden (LoE +, GoR C).

Die NICE 2009 early und die NZGG empfehlen einen **tumorfreien Randsaum bei DCIS von mind. 2mm** (LoE 3, GoR n.a., LoE n.a., GoR C) und eine Nachresektion, falls dieser nicht erreicht wurde, die NZGG nennt dafür Kriterien (LoE n.a., GoR C). Die S3-Leitlinie Mammakarzinom 2008 empfiehlt 5mm, Nachresektionen werden nicht explizit thematisiert.

Im Falle einer Strahlentherapie spricht die NZGG aufgrund insuffizienter Evidenz **keine Empfehlung für einen Boost** aus (GoR I).

Während die NICE 209 early keine **Tamoxifentherapie bei DCIS** empfiehlt („there is conflicting evidence, LoE 1+ bis 1-, GoR n.a.), empfiehlt die NZGG das individuelle Abwägen im Rahmen der Diskussion einer interdisziplinären Tumorkonferenz („good practice point"). Die S3-Leitlinie Mammakarzinom 2008 empfiehlt keine Routinegabe, sondern im Einzelfall eine individuelle Abwägung.

Zum inflammatorischen oder inoperablen Mammakarzinom wurden keine in der S3-Leitlinie Mammakarzinom 2008 nicht enthaltenen oder diskrepanten Empfehlungen identifiziert.

Tabelle 14: Sonderformen (DCIS, inflammatorisches Mammakarzinom, inoperables Mammakarzinom)

Leitlinie	Empfehlung	LoE[19]	GoR[1]	Referenzen
Sonderformen (DCIS, inflammatorisches Mammakarzinom, inoperables Mammakarzinom)				
DCIS				
NICE 2009 early	▪ The routine use of MRI of the breast is not recommended in the preoperative assessment of patients with biopsy-proven invasive breast cancer or DCIS. (Qualifying statement: There is insufficient evidence (a) to recommend the routine use of preoperative MRI in invasive breast cancer and no evidence that detection with MRI makes a difference to outcomes, and (b) on which to base any recommendation on the use of MRI in the assessment of the breast with a diagnosis of pure DCIS.)	1++	n.a.	[Blue Cross Blue Shield Association (BCBS) 2004]
		2++		[Shiraishi et al. 2003; Schnall et al. 2005; Deurloo et al. 2006; Kvistad et al. 2000; Fischer et al. 2004]
		2+		[Francescutti et al. 2002; Chung et al.

[19] Für Erläuterungen des Level of Evidence (LoE) und Grade of Recommendation (GoR) siehe Anhang 5.6.

Leitlinie	Empfehlung	LoE[19]	GoR[1]	Referenzen
Sonderformen (DCIS, inflammatorisches Mammakarzinom, inoperables Mammakarzinom)				
	▪ Offer MRI of the breast to patients with invasive breast cancer: o if there is discrepancy regarding the extent of disease from clinical examination, mammography and ultrasound assessment for planning treatment o if breast density precludes accurate mammographic assessment o to assess the tumour size if breast conserving surgery is being considered for invasive lobular cancer. (Qualifying statement: There is good quality evidence that MRI is effective at detecting size and multifocality. There is some published evidence and GDG consensus, based on the difficulties of assessing and treating lobular cancer, to support this recommendation. There is no satisfactory health economic evidence to assist in this recommendation.)	3 n.a.		2005] [Menell et al. 2005; Boetes et al. 2004; Schelfout et al. 2004] [Bremner et al. 2007; Del Frate et al. 2007; Esserman et al. 1999]
NICE 2009 early	▪ For all patients treated with breast conserving surgery for DCIS a minimum of 2 mm radial margin of excision is recommended with pathological examination to NHSBSP reporting standards. Re-excision should be considered if the margin is less than 2 mm after discussion of the risks and benefits with the patient. ▪ Enter patients with screen-detected DCIS into the Sloane Project (UK DCIS audit). ▪ All breast units should audit their recurrence rates after treatment for DCIS. (Qualifying statement: The evidence is from observational studies shows that there is no single size of clear margin that is the optimum for reduced local recurrence rate. These recommendations are based on GDG consensus.)	1- 2 3	n.a.	[Bijker et al. 2001] [Silverstein et al. 1999] [Boland et al. 2001; Boland et al. 2003; Cabioglu et al. 2007; Chan et al. 2001; Cheng et al. 1997; Denoux et al. 2001; Dillon et al. 2007; Goldstein et al. 1999; Goldstein et al. 2000; Goldstein et al. 1998; Hetelekidis et al. 1999; Holland et al. 1998; Macdonald et al. 2005; Macdonald et al. 2006; Neuschatz et al. 2001; Neuschatz et al. 2003; Ratanawichitrasin et al. 1999; Rodrigues et al. 2002; Sahoo et al.

Leitlinie	Empfehlung	LoE[19]	GoR[1]	Referenzen
Sonderformen (DCIS, inflammatorisches Mammakarzinom, inoperables Mammakarzinom)				
				2005; Sigal-Zafrani et al. 2004; Silverstein et al. 1994; Silverstein et al. 1997; Silverstein et al. 2003; Solin et al. 2005; Tunon-de-Lara et al. 2001; Vargas et al. 2005; Vicini et al. 2001; Wong et al. 2006; Yau et al. 2006]
		4		[Boyages et al. 1999; Kell et al. 2005]
NICE 2009 early	▪ Do not perform SLNB routinely in patients with a preoperative diagnosis of DCIS who are having breast conserving surgery, unless they are considered to be at a high risk of invasive disease[20]. (Qualifying statement: There was insufficient evidence to support the routine use of SLNB in patients with DCIS. There was GDG consensus that patients at a high risk of having unsuspected invasive disease would benefit from SLNB.)	3	n.a.	[Ansari et al. 2008; Camp et al. 2005; Cox et al. 1998; Cserni 2002; Farkas et al. 2004; Katz et al. 2006; Kelly et al. 2003; Klauber-DeMore et al. 2000; Liu et al. 2003; Mittendorf et al. 2005; Pendas et al. 2000; Trisal et al. 2004; Veronesi et al. 2005; Wilkie et al. 2005; Zavagno et al. 2005; Zavagno et al. 2005; Zavotsky et al. 1999]
		n.a.		[Intra et al. 2003; Jeruss et al. 2006; Fortunato et al. 2004; Ronka et al. 2004; Chirikos et al. 2001; Gemignani et al. 2000; Perrier et al. 2004]

[20] NHS Breast Screenign Programme Quality assurance guidelines for surgeons in breast cancer screening.

Leitlinie	Empfehlung	LoE[19]	GoR[1]	Referenzen
Sonderformen (DCIS, inflammatorisches Mammakarzinom, inoperables Mammakarzinom)				
NICE 2009 early	▪ Offer SLNB to all patients who are having a mastectomy for DCIS. (Qualifying statement: This recommendation was based on GDG consensus.)	n.a.	n.a.	GDG Consensus
NICE 2009 early	▪ Patients with early invasive breast cancer who have had breast conserving surgery with clear margins should have breast radiotherapy. ▪ Offer adjuvant radiotherapy to patients with DCIS following adequate breast conserving surgery3 and discuss with them the potential benefits and risks. (Qualifying statement: There is good quality randomised controlled trial evidence that radiotherapy reduces absolute risk of further recurrence. There was GDG consensus that there may be a subgroup of patients with DCIS who have a lowrisk of recurrence and thus for whom the addition)	1++	n.a.	[Clarke et al. 2005; Vinh-Hung et al. 2004; Ford et al. 2006; Johansen et al. 2002; Rayan et al. 2003; Whelan et al. 2000] DCIS: [Bijker et al. 2006; Emdin et al. 2006; Holmberg et al. 2008]
		1+	n.a.	[Liljegren 2002; Lee et al. 2008] DCIS: [Fisher et al. 1998]
		1-		[Rutqvist et al. 2003; Mul et al. 2007; Cuncins-Hearn et al. 2004; Sarin 2005] DCIS: [Houghton et al. 2003]
		2+		[Vinh-Hung et al. 2003] DCIS: [Shelley et al. 2006]
		2-		[Deutsch et al. 2003]
		3		[Back et al. 2005] DCIS: [Omlin et al. 2006; Boyages et al. 1999; Fonseca et al. 1997; Baxter et al. 2005; Smith et al. 2006]

Leitlinie	Empfehlung	LoE[19]	GoR[1]	Referenzen
Sonderformen (DCIS, inflammatorisches Mammakarzinom, inoperables Mammakarzinom)				
		4		[Kuerer et al. 2004; Shelley et al. 2002; Whelan et al. 2003; Morrow et al. 2002; Sautter-Bihl et al. 2007]
		n.a.		[Kunkler et al. 2006]
NICE 2009 early	▪ Do not offer adjuvant tamoxifen after breast conserving surgery to patients with DCIS.	1+	n.a.	[Fisher et al. 1999]
	(Qualifying statement: There is conflicting evidence to support the use of tamoxifen in reducing local recurrence particularly when surgery is adequate (although the GDG recognises that there is a small reduction in the incidence of contralateral breast cancers).)	1-		[Houghton et al. 2003]
NZGG 2009	When making the choice between breast conserving surgery and mastectomy the following factors should be considered in discussion with the woman:	+	C	[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Christiaens et al. 2007; Antonini et al. 2007]
	▪ ratio of the size of the tumour to the size of the breast and tumour location in terms of acceptable cosmesis ▪ the presence of multifocal/multicentric disease or extensive malignant microcalcification on mammogram which cannot be adequately cleared with an acceptable cosmetic result with breast conserving surgery ▪ potential contraindications to local radiotherapy (eg, previous radiotherapy at this site, connective tissue disease, severe heart and lung disease, pregnancy) ▪ fitness for surgery ▪ patient choice	n.a.		[Fisher et al. 1991; Federation of French Cancer Centres (FNCLCC) 20047; Boyages et al. 1990; Zuiden 2005; Wright et al. 2003]

Leitlinie	Empfehlung	LoE[19]	GoR[1]	Referenzen
Sonderformen (DCIS, inflammatorisches Mammakarzinom, inoperables Mammakarzinom)				
NZGG 2009	Ductal carcinoma in situ (DCIS) extending up to a margin of excision requires further surgery – either wider excision or mastectomy to achieve clear margins in the absence of contraindications	+		[Scottish Intercollegiate Guidelines Network (SIGN) 2005; National Breast Cancer Centre (NBCC) 2001]
		n.a.	A	[Fisher et al. 2001; Bijker et al. 2006; Houghton et al. 2003; Emdin et al. 2006; Morrow et al. 2007; Silverstein et al. 1999; Sneige et al. 2002; National Breast and Ovarian Cancer Centre (NBOCC) 2008]
NZGG 2009	Detailed pathological assessment of the distance of the in situ carcinoma from the margins should be made	n.a.	C	n.a.
NZGG 2009	A circumferential or radial margin of greater than or equal to 2 mm should be achieved where possible	n.a.	C	n.a.
NZGG 2009	For women with margin widths of less than 2 mm several factors should be considered in determining whether re-excision is required. These include: ▪ age ▪ size, grade, and the presence or absence of comedo necrosis ▪ which margin is approximated by DCIS (smaller margins may be acceptable for deep and superficial margins as by definition DCIS does not go into muscle or subcutaneous fat) ▪ extent of DCIS approaching the margin	n.a.	C	n.a.
NZGG 2009	If a clear margin cannot be achieved surgically after either breast conserving surgery or mastectomy, radiotherapy should be considered	n.a.	GPP	n.a.

Leitlinie	Empfehlung	LoE[19]	GoR[1]	Referenzen
Sonderformen (DCIS, inflammatorisches Mammakarzinom, inoperables Mammakarzinom)				
NZGG 2009	Pathology reports should state the proximity of pleomorphic lobular carcinoma in situ (LCIS) to excision margins to allow assessment of whether further excision would be appropriate in the setting of breast conserving surgery	n.a.	GPP	n.a.
NZGG 2009	Axillary dissection should not be performed for women with ductal carcinoma in situ	+	I	[Christiaens et al. 2007]
NZGG 2009	In a woman with a larger volume and higher grade ductal carcinoma in situ or where there is suspicion of invasive disease or for women undergoing mastectomy, sentinel lymph node biopsy to stage the axilla may be considered	+	B	[Christiaens et al. 2007]
NZGG 2009	A woman who has undergone breast conserving surgery for ductal carcinoma in situ should have their case discussed at a multidisciplinary meeting with a radiation oncologist and/or should be offered consultation with a radiation oncologist	+	A	[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Christiaens et al. 2007; Shelley et al. 2006; Viani et al. 2007]
		n.a.		[Fisher et al. 1998; Bijker et al. 2006; Houghton et al. 2003; Emdin et al. 2006; Silverstein et al. 1999; Julien et al. 2000]
NZGG 2009	Due to lack of evidence no recommendations were made for the routine use of a boost dose of radiotherapy in women with ductal carcinoma in situ	n.a.	I	n.a.
NZGG 2009	For women with hormone receptor positive ductal carcinoma in situ, the benefits and risks of endocrine therapy should be discussed and treatment decisions made based on individual circumstances	+	GPP	[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Christiaens et al. 2007; Stebbing et al. 2007]

Leitlinie	Empfehlung	LoE[19]	GoR[1]	Referenzen
Sonderformen (DCIS, inflammatorisches Mammakarzinom, inoperables Mammakarzinom)				
		n.a.		[Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 1998; Houghton et al. 2003; Hind et al. 2006]
Inflammatorisches /primär inoperables Mammakarzinom				
NICE 2009 early	▪ Offer local treatment by mastectomy (or in exceptional cases, breast conserving surgery) followed by radiotherapy to patients with locally advanced or inflammatory breast cancer who have been treated with chemotherapy,. (Qualifying statement: This recommendation is based on evidence from a RCT and retrospective studies and GDG consensus.)	1++	n.a.	[Mieog et al. 2007]
		1+		[Mauri et al. 2005; Veyret et al. 2006]
		1-		[Buchholz et al. 2006]
		2+		[Shenkier et al. 2004]
		3		[Huang et al. 2004; McGuire et al. 2007]
NZGG 2009	Preoperative chemotherapy is recommended for a woman with inflammatory or inoperable locally advanced breast cancer without evidence of systemic spread	+	A	[Rastogi et al. 2008; van Nes et al. 2009; Boughey et al. 2006; Mieog et al. 2007; Stebbing et al. 2007; National Breast Cancer Centre (NBCC) 2001; Scottish Intercollegiate Guidelines Network (SIGN) 2005; Christiaens et al. 2007]
		n.a.		[Wolmark et al. 2001]

GPP = Good Practice Point: Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available; DCIS = ductal carcinoma in situ; MRI = magnetic resonance imaging; GDG = guideline development group; SLNB = sentinel lymph node biopsy; lobular carcinoma in situ

Leitlinie	Empfehlung	LoE[19]	GoR[1]	Referenzen
Sonderformen (DCIS, inflammatorisches Mammakarzinom, inoperables Mammakarzinom)				
(LCIS)				

4.2.12 Empfehlungen zum Thema Lokalrezidiv

Zum Thema Lokalrezidiv wurden keine eigenständigen Empfehlungen in den Leitlinien identifiziert.

4.2.13 Empfehlungen zum Thema Fernmetastasen: Systemtherapie

4.2.13.1 Eingeschlossene Leitlinien

Zum Thema Systemtherapie bei Fernmetastasen konnten drei Leitlinien der Gruppe 1 extrahiert werden [National Institute for Clinical Excellence (NICE) 2009; National Breast and Ovarian Cancer Centre (NBOCC) 2008; National Breast and Ovarian Cancer Centre (NBOCC) 2010] Eine Leitlinie wurde vom National Institute for Health and Clinical Excellence (NICE) aus Großbritannien in 2009 herausgegeben und adressiert die Therapie des fortgeschrittenen Mammakarzinoms. Für die Extraktion dieser Leitlinie (insbesondere der Evidenzklassifikationen [LoE]) wurde ein Hintergrund- bzw. Methodendokumente ausgewertet [National Institute for Clinical Excellence (NICE) 2009]. Zu den Empfehlungen haben die Autoren der NICE-Leitlinien sogenannte ‚Qualifying Statements' angeführt. Diese beschreiben zusammenfassend die zugrundeliegende Evidenz der Empfehlungen. Die ‚Qualifying Statements' wurden mit den Empfehlungen extrahiert, um als Ergänzung zu den berücksichtigten Referenzen auch die entsprechenden zusammenfassenden Einschätzungen der Autoren wiederzugeben. Die Leitlinien von NICE enthalten außerdem Empfehlungen für die weitere Erforschung bestimmter Aspekte (Research Recommendations). Diese Empfehlungen wurden extrahiert und entsprechend gekennzeichnet.

Zwei der extrahierten Leitlinien wurden vom National Breast and Ovarian Cancer Centre (NBOCC) aus Australien in 2008 bzw. 2010 herausgegeben. Die Leitlinien geben Empfehlungen zur endokrinen Therapie bei hormonrezeptorpositivem fortgeschrittenem Mammakarzinom (2008) und zur Chemotherapie bei fortgeschrittenem Mammakarzinom (2010). Für die Extraktion dieser Leitlinien wurden keine weiteren Dokumente ausgewertet. Die Leitlinien des NBOCC enthalten Statements, in denen evidenzbasierte Aussagen zusammengefasst werden und Empfehlungen, die eine Handlungsanweisung enthalten. Sowohl Statements, als auch die Empfehlungen wurden für die Synopse extrahiert.

4.2.13.2 In der S3-Leitlinie Mammakarzinom 2008 nicht enthaltene oder diskrepante Empfehlungs-Inhalte

Für Männer mit metastasiertem Brustkrebs wird in der NICE 2009 advanced **Tamoxifen als endokrine Therapie erster Wahl** genannt (LoE 3; GoR n.a.). Dies wird in der S3-Leitlinie Mammakarzinom 2008 nicht thematisiert. Die NICE 2009 early und die NBOCC 2008 nennen für Patientinnen entsprechend der S3-Leitlinie Mammakarzinom 2008 Aromatasehemmer als Therapie erster Wahl. Die NBOCC enthält in Bezug auf die **Evidenz zu Nutzen und Schaden von Aromatasehemmern** (im Vergleich zu Tamoxifen) spezifischere Statements und Empfehlungen im Vergleich zur S3-Leitlinie Mammakarzinom 2008. **Fulvestrant** wird explizit **nicht als Mittel erster Wahl empfohlen** (LoE, GoR n.a.) In Bezug auf die **Second-Line-Therapie** weist die NBOCC ebenfalls spezifischere Statements und

Empfehlungen im Vergleich zur S3-Leitlinie Mammakarzinom 2008 auf. Im Vergleich zu Gestagenen werden (weitere) **Aromatasehemmer der 3. Generation bevorzugt empfohlen** (LoE I, GoR n.a.).

Bei prämenopausalen Frauen gibt die NBOCC 2008 **insuffiziente Evidenz für die Kombination von Aromatasehemmern mit LH-RH-Analoga** an. Die S3-Leitlinie Mammakarzinom gibt diese Kombination als Option an.

Im Hinblick auf **Chemotherapie beim metastasierten Mammakarzinom** nennen NICE 2009 advanced und NBOCC 2010 die gleichen Indikationen wie die S3-Leitlinie Mammakarzinom 2008 und geben ebenso wie diese Anthrazykline als Mittel erster Wahl an. Insbesondere die NBOCC-Leitlinie enthält **spezifischere Empfehlungen zur Evidenz weiterer Chemotherapiesubstanzen** (u.a.Taxane, Gemcitabine).

Bei den Empfehlungen zur **Antikörpertherapie** empfiehlt die NICE 2009 advanced das **Absetzen von Trastuzumab bei Progression** (LoE 3+, 3-). **Lapatinib nach Progression unter Trastuzumab** wird in der NBOCC 2010 mit einem Evidenzgrad von II empfohlen. Für Lapatinib wird in der S3-Leitlinie Mammakarzinom 2008 ausgeführt, dass noch keine Daten zum Überleben vorliegen. Die NBOCC 2010 führt aus, dass das Gesamtüberleben nicht verlängert wird. Die **routinemäßige Gabe von Bevacizumab** (first-line oder auch second – und third-line) wird in der NBOCC 2010 mit einem Evidenzgrad von II **aufgrund ungünstiger Nutzen-Risiko-Bilanz nicht empfohlen.** Dabei wird im Evidenzstatement ausgeführt, dass das Gesamtüberleben nicht verbessert wird, jedoch eine erhöhte Toxizität vorliegt. In der S3-Leitlinie Mammakarzinom 2008 wird Bevacizumab ohne Evidenzgrad empfohlen.

Tabelle 15: Fernmetastasen: Systemtherapie

Leitlinie	Empfehlung	LoE[21]	GoR[1]	Referenzen
Fernmetastasen: Systemtherapie				
Indikationsstellung endokrine Therapie (in Abwägung zu Chemotherapie)				

[21] Für Erläuterungen des Level of Evidence (LoE) und Grade of Recommendation (GoR) siehe Anhang 5.6.

Leitlinie	Empfehlung	LoE[21]	GoR[1]	Referenzen
Fernmetastasen: Systemtherapie				
NBOCC 2008-E[22]	«In women with hormone receptor-positive advanced breast cancer» Statement: Endocrine therapy is preferred for women with hormone receptor-positive advanced breast cancer in preference to chemotherapy except in the presence of rapidly progressive visceral disease	I	n.a.	[Wilcken et al. 2003]
NBOCC 2008-E	«In women with hormone receptor-positive advanced breast cancer» Statement: Endocrine therapy shows no significant difference in overall survival compared with chemotherapy	I	n.a.	[Wilcken et al. 2003]
NBOCC 2008-E	«In women with hormone receptor-positive advanced breast cancer» Statement: Incidence of adverse events including nausea, vomiting and alopecia is less frequent with endocrine therapy compared with chemotherapy	I	n.a.	[Wilcken et al. 2003]
NBOCC 2008-E	«In women with hormone receptor-positive advanced breast cancer» Recommendation: Endocrine therapy is recommended in preference to chemotherapy except in the presence of rapidly progressive visceral disease	I	n.a.	[Wilcken et al. 2003]
NBOCC 2008-E	«In women with hormone receptor-positive advanced breast cancer» Recommendation: Information about the treatment should be discussed with the patient. The patient should be adequately prepared for the treatment	I	n.a.	[National Breast Cancer Centre (NBCC) 2003]

[22] Erläuterung in der Leitlinien zur adressierten Population: “The evidence review is about the use of endocrine therapy in post-menopausal women with hormone receptor-positive advanced breast cancer. The evidence is not specific to women with metastatic (stage IV) breast cancer. While the majority of women had stage IV metastatic disease, a small number of women with locally advanced disease and/or locoregional recurrence were included in the trials. In the majority of trials, women with tumours of unknown hormone receptor status were also eligible for participation.”

Leitlinie	Empfehlung	LoE[21]	GoR[1]	Referenzen
Fernmetastasen: Systemtherapie				
NICE 2009 advanced	• Offer endocrine therapy as first-line treatment for the majority of patients with ERpositive advanced breast cancer,. • Offer chemotherapy as first-line treatment for patients with ER-positive advanced breast cancer whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement, providing they understand and are prepared to accept the toxicity. • For patients with ER-positive advanced breast cancer who have been treated with chemotherapy as their first line treatment, offer endocrine therapy following the completion of chemotherapy. (Qualifying statement: These recommendations are based on one systematic review and GDG consensus.)	1++	n.a.	[Wilcken et al. 2006]
NICE 2009 advanced	«Research recommendations» • Clinical trials are needed to investigate the most effective endocrine therapy for postmenopausal women with ER-positive tumours who progress on treatment with an aromatase inhibitor. • Clinical trials are needed to investigate the effectiveness of ovarian suppression in combination with an aromatase inhibitor compared with that of ovarian suppression in combination with tamoxifen in pre-menopausal women with ER-positive tumours. • All randomised controlled trials of treatment after failure of all available treatments for which good quality evidence exists should either contain a placebo arm, or provide a valid justification for not doing so. • An observational study examining levels of oestrogen suppression in men being treated with either single agent aromatase inhibitors or aromatase inhibitors in combination with a GNRH agonist are needed.	n.a.	n.a.	n.a.

Leitlinie	Empfehlung	LoE[21]	GoR[1]	Referenzen
Fernmetastasen: Systemtherapie				
Endokrine Therapie (first line) bei postmenopausalen Patientinnen mit metastasiertem Brustkrebs				
NICE 2009 advanced	• Offer an aromatase inhibitor (either non-steroidal or steroidal) to: o postmenopausal women with ER-positive breast cancer and prior history of endocrine therapy o postmenopausal women with ER-positive breast cancer previously treated with tamoxifen. Qualifying statement: These recommendations are based on high quality evidence of clinical and cost effectiveness. There is no evidence directly comparing these agents so it is not possible to recommend any particular aromatase inhibitor. All aromatase inhibitors appear to be equally effective in terms of primary outcome (overall survival).	1++	n.a.	[Gibson et al. 2007; Eisen et al. 2004]
		1+		[Mauri et al. 2006]
		1		[Taylor et al. 1998]
		1-		[Crump et al. 1997; Ferretti et al. 2006]
		2+		[Goss et al. 2007]
		2-		[Chia et al. 2008; Mouridsen 2007]
		3		[Catania et al. 2007].
		n.a		[Howell et al. 2005; Karnon et al. 2003; Karnon et al. 2003; Lindgren et al. 2002; Drummond et al. 1999; Nuijten et al. 1999]
NICE 2009 advanced	• Offer tamoxifen as first-line treatment to men with ER-positive advanced breast cancer. (Qualifying statement: This recommendation is based on evidence from two small retrospective case series and GDG consensus that this was an appropriate and effective treatment.)	3	n.a.	[Ribeiro 1983; Patterson et al. 1980]

Leitlinie	Empfehlung	LoE[21]	GoR[1]	Referenzen
Fernmetastasen: Systemtherapie				
NBOCC 2008-E	«First-line therapy in post-menopausal women with hormone receptor-postive advanced breast cancer» Statement: Third generation aromatase inhibitors[23] show no significant difference in overall survival compared with tamoxifen	I	n.a.	[National Breast and Ovarian Cancer Centre (NBOCC) 2008]
NBOCC 2008-E	«First-line therapy in post-menopausal women with hormone receptor-postive advanced breast cancer» Statement: Third generation aromatase inhibitors[24] show significant benefit in progression-free survival compared with tamoxifen	I	n.a.	[National Breast and Ovarian Cancer Centre (NBOCC) 2008]
NBOCC 2008-E	«First-line therapy in post-menopausal women with hormone receptor-postive advanced breast cancer» Statement: Third generation aromatase inhibitorsc show significant benefit in overall response rate compared with tamoxifen	I	n.a.	[National Breast and Ovarian Cancer Centre (NBOCC) 2008]
NBOCC 2008-E	«First-line therapy in post-menopausal women with hormone receptor-postive advanced breast cancer» Statement: Overall incidence of adverse events is not significantly different between third generation aromatase inhibitors and tamoxifen	I	n.a.	[National Breast and Ovarian Cancer Centre (NBOCC) 2008]
NBOCC 2008-E	«First-line therapy in post-menopausal women with hormone receptor-postive advanced breast cancer» Statement: Incidence of thromboembolic events and vaginal bleeding is	I	n.a.	[National Breast and Ovarian Cancer Centre (NBOCC) 2008]

[23] Trials relate to anastrozole
[24] Trials relate to anastrozole, letrozole

Leitlinie	Empfehlung	LoE[21]	GoR[1]	Referenzen
Fernmetastasen: Systemtherapie				
	significantly lower with third generation aromatase inhibitors compared with tamoxifen			
NBOCC 2008-E	«First-line therapy in post-menopausal women with hormone receptor-postive advanced breast cancer» Statement: Incidence of arthralgia, diarrhoea, dyspnoea, hot flushes, and nausea is not significantly different with third generation aromatase inhibitors compared with tamoxifen	I	n.a.	[National Breast and Ovarian Cancer Centre (NBOCC) 2008]
NBOCC 2008-E	«First-line therapy in post-menopausal women with hormone receptor-postive advanced breast cancer» Statement: There are insufficient data to indicate any differences in quality of life between third generation aromatase inhibitors and tamoxifen	n.a.	n.a.	n.a.
NBOCC 2008-E	«First-line therapy in post-menopausal women with hormone receptor-postive advanced breast cancer» Recommendation: Third generation aromatase inhibitors are recommended in preference to tamoxifen	I	n.a.	[National Breast and Ovarian Cancer Centre (NBOCC) 2008]
CCO-F-2008	▪ Fulvestrant is NOT recommended as an alternative to tamoxifen for first-line therapy of locally advanced or metastastic breast cancer in postmenopausal women who had no prior endocrine or cytotoxic therapy for advanced disease and no recent endocrine therapy (within previous twelve months)	n.a.	n.a.	[Howell et al. 2004]
Endokrine Therapie (second line) bei postmenopausalen Patientinnen mit metastasiertem Brustkrebs				

Leitlinie	Empfehlung	LoE[21]	GoR[1]	Referenzen
Fernmetastasen: Systemtherapie				
NBOCC 2008-E	«Second-line therapy following progression on tamoxifen in post-menopausal women with hormone receptor-postive advanced breast cancer» Statement: Third generation aromatase inhibitorsc show significant benefit in overall survival and progression-free survival compared with progestins[25]	I	n.a.	[National Breast and Ovarian Cancer Centre (NBOCC) 2008]
NBOCC 2008-E	«Second-line therapy following progression on tamoxifen in post-menopausal women with hormone receptor-postive advanced breast cancer» Statement: Third generation aromatase inhibitorsc show no significant difference in overall response rate compared with progestins	I	n.a.	[National Breast and Ovarian Cancer Centre (NBOCC) 2008]
NBOCC 2008-E	«Second-line therapy following progression on tamoxifen in post-menopausal women with hormone receptor-postive advanced breast cancer» Statement: Third generation aromatase inhibitors show no significant difference in overall survival compared with fulvestrant	II	n.a.	[National Breast and Ovarian Cancer Centre (NBOCC) 2008]
NBOCC 2008-E	«Second-line therapy following progression on tamoxifen in post-menopausal women with hormone receptor-postive advanced breast cancer» Statement: Third generation aromatase inhibitors show no significant difference in progression-free survival and overall response rate compared	I	n.a.	[National Breast and Ovarian Cancer Centre (NBOCC) 2008]

[25] Trials relate to megastrol acetate

Leitlinie	Empfehlung	LoE[21]	GoR[1]	Referenzen
Fernmetastasen: Systemtherapie				
	with fulvestrant[26]			
NBOCC 2008-E	«Second-line therapy following progression on tamoxifen in post-menopausal women with hormone receptor-postive advanced breast cancer» Statement: Overall incidence of adverse events is not significantly different with third generation aromatase inhibitors compared with progestins	I	n.a.	[National Breast and Ovarian Cancer Centre (NBOCC) 2008]
NBOCC 2008-E	«Second-line therapy following progression on tamoxifen in post-menopausal women with hormone receptor-postive advanced breast cancer» Statement: Incidence of dyspnoea is significantly lower with third generation aromatase inhibitors compared with progestins	I	n.a.	[National Breast and Ovarian Cancer Centre (NBOCC) 2008]
NBOCC 2008-E	«Second-line therapy following progression on tamoxifen in post-menopausal women with hormone receptor-postive advanced breast cancer» Statement: Incidence of nausea, hot flushes and diarrhoea is significantly higher with third generation aromatase inhibitors compared with progestins	I	n.a.	[National Breast and Ovarian Cancer Centre (NBOCC) 2008]
NBOCC 2008-E	«Second-line therapy following progression on tamoxifen in post-menopausal women with hormone receptor-postive advanced breast cancer»	I	n.a.	[National Breast and Ovarian Cancer Centre (NBOCC) 2008]

[26] Trials relate to anastrozole and exemestane

Leitlinie	Empfehlung	LoE[21]	GoR[1]	Referenzen
Fernmetastasen: Systemtherapie				
	Statement: There are no significant differences in the incidence of thromboembolic events, vaginal bleeding and arthralgia between third generation aromatase inhibitors and progestins			
NBOCC 2008-E	«Second-line therapy following progression on tamoxifen in post-menopausal women with hormone receptor-postive advanced breast cancer» Statement: Where reported there is conflicting evidence about quality of life and no firm conclusions can be drawn	II	n.a.	[National Breast and Ovarian Cancer Centre (NBOCC) 2008]
NBOCC 2008-E	«Second-line therapy following progression on tamoxifen in post-menopausal women with hormone receptor-postive advanced breast cancer» Recommendation: Third generation aromatase inhibitors are recommended in preference to progestins	I	n.a.	[National Breast and Ovarian Cancer Centre (NBOCC) 2008]
NBOCC 2008-E	«Optimal dose, schedule and duration of administration» Recommendation: Continued use of third generation aromatase inhibitors is recommended until disease progression or unacceptable toxicity	I	n.a.	[National Breast and Ovarian Cancer Centre (NBOCC) 2008]
NBOCC 2008-E	«Optimal dose, schedule and duration of administration» Recommendation: Recommended doses and schedules for third generation aromatase inhibitors are: Anastrozole 1.0 mg/day Exemestane 25 mg/day Letrozole 2.5 mg/day	I	n.a.	[National Breast and Ovarian Cancer Centre (NBOCC) 2008]

Leitlinie	Empfehlung	LoE[21]	GoR[1]	Referenzen
Fernmetastasen: Systemtherapie				
NBOCC 2008-E	«Optimal dose, schedule and duration of administration» Recommendation: There are insufficient data to recommend one type of endocrine therapy over another for women who have progressed during or after treatment with adjuvant aromatase inhibitors	n.a.	n.a.	n.a.
NBOCC 2008-E	«Aromatase inhibitor vs aromatase inhibitor» Statement: There are insufficient data to indicate a significant difference in overall survival, progression free survival or overall response rate for one aromatase inhibitor over another aromatase inhibitor	n.a.	n.a.	n.a.
CCO-F-2008	▪ Fulvestrant may be considered as alternative therapy to anastrozole for locally advanced or metastatic breast cancer in postmenopausal women with hormon-receptor-positive (ER+ and/or PgR+) breast cancer that has recurred on prior adjuvant tamoxifen therapy or progressed on prior tamoxifen therapy for advanced disease. Clinicians shoud be aware of the methodological concerns of the key evidentiary trials used in formulation this recommendation. ▪ Factors that may influence the choice ot fulvestrant versus anastrozole therapy include a slightly decreased, although still	n.a.	n.a.	[Howell et al. 2002; Osborne et al. 2002; Howell et al. 2005; Howell et al. 2005; Dodwell et al. 2006; Jones et al. 2004; Parker et al. 2002; Pippen 2005; Jones et al. 2004; Mauriac et al. 2003]
CCO-F-2008	▪ Fulvestrant may be considered as alternative therapy to exemestane for locally advanced or metastatic breast cancer in postmenopausal women with hormone-receptor-positive (ER+ and/or PgR+) breast cancer that has recurred on prior adjuvant nonsteroidal aromatase inhibitor (NSAI) therapy (during or within six months of discontinuation) or progressed on prior NSAI therapy for advanced disease. ▪ Factors that influence the choice of fulvestrant versus exemestane therapy include the potential for improved compliance in favour of	n.a.	n.a.	[Chia et al. 2008; Chia et al. 2011]

Leitlinie	Empfehlung	LoE[21]	GoR[1]	Referenzen
Fernmetastasen: Systemtherapie				
	fulvestrant.			
CCO-F-2008	▪ The recommended dose of fulvestrant for the treatment of locally advanced or metastatic breast cancer is 250 mg IM every month OR a loading dose schedule of 500mg IM day 0, 250mg IM on days 14 and 28, and 250 mg IM injection monthly thereafter. ▪ Factors that may influence the choice of a loading dose include a shortened time to reach stady state (within one month vs. three to six months for standard dosage) although this may require further verification.	n.a.	n.a.	[Howell et al. 2004; Howell et al. 2002; Osborne et al. 2002; Chia et al. 2008]
Endokrine Therapie bei prämenopausalen Patientinnen mit metastasiertem Brustkrebs				
NICE 2009 advanced	• Offer tamoxifen and ovarian suppression as first-line treatment to premenopausal and perimenopausal women with ER-positive advanced breast cancer not previously treated with tamoxifen. • Offer ovarian suppression to premenopausal and perimenopausal women who have previously been treated with tamoxifen and then experience disease progression. Qualifying statement: These recommendations are based on one moderate quality RCT report showing a survivial benefit for combination therapy over single agents in pre-menopausal patients. There is also evidence of clinical effectiveness from one high-quality systematic review of randomised trials in pre-menopausal women. There was GDG consensus that peri-menopausal women should be treated in the same manner. The GDG has made no recommendation on the optimal endocrine management	1-	n.a.	[Klijn et al. 2001; Klijn et al. 2000]

Leitlinie	Empfehlung	LoE[21]	GoR[1]	Referenzen
Fernmetastasen: Systemtherapie				
	of patients with ER-positive disease who relapse whilst on adjuvant tamoxifen as there is no data in this area. Current UK practice varies, with the use of either ovarian suppression or ovarian suppression in combination with aromatase inhibitors being used.			
NBOCC 2008-E	«In pre-menopausal women with hormone receptor-positive advanced breast cancer» Statement: Combination of luteinising hormone-releasing hormone (LH-RH) agonist and tamoxifen shows significant benefit in overall survival, progression-free survival and overall response rate compared with LH RH agonist alone	I	n.a.	[Klijn et al. 2001]
NBOCC 2008-E	«In pre-menopausal women with hormone receptor-positive advanced breast cancer» Statement: Combination of LH-RH agonist and tamoxifen shows significant benefit in overall survival, progression-free survival and overall response rate compared with tamoxifen alone	III	n.a.	[Klijn et al. 2000]
NBOCC 2008-E	«In pre-menopausal women with hormone receptor-positive advanced breast cancer» Statement: Incidence of hot flushes is significantly higher in women treated with combined tamoxifen and LH-RH agonist compared with tamoxifen alone	III	n.a.	[Klijn et al. 2000]
NBOCC 2008-E	«In pre-menopausal women with hormone receptor-positive advanced breast cancer» Statement: There are insufficient data to guide the use of third generation aromatase inhibitors in combination with functional ovarian ablation/suppression or fulvestrant in pre-menopausal women	n.a.	n.a.	n.a.

Leitlinie	Empfehlung	LoE[21]	GoR[1]	Referenzen
Fernmetastasen: Systemtherapie				
NBOCC 2008-E	«In pre-menopausal women with hormone receptor-positive advanced breast cancer» Recommendation: Tamoxifen combined with luteinising hormone-releasing hormone (LH-RH) agonist is recommended in favour of a LH-RH agonist alone	I	n.a.	[Klijn et al. 2001]
NBOCC 2008-E	«In pre-menopausal women with hormone receptor-positive advanced breast cancer» Recommendation: If commencing treatment with tamoxifen alone, consideration should be given to adding a LH-RH agonist, if response is not optimal	III	n.a.	[Klijn et al. 2000]
NBOCC 2008-E	«In pre-menopausal women with hormone receptor-positive advanced breast cancer» Recommendation: Recommended doses and schedule are: Tamoxifen 20mg/day Goserelin 3.6mg subcutaneously monthly	n.a.	n.a.	[Therapeutic Good Administration (TGA) 2011]
Chemotherapie bei metastasiertem Brustkrebs				
NICE 2009 advanced	• On disease progression, offer systemic sequential therapy to the majority of patients with advanced breast cancer who have decided to be treated with chemotherapy. (Qualifying statement: These recommendations are based on limited	1 1-	n.a.	[Chlebowski et al. 1979] [Baker et al. 1974; Creech et al. 1979; Sledge et al. 2003; Smalley et al. 1976]

Leitlinie	Empfehlung	LoE[21]	GoR[1]	Referenzen
Fernmetastasen: Systemtherapie				
	randomised trial evidence and GDG consensus.)	3		[Chlebowski et al. 1989].
NICE 2009 advanced	• Consider using combination chemotherapy to treat patients with advanced breast cancer for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity. (Qualifying statement: This recommendation is based on randomised trial evidence confirming increased response rate and toxicity from combination chemotherapy and uncertainty over overall survival benefit compared with sequential single agent chemotherapy.)	1++	n.a.	[Carrick et al. 2005]
		1-		[Ejlertsen et al. 2004; Martin et al. 2007]
		2-		[Pacilio et al. 2006]
		3		[Leonard et al. 2006; Miles et al. 2004; Takeda et al. 2007]
NICE 2009 advanced	• For patients with advanced breast cancer who are not suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), systemic chemotherapy should be offered in the following sequence: o first line: single-agent docetaxel o second line: single-agent vinorelbine or capecitabine o third line: single-agent capecitabine or vinorelbine (whichever was not used as second-line treatment). (Qualifying statement: This recommendation was based on the findings of a health economic analysis that compared the cost-effectiveness of various	1++	n.a.	[Ghersi et al. 2005]
		1+		[Bria et al. 2005]
		1		[Bontenbal et al. 2005]
		1-		[Jones et al. 2005]
		2-		[Chan 2005; Bonneterre et al. 2002; Martin et al. 2007; Cassier et al. 2008]

Leitlinie	Empfehlung	LoE[21]	GoR[1]	Referenzen
Fernmetastasen: Systemtherapie				
	sequences of single-agent and combination chemotherapy regimens, for patients who are anthracycline resistant or for whom anthracycline therapy is contraindicated. While it was acknowledged that there is no direct evidence comparing alternative chemotherapy sequences, the GDG considered it important to explore the cost effectiveness of plausible sequences using the best available data. An indirect treatment comparison methodology was an important component of this, but it was restricted to an assessment of the relative effectiveness of alternative first-line treatments based on the available RCT data. The base case analysis showed that the most cost-effective treatment sequence based on a threshold of £30,000 per QALY was docetaxel monotherapy followed by capecitabine monotherapy followed by vinorelbine monotherapy. The ICER for this sequence was estimated to be £23,332 per QALY. When applying a threshold of £20,000 per QALY, the most cost-effective sequence was docetaxel monotherapy followed by capecitabine monotherapy, followed by no further chemotherapy. The GDG however acknowledged that the economic analysis was subject to a level of uncertainty that would make distinguishing between certain strategies difficult. In addition, it was the GDG's view that the benefit from three lines of therapy was potentially underestimated in the analysis leading to ICERs that were too high. The GDG noted that the there was no strong evidence underpinning the effectiveness estimates of third-line interventions (including 'no chemotherapy') in any of the alternative strategies considered. The difference in expected benefits and costs between the optimal strategy beneath a threshold of £30,000 and the sequence docetaxel-vinorelbine-capecitabine (dominated in the base-case analysis) was very small. It was the GDG's view that essentially these two alternatives were equivalent and that the sequence docetaxel-vinorelbine-capecitabine would also be a cost effective option. The GDG acknowledged that the existence of price discounts for paclitaxel can significantly alter the cost effectiveness of the sequences examined in the analysis. While there is evidence to suggest that combination therapy (for example when capecitabine is used concurrently	3		[Pajk et al. 2008; Bartsch et al. 2007; Catania et al. 2007; Ghosn et al. 2006; Burstein et al. 2003; Chan et al. 2006; Jahanzeb et al. 2002; Mayordomo et al. 2004; Udom et al. 2000; Zelek et al. 2001; Ardavanis et al. 2007; Davis.A.J. 2007; De Maio E. et al. 2007; Onyenadum et al. 2007; Shamseddine et al. 2006; Ghosn et al. 2008; Colomer et al. 2006; El-Helw et al. 2005; Lee et al. 2004; Fumoleau et al. 2004; Chan et al. 2006; Pierga et al. 2004; Reichardt et al. 2003; Wist et al. 2004; Sezgin et al. 2007; Venturini et al. 2007; Yap et al. 2007; Leonard et al. 2002; Mackey et al. 2004; Miles et al. 2004; Mrozek et al. 2006; Silva et al. 2008; Stuart et al. 2008; Lin et al. 2007]
		n.a.		[O'Shaughnessy et al. 2002; Verma et al. 2003; Cooper et al. 2003]

Leitlinie	Empfehlung	LoE[21]	GoR[1]	Referenzen
Fernmetastasen: Systemtherapie				
	with docetaxel) may lead to improved survival, this can be associated with an unacceptable side-effect profile. However, the GDG considered that there will be circumstances when combination therapy would be appropriate and cost-effective. For example, patients may consider that a greater probability of response is important to them. Under these circumstances, patients should be made fully aware of the expected side effect profile and be likely to tolerate the additional toxicity. The recommendations contained in the recent NICE technology appraisal guidance 116 are being incorporated into this guideline. The combination of gemcitabine and paclitaxel is only recommended as an option if docetaxel monotherapy or the combination of docetaxel and capecitabine would also be appropriate. However, the GDG considered that in the majority of circumstances, patients should start treatment with taxane monotherapy (preferably docetaxel) followed by capecitabine or vinorelbine monotherapy second line then vinorelbine or capecitabine monotherapy third line. This is because there is additional toxicity with combination chemotherapy (compared with single agent chemotherapy) for a small increase in response rate.			
NICE 2009 advanced	«Recommendation (from NICE technology appraisal guidance 116) » • Gemcitabine in combination with paclitaxel, within its licensed indication, is recommended as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate. (Qualifying statement: This recommendation is from 'Gemcitabine for the treatment of metastatic breast cancer', NICE technology appraisal guidance 116 (2007). It was formulated by the technology appraisal and not by the guideline developers It has been incorporated into this guideline in line with NICE procedures for developing clinical guidelines, and the evidence to support the recommendation can be found at www.nice.org.uk/TA116.)	n.a.	n.a.	NICE technology appraisal guidance 116 (www.nice.org.uk/TA116)

Leitlinie	Empfehlung	LoE[21]	GoR[1]	Referenzen
Fernmetastasen: Systemtherapie				
NICE 2009 advanced	«Research recommendation» • Randomised clinical trials should evaluate the clinical and cost effectiveness of different sequences of chemotherapy for advanced breast cancer.	n.a.	n.a.	n.a.
NBOCC 2010	«In women with advanced breast cancer» Statement: Combination chemotherapy increases response rates, time to progression, toxicity and overall survival, compared with singleagent chemotherapy, not including sequential use of the same drugs	I	n.a.	[Carrick et al. 2005]
NBOCC 2010	«In women with advanced breast cancer» Statement: Combination chemotherapy increases response rates and toxicity, but not time to progression or overall survival, compared with sequential use of the same drugs as single agents	II	n.a.	[Sledge et al. 2003; Soto et al. 2006]
NBOCC 2010	«In women with advanced breast cancer» Statement: In women with hormone receptor-positive disease: ▪ initial chemotherapy achieves similar overall survival to initial endocrine therapy, except in those with visceral disease that is extensive or rapidly progressing, where initial chemotherapy shows improved survival ▪ endocrine therapy has fewer adverse effects than chemotherapy	I	n.a.	n.a.

Leitlinie	Empfehlung	LoE[21]	GoR[1]	Referenzen
Fernmetastasen: Systemtherapie				
NBOCC 2010	«In women with advanced breast cancer» Recommendation: There are several specific chemotherapy drugs and/or and combinations with similar efficacy in any given situation In general: ▪ combination chemotherapy should be considered for women with little or no previous exposure to chemotherapy, widespread or rapidly progressing disease, and few or no co-morbidities ▪ sequential single-agent chemotherapy should be considered for women with limited or indolent disease, previous exposure to chemotherapy, or significant co-morbidities	I II III	n.a. n.a. n.a.	[Carrick et al. 2005] [Sledge et al. 2003] [Soto et al. 2006]
NBOCC 2010	«In women with advanced breast cancer» Recommendation: In women with visceral hormone receptor-positive disease that is extensive or rapidly progressing, initial chemotherapy should be considered in preference to initial endocrine therapy	I	n.a.	[Carrick et al. 2005]
NBOCC 2010	Statement: Higher-than-standard doses of chemotherapy increase tumour response and toxicity, but not time to progression or overall survival, compared with standard doses	I	n.a.	[Carrick et al. 2005]
NBOCC 2010	Statement: Lower-than-standard doses of chemotherapy do not improve quality of life and survival, compared with standard doses	II	n.a.	[Tannock et al. 1988]
NBOCC 2010	Statement: Extending chemotherapy beyond the standard duration (18–24 weeks; 6-8 cycles) delays progression but has limited effect on overall survival	I	n.a.	[Gennari et al. 2008]

Leitlinie	Empfehlung	LoE[21]	GoR[1]	Referenzen
Fernmetastasen: Systemtherapie				
NBOCC 2010	Statement: Shorter-than-standard durations (<18-24 weeks) of chemotherapy result in reduced overall survival and quality of life	II	n.a.	[Coates et al. 1987]
NBOCC 2010	Recommendation: Tumour response should be assessed every 6–12 weeks (2–3 cycles) during chemotherapy	IV	n.a.	n.a.
NBOCC 2010	Recommendation: If disease control (stable disease or better) is confirmed and toxicity is tolerable, then chemotherapy should be continued for 18–24 weeks (6–8 cycles)	I	n.a.	n.a.
NBOCC 2010	Recommendation: Extending chemotherapy beyond the standard duration (18–24 weeks; 6–8 cycles) is an option if toxicity is minimal and the goal is to delay progression Extending chemotherapy beyond the standard duration has little or no effect on overall survival	I	n.a.	n.a.
NBOCC 2010	Statement: Single-agent taxanes give similar response rates and overall survival, but shorter time to progression compared with anthracyclines	I	n.a.	[Piccart-Gebhart et al. 2008]
NBOCC 2010	Statement: Taxane-based combination chemotherapy increases response rates and time to progression, but not overall survival, compared with anthracyclines	II	n.a.	[Sledge et al. 2003]
NBOCC 2010	Recommendation: Single-agent taxanes are an alternative to anthracyclines for first-line treatment for women with advanced breast cancer	I	n.a.	[Piccart-Gebhart et al. 2008]
NBOCC 2010	Recommendation: Combination chemotherapy that includes a taxane should be considered for women who have rapidly progressing or extensive visceral disease and limited previous exposure	II	n.a.	[Sledge et al. 2003]

Leitlinie	Empfehlung	LoE[21]	GoR[1]	Referenzen
Fernmetastasen: Systemtherapie				
NBOCC 2010	Statement: When compared with 3-weekly paclitaxel, use of weekly paclitaxel: ▪ increases time to progression and overall survival ▪ causes less myelosuppression, but more neuropathy ▪ requires more clinic visits	II	n.a.	[Seidman et al. 2008]
NBOCC 2010	Statement: For 3-weekly paclitaxel: ▪ increasing the dose beyond 175mg/m2 increases toxicity, but not response rate, survival or quality of life	II	n.a.	[Winer et al. 2004]
NBOCC 2010	Recommendation: The recommended dose and schedule for weekly paclitaxel is 80 mg/m2, with a one week break every 4–8 weeks according to toxicity and the woman's preferences	II	n.a.	[Seidman et al. 2008]
NBOCC 2010	Recommendation: The recommended dose for 3-weekly paclitaxel is 175 mg/m2 given over 3 hours	II	n.a.	[Winer et al. 2004]
NBOCC 2010	Statement: For 3-weekly docetaxel: ▪ increasing the dose from 75 mg/m2 to 100 mg/m2 increases response rates and toxicity, but not time to progression or overall survival ▪ reducing the dose from 75 mg/m2 to 60 mg/m2 decreases toxicity	II	n.a.	[Harvey et al. 2006]

Leitlinie	Empfehlung	LoE[21]	GoR[1]	Referenzen
Fernmetastasen: Systemtherapie				
NBOCC 2010	Statement: 3-weekly docetaxel and weekly paclitaxel both increase response rates, time to progression and overall survival, when compared with 3-weekly paclitaxel No randomised trials in advanced breast cancer have directly compared 3-weekly docetaxel with weekly paclitaxel	II	n.a.	[Jones et al. 2005; Seidman et al. 2008]
NBOCC 2010	Statement: When compared with paclitaxel, docetaxel causes: ▪ more myelosuppression and gastro-intestinal toxicity ▪ less neuropathy and allergic reactions	II	n.a.	[Jones et al. 2005]
NBOCC 2010	Recommendation: The recommended dose and schedule for 3-weekly docetaxel is 75–100 mg/m2	II	n.a.	[Harvey et al. 2006]
NBOCC 2010	Statement: When compared with standard 3-weekly paclitaxel, nanoparticle albumin-bound paclitaxel: ▪ increases response rate and time to progression, but not overall survival	II	n.a.	[Gradishar et al. 2005]
	▪ causes more neuropathy, fatigue and gastrointestinal toxicity, but less neutropenia and allergic reactions Nanoparticle albumin-bound paclitaxel has not been compared with standard paclitaxel given weekly	II	n.a.	[Guan et al. 2007]

Leitlinie	Empfehlung	LoE[21]	GoR[1]	Referenzen
Fernmetastasen: Systemtherapie				
NBOCC 2010	Recommendation: Nanoparticle albumin-bound paclitaxel is an alternative to 3-weekly paclitaxel, but has not been compared with standard paclitaxel given weekly[27]	II	n.a.	[Gradishar et al. 2005; Guan et al. 2007]
NBOCC 2010	«Capecitabine as first-line chemotherapy for metastatic breast cancer» Statement: For women for whom more intensive chemotherapy is not appropriate, capecitabine improves overall survival and is better tolerated than oral cyclophosphamide, methotrexate and fluorouracil 5FU (CMF)	II	n.a.	[Stockler et al. 2007]
NBOCC 2010	«Capecitabine as first-line chemotherapy for metastatic breast cancer» Recommendation: Single-agent capecitabine is an option for women for whom more intensive chemotherapy is not appropriate	II	n.a.	[Stockler et al. 2007]
NBOCC 2010	Statement: In women previously treated with an anthracycline, the combination of capecitabine and docetaxel, compared with single-agent 3-weekly docetaxel: ▪ increases response rates, time to progression and overall survival ▪ increases toxicity	II	n.a.	[O'Shaughnessy et al. 2002]

[27] A recent trial showed that first-line treatment with nab-paclitaxel significantly improved progression-free survival for women with metastatic breast cancer compared with 3-weekly docetaxel.(Gradishar et al. 2009)

Leitlinie	Empfehlung	LoE[21]	GoR[1]	Referenzen
Fernmetastasen: Systemtherapie				
NBOCC 2010	Recommendation: The combination of capecitabine and docetaxel is an option for women with rapidly progressing or extensive visceral disease, good performance status and limited exposure to previous chemotherap	II	n.a.	[O'Shaughnessy et al. 2002]
NBOCC 2010	Statement: In women previously treated with an anthracycline, the combination of gemcitabine and paclitaxel, compared with single-agent 3-weekly paclitaxel: ▪ increases response rate, time to progression and overall survival ▪ increases toxicity	II	n.a.	[Albain et al. 2008]
NBOCC 2010	Recommendation: The combination of gemcitabine and paclitaxel is an option for women with rapidly progressing or extensive visceral disease, good performance status and limited exposure to previous chemotherapy[28]	II	n.a.	[Albain et al. 2008]
Antikörpertherapie bei metastasiertem Brustkrebs				
NICE 2009 advanced	• For patients who are receiving treatment with trastuzumab[29] for	2		[Tripathy et al. 2004]

[28] Preliminary results from a recent trial indicate that the addition of a PARP inhibitor to gemcitabine/ carboplatin compared with gemcitabine/carboplatin alone shows potential benefit for progression-free survival and overall survival for women with triple negative metastatic breast cancer.28

[29] Recommendations on the use of trastuzumab are covered by NICE technology appraisal guidance 34 (2002) which will be updated.

Leitlinie	Empfehlung	LoE[21]	GoR[1]	Referenzen
Fernmetastasen: Systemtherapie				
	advanced breast cancer, discontinue treatment with trastuzumab at the time of disease progression outside the central nervous system. Do not discontinue trastuzumab if disease progression is within the central nervous system alone.	3		[Fountzilas et al. 2003; Gelmon et al. 2004; Montemurro et al. 2006; Stemmler et al. 2005; Bartsch et al. 2006]
	(Qualifying statement: The GDG were aware of limited, very recent evidence of clinical benefit for the use of trastuzumab on disease progression. This recommendation is based on the fact that it would not be appropriate to recommend the use of trastuzumab on disease progression without robust evidence of the cost effectiveness of this high cost treatment.)	3-		[Garcia-Saenz et al. 2005]
NICE 2009 advanced	«Research recommendations» • The use of continued trastuzumab in patients with progressive metastatic disease should be investigated as part of a randomised controlled trial. Trial design should incorporate collection of data required for prospective cost-effectiveness analysis. • Randomised controlled trials are needed to assess whether patients who have had adjuvant trastuzumab should be offered further biological therapy. Trial design should incorporate collection of data required for prospective cost-effectiveness analysis.	n.a.	n.a.	n.a.
NBOCC 2008-E	«In post-menopausal women with hormone receptor-postive advanced breast cancer» Statement: Combination of aromatase inhibitors and trastuzumab in women with HER2-positive hormone dependent advanced breast cancer leads to improved progression-free survival compared with aromatase inhibitors alone	II	n.a.	[Klijn et al. 2001]

Leitlinie	Empfehlung	LoE[21]	GoR[1]	Referenzen
Fernmetastasen: Systemtherapie				
NBOCC 2008-E	«In post-menopausal women with hormone receptor-postive advanced breast cancer» Recommendation: Aromatase inhibitors with trastuzumab are recommended for the treatment of women with HER2-positive hormone dependent advanced breast cancer in preference to aromatase inhibitors alone	II	n.a.	[National Breast Cancer Centre (NBCC) 2007]
NBOCC 2010	«Bevacizumab with first-line chemotherapy for metastatic breast cancer» Statement: When compared with weekly paclitaxel alone, the addition of bevacizumab: ▪ improves response rates and time to progression, but not overall survival ▪ causes more hypertension and proteinuria	II	n.a.	[Zon et al. 2006; Miller et al. 2007; Wagner et al. 2006]
NBOCC 2010	«Bevacizumab with first-line chemotherapy for metastatic breast cancer» Statement: When compared with 3-weekly docetaxel alone, the addition of bevacizumab: ▪ improves response rates and time to progression, but not overall survival ▪ causes more febrile neutropenia	II	n.a.	[Miles et al. 2008]
NBOCC 2010	«Bevacizumab with second- or third-line chemotherapy for metastatic breast cancer» Statement: In women previously treated with an anthracycline and taxane, the addition of bevacizumab to capecitabine, compared with capecitabine alone: ▪ improves response rates, but not time to progression or overall survival	II	n.a.	[Miller et al. 2005]

Leitlinie	Empfehlung	LoE[21]	GoR[1]	Referenzen
Fernmetastasen: Systemtherapie				
	▪ causes more hypertension, proteinuria and hand-foot syndrome			
NBOCC 2010	Recommendation: The routine addition of bevacizumab to chemotherapy is not recommended because the benefits do not outweigh the additional adverse effects[30]	II	n.a.	[Zon et al. 2006; Miles et al. 2008; Miller et al. 2005]
NBOCC 2010	«Lapatinib after progression on trastuzumab» Statement: When compared with capecitabine alone, the addition of lapatinib after progression on trastuzumab: improves response rates and time to progression, but not overall survival causes more diarrhoea, dyspepsia, liver dysfunction and rash	II	n.a.	[Geyer et al. 2006; Geyer et al. 2007]
NBOCC 2010	«Lapatinib after progression of disease on trastuzumab» Recommendation: The combination of lapatinib and capecitabine is a good option for women with disease that has progressed after chemotherapy with an anthracycline, a taxane and trastuzumab[31]	II	n.a.	[Geyer et al. 2006; Geyer et al. 2007]
Abkürzungen: GDG = guideline development group, HER2 = human epidermal growth factor receptor 2; ICER = incremental cost-effectiveness ratio, LH-RH = luteinising hormone-releasing hormone; n.a. = nicht angegeben; NSAI = nonsteroidal aromatase inhibitor; QALY = quality adjusted life year;				

[30] A recent trial showed that the addition of bevacizumab to first-line treatment with capecitabine/taxane/ anthracycline significantly improved progression-free survival for women with HER2-negative metastatic breast cancer.29

[31] A recent trial showed that the combination of lapatinib and trastuzumab significantly improved progression-free survival compared with lapatinib alone for women with HER2-positive metastatic breast cancer.30

4.2.14 Empfehlungen zum Thema Fernmetastasen – spezifische Diagnostik und Therapie

4.2.14.1. Eingeschlossene Leitlinien

Zum Thema spezifische Diagnostik und Therapie bei Fernmetastasen konnten drei Leitlinien der Gruppe 1 extrahiert werden [National Institute for Clinical Excellence (NICE) 2009; Feyer et al. 2010; Souchon et al. 2009]. Eine Leitlinie wurde vom National Institute for Health and Clinical Excellence (NICE) aus Großbritannien in 2009 herausgegeben und adressiert die Therapie des fortgeschrittenen Mammakarzinoms. Für die Extraktion dieser Leitlinie (insbesondere der Evidenzklassifikationen [LoE]) wurde ein Hintergrund- bzw. Methodendokumente ausgewertet [National Institute for Clinical Excellence (NICE) 2009]. Zu den Empfehlungen haben die Autoren der NICE-Leitlinien sogenannte ‚Qualifying Statements' angeführt. Diese beschreiben zusammenfassend die zugrundeliegende Evidenz der Empfehlungen. Die ‚Qualifying Statements' wurden mit den Empfehlungen extrahiert, um als Ergänzung zu den berücksichtigten Referenzen auch die entsprechenden zusammenfassenden Einschätzungen der Autoren wiederzugeben. Die Leitlinien von NICE enthalten außerdem Empfehlungen für die weitere Erforschung bestimmter Aspekte (Research Recommendations). Diese Empfehlungen wurden extrahiert und entsprechend gekennzeichnet.

Zwei der extrahierten Leitlinien wurden von der Deutschen Gesellschaft für Radioonkologie (DEGRO) in 2009 bzw. 2010 herausgegeben. Die Leitlinien geben Empfehlungen zur Strahlentherapie bei Knochenmetastasen und metastatisch bedingter Rückenmarkskompression (MSCC) sowie bei Hirnmetastasen und leptomeningealer Karzinose. Für die Extraktion dieser Leitlinien wurden keine weiteren Dokumente ausgewertet. Da die Empfehlungen der DEGRO-Leitlinien nicht durchgehend eindeutig dargestellt sind, wurden die Empfehlungen der Leitlinien durch zwei Reviewer unabhängig voneinander identifiziert und die Differenzen durch Diskussion gelöst.

4.2.14.2 In der S3-Leitlinie Mammakarzinom nicht enthaltene oder diskrepante Empfehlungs-Inhalte

Die NICE 2009 advanced enthält eine Empfehlung zu **lokal unkontrolliertem Tumor** – in Bezug auf Therapieplanung mit einem multidisziplinären Team, Hinzuziehen eines „wound care teams" bei Pilzbefall und Hinzuziehen eines Palliativ-Care-Teams (LoE n.a.). Die S3-Leitlinie Mammakarzinom 2008 thematisiert den lokal unkontrollierten Tumor bei Vorliegen von Fernmetastasen nicht.

Im Hinblick auf **ossäre Metastasen** enthält die DEGRO 2009 **spezifischere Empfehlungen** im Vergleich zur S3-Leitlinie Mammakarzinom 2008 zu Bestrahlungsdosen und zur Diagnostik und Therapie des spinalen Kompressionssyndroms. Dies trifft ebenso für die **Diagnostik und Therapie von Hirnmetastasen und leptomeningealer Karzinomatose** (DEGRO 2010) zu (z.B. spezifischere Empfehlungen zur Diagnostik und zur Steroidmedikation sowie zur strahlentherapeutischen und intrathekalen Behandlung der

leptomeningealen Karzinomatose). Weiterhin finden sich Empfehlungen zur Abwägung von Bestrahlung und Operation bei Hirnmetastasen, die in der S3-Leitlinie Mammakarzinom 2008 nicht enthalten sind.

Zur Behandlung von viszeralen Fernmetastsaen wurden keine spezifischen Empfehlungen identifiziert, zur Diagnostik siehe Abschnitt Diagnostik.

Tabelle 16: Fernmetastasen - spezifische Diagnostik und Therapie

Leitlinie	Empfehlung	LoE[32]	GoR[1]	Referenzen
Fernmetastasen – spezifische Diagnostik und Therapie				
Lokale Therapie				
NICE 2009 advanced	▪ A breast cancer multidisciplinary team should assess all patients presenting with uncontrolled local disease and discuss the therapeutic options for controlling the disease and relieving symptoms.	3	n.a.	[Bower et al. 1992; Faneyte et al. 1997; Kolodziejski et al. 2005; Kuge et al. 1996; Kumar et al. 1987; Lund-Nielsen et al. 2005; Pameijer et al. 2005]
	▪ A wound care team should see all patients with fungating tumours to plan a dressing regimen and supervise management with the breast care team.			
	▪ A palliative care team should assess all patients with uncontrolled local disease in order to plan a symptom management strategy and provide psychological support.	n.a.		Appendix B des Evidence Review zu dieser Leitlinie (NICE 2009: Advanced breast cancer: diagnosis and treatment)
	(Qualifying statement: These recommendations are based on poor quality evidence, expert position papers and GDG consensus.)			

[32] Für Erläuterungen des Level of Evidence (LoE) und Grade of Recommendation (GoR) siehe Anhang 5.6.

Leitlinie	Empfehlung	LoE[32]	GoR[1]	Referenzen
Fernmetastasen – spezifische Diagnostik und Therapie				
NICE 2009 advanced	«Research recommendation» The relevant research organisations should be encouraged to address the topic of uncontrolled local disease and devise appropriate research studies. This might include development of a national register.	n.a.	n.a.	n.a.
Diagnostik und Therapie bei ossärer Metastasierung (s.a. Kapitel zu Diagnostik)				
NICE 2009 advanced	• Consider offering bisphosphonates to patients newly diagnosed with bone metastases to prevent skeletal-related events and reduce pain. (Qualifying statement: This recommendation is based on strong evidence of clinical effectiveness in reducing skeletal related events and pain, and reasonable evidence of cost effectiveness for the NHS in preventing skeletal related events.)	1++	n.a.	[Pavlakis et al. 2005; Warr et al. 2002]
		1+		[Tripathy et al. 2004]
		1-		[Wardley et al. 2005]
		2-		[Weinfurt et al. 2004; Pecherstorfer et al. 2006]
NICE 2009 advanced	• The choice of bisphosphonate for patients with bone metastases should be a local decision, taking into account patient preference and limited to preparations licensed for this indication. (Qualifying statement: This recommendation was based on GDG consensus that there was no strong evidence of comparative clinical effectiveness and conflicting evidence of comparative cost effectiveness.)	n.a.	n.a.	[Ross et al. 2004; Botteman et al. 2006; De Cock et al. 2005; De Cock et al. 2005]
NICE 2009 advanced	• Use external beam radiotherapy in a single fraction of 8 Gy to treat patients with bone metastases and pain. (Qualifying statement: This recommendation was based on evidence from	1++	n.a.	[Sze et al. 2002]
		1+		[Hartsell et al. 2005]

Leitlinie	Empfehlung	LoE[32]	GoR[1]	Referenzen
Fernmetastasen – spezifische Diagnostik und Therapie				
	randomised trials.)	1-		[Rasmusson et al. 1995; Salazar et al. 2001]
		3		[Scarantino et al. 1996]
		3-		[Borojevic et al. 1999]
NICE 2009 advanced	• An orthopaedic surgeon should assess all patients at risk of a long bone fracture, to consider prophylactic surgery. (Qualifying statement: This recommendation was based on GDG consensus.)	3	n.a.	[Durr et al. 2002]
		3-		[Gerszten et al. 2005; Gristina et al. 1983]
		4		[Broos et al. 1993]
NICE 2009 advanced	▪ Do not use bone scintigraphy to monitor the response of bone metastases to treatment. (Qualifying statement: There is a poor evidence base with a single prospective study. There is no evidence that bone scintigraphy can be used to assess the response to treatment.)	3	n.a.	[Ciray et al. 2001; Huber et al. 2002; Stafford et al. 2002; Linden et al. 2006; Mortimer et al. 1996]
	▪ Do not use PET-CT to monitor advanced breast cancer (Qualifying statement: There is no evidence that monitoring with PET-CT improves management compared to standard imaging modalities in patients with advanced breast cancer.)	n.a.		[Couturier et al. 2006]
DEGRO 2009 (Souchon)	«Bei ossärer Metastasierung» Therapeutic goal: pain reduction • Single dose radiotherapy 1x 8Gy (Cave: > 8 Gy to the myelon may	III	n.a.	[Sze et al. 2003]

Leitlinie	Empfehlung	LoE[32]	GoR[1]	Referenzen
Fernmetastasen – spezifische Diagnostik und Therapie				
	cause paresis)			
DEGRO 2009 (Souchon)	«Bei ossärer Metastasierung» Therapeutic goal: stabilization, good prognosis • Fractioned regimen preferable, e.g., 10-12 x 3 Gy	IIb	n.a.	[Rades et al. 2006; Rades et al. 2006]
DEGRO 2009 (Souchon)	«Bei ossärer Metastasierung» Oligometastases • Full-dose fractionated regimen recommended, e.g., 20-25 x 2 to 40-50 Gy	IIB, III	n.a.	n.a.
DEGRO 2009 (Souchon)	«Diagnostische Schritte bei Verdacht auf metastatisch bedingtem spinalen Kompressionssyndrom»: • History with specific focus on: o Beginning of signs and symptoms o Localization o Character of pain (dependence on stress, motion, and /or position) o Time course o Duration of neurologic deficit / back pain / loss of continence • Clinical examination o Neurologic examination (motor / sensory deficits) o Clinical estimation of level of spinal compression o Work-up of extent of extraspinal metastases	IIb	A	[Walker et al. 2003]

Leitlinie	Empfehlung	LoE[32]	GoR[1]	Referenzen
Fernmetastasen – spezifische Diagnostik und Therapie				
	• Imaging o Targeted according to clinical examination o MRI (extent; intradural / extradural / intraspinal masses) o CT (stability; extent of destruction o Conventional X-rays[extent of deformity, stability])			
DEGRO 2009 (Souchon)	«Bei metastischem spinalen Kompressionssyndrom» Instability of vertebral column, bony compression and / or paresis / paraplegia • Immediate (within maximally 24-48 h) surgical intervention and postoperative radiotherapy	IIb	A	[Patchell et al. 2005]
DEGRO 2009 (Souchon)	«Bei metastischem spinalen Kompressionssyndrom» Spinal cord compression without neurologic deficits			
	• In ambulatory patients: radiotherapy	IIb	n.a	[Maranzano et al. 1995; Rades et al. 2007; Rades et al. 2002; Rades et al. 2007; Rades et al. 2006; Rades et al. 2007; Regine et al. 2003; Walker et al. 2003]
	• In case of analgesia as additional goal: short course of radiotherapy with increased single doses	n.a.		[Walker et al. 2003]
	• In case if remineralisation as additional goal: fractionated radiotherapy with conventional single doses	n.a.		[Koswig et al. 1999; Rieden et al. 1989]

Leitlinie	Empfehlung	LoE[32]	GoR[1]	Referenzen
Fernmetastasen – spezifische Diagnostik und Therapie				
DEGRO 2009 (Souchon)	«Bei metastischem spinalen Kompressionssyndrom» Acute onset of paresis / paraplegia			
	• Surgical decompression followed by radiotherapy	n.a.	n.a.	[Galasko et al. 2000; Hoskin et al. 2003; Loblaw et al. 1998; Patchell et al. 2005; Prasad et al. 2005; Regine et al. 2003]
	• Radiotherapy when decompression is not possible	III		n.a.
DEGRO 2009 (Souchon)	«Bei metastischem spinalen Kompressionssyndrom» Inoperability • Radiotherapy; choice of fractionation depending on life expectancy	III	n.a.	n.a.
DEGRO 2009 (Souchon)	«Bei metastischem spinalen Kompressionssyndrom» After surgical decompression • Radiotherapy	IIb	A	[Helweg-Larsen et al. 2000; Poortmans et al. 2001; Rades et al. 2005; Rades et al. 2006; Regine et al. 2003]
DEGRO 2009 (Souchon)	«Bei metastischem spinalen Kompressionssyndrom» In case of (in-field) recurrence after previous radiotherapy • Surgery (when possible)	n.a.	n.a.	n.a.
	• Reirradiation (using high-precision techniques)	IV	0	[Rades et al. 2006; Rades et al. 2005; Letourneau et al. 2007; Milker-Zabel et al. 2003; Rades et al. 2007; Rades et al. 2005; Rades et al. 2007]

Leitlinie	Empfehlung	LoE[32]	GoR[1]	Referenzen
Fernmetastasen – spezifische Diagnostik und Therapie				
Diagnostik und Therapie von Hirnmetastasen und leptomningealer Karzinomatose				
NICE 2009 advanced	• Offer surgery followed by whole brain radiotherapy to patients who have a single or small number of potentially resectable brain metastases, a good performance status and who have no or well-controlled other metastatic disease. • Offer whole brain radiotherapy to patients for whom surgery is not appropriate, unless they have a very poor prognosis. • Offer active rehabilitation to patients who have surgery and/or whole brain radiotherapy. • Offer referral to specialist palliative care to patients for whom active treatment for brain metastases would be inappropriate. (Qualifying statement: These recommendations are based on evidence from retrospective case series.)	3		Surgery: [Wroski et al. 1997; Pieper et al. 1997] Radiosurgery: [Amendola et al. 2000; Combs et al. 2004; Lederman et al. 2001; Levin et al. 2002; Akyurek et al. 2007; Muacevic et al. 2004; Firlik et al. 2000] Chemotherapy: [Fizazi et al. 1996; Rudnicka et al. 2007; Rivera et al. 2006; Rosner et al. 1986; Boogerd et al. 1992; Franciosi et al. 1999; Lassman et al. 2006; Trudeau et al. 2006; Oberhoff et al. 2001] WBRT: [Bartsch et al. 2006; Fokstuen et al. 2000; Korzeniowski et al. 1987; Lentzsch et al. 1999; Liu et al. 2006; Ogura et al. 2003; Mahmoud-Ahmed et al. 2002; Viani et al. 2007; Johansen et al. 2008]
NICE 2009 advanced	«Research recommendation» • A randomised controlled trial is needed to compare stereotactic radiotherapy with whole brain radiotherapy in patients with advanced breast cancer and solitary or a limited number of brain metastases.	n.a.	n.a.	n.a.

Leitlinie	Empfehlung	LoE[32]	GoR[1]	Referenzen
Fernmetastasen – spezifische Diagnostik und Therapie				
DEGRO 2010 (Feyer)	If specific local treatment such as surgery or stereotactic radiotherapy is an option, MRI is superior to CT for delineation of metastases and detection of multiple lesions.	n.a.	n.a.	n.a.
DEGRO 2010 (Feyer)	Differential diagnosis of LC may be difficult [3, 4], as cerebrospinal fluid (CSF) cytology may be false-negative in up to 20% of the patients [13, 39]. Nevertheless, CSF examination remains the most useful test, and the presence of malignant cells is evidentiary of LC.	n.a.	n.a.	[Astner et al. 2007; Deutsche Gesellschaft für Neurologie (DGN) 2008; Chamberlain et al. 1997; Deutsche Gesellschaft für Neurologie et al. 2005]
DEGRO 2010 (Feyer)	MRI of the complete craniospinal axis with gadolinium enhancement is the imaging technique of choice and should be performed prior to lumbar puncture, as this procedure may induce contrast medium enhancement and thus may compromise imaging accuracy [39].	n.a.	n.a.	[Deutsche Gesellschaft für Neurologie et al. 2005]
DEGRO 2010 (Feyer)	Any treatment decision should be based on the predominant symptoms and the probability of extra-CNS tumor control.	n.a.	n.a.	n.a.
DEGRO 2010 (Feyer)	Treatment choice for BM is based on clinical symptoms and verification in diagnostic imaging. In asymptomatic patients, the decision depends on the individual situation: for patients in RPA class I, specific treatment is mandatory, whereas in patients with RPA class III, symptomatic therapy may be preferable.	n.a.	n.a.	n.a.
DEGRO 2010 (Feyer)	In case of a long recurrence-free interval and lack of extracerebral tumor spread, histological verification should be considered prior to treatment [66].	n.a.	n.a.	[Tsao et al. 2005]
DEGRO 2010 (Feyer)	Treatment of LC is preferentially multidisciplinary and mostly indicated when the diagnosis is unequivocal or symptoms are strongly suggestive in	n.a.	n.a.	n.a.

Leitlinie	Empfehlung	LoE[32]	GoR[1]	Referenzen
Fernmetastasen – spezifische Diagnostik und Therapie				
	case of negative cytology			
DEGRO 2010 (Feyer)	Systemic application of corticosteroids is the standard treatment for brain edema. The optimal dose has been investigated in patients with primary brain tumors [68 (LoE 1b)].	1b	n.a.	[Vecht et al. 1994]
DEGRO 2010 (Feyer)	With dexamethasone, symptoms of intracranial pressure are rapidly alleviated within 4–24 h. A dose of 4 mg is adequate to start with and may be increased according to remaining symptoms. Doses of 4, 8, or 16 mg showed equivalent effectiveness after 1 week of medication; however, side effects after 4 weeks were more pronounced with 16 mg. As symptoms may recur in case of rapid reduction, the dose should be reduced stepwise over a period of 4 weeks.	n.a.	n.a.	n.a.
DEGRO 2010 (Feyer)	Corticosteroids have a limited value in LC-related neurologic symptoms but can be useful to treat vasogenic edema associated with intraparenchymal or epidural metastases [13].	n.a.	n.a.	[Chamberlain 2008]
DEGRO 2010 (Feyer)	Prophylactic administration of anticonvulsant drugs is not recommended; when necessary, interactions with other drugs such as chemotherapeutic agents or steroids have to be taken into consideration and dose monitoring is mandatory. Regarding metabolic interactions, valproinate seems to be superior to other drugs when combined with chemotherapy [24].	n.a.	n.a.	[Glantz et al. 2000]
DEGRO 2010 (Feyer)	In patients with low performance status (KPS < 50%) for whom specific tumor treatment is not indicated and steroids are not effective, pain medication and sedative treatment should be administered as supportive care	n.a.	n.a.	n.a.

Leitlinie	Empfehlung	LoE[32]	GoR[1]	Referenzen
Fernmetastasen – spezifische Diagnostik und Therapie				
DEGRO 2010 (Feyer)	«Solitary Brain Metastasis» There are no randomized studies or data permitting a definite conclusion whether surgery and stereotactic radiotherapy are equally effective. Retrospective studies indicate that both treatments may achieve comparable results [45 (LoE 2b), 54]. Therefore, treatment decision should be made individually regarding anatomic localization and size of the lesion, amenability to surgery, acute clinical risk, and patients' preference.	2b n.a.	n.a.	[O'Neill et al. 2003] [Rades et al. 2009]
DEGRO 2010 (Feyer)	Factors in favor of primary surgery: • histological verification after a long recurrence-free interval; • need for immediate decompression in case of rapidly developing clinical deterioration or life-threatening symptoms; • tumor size > 3.5 cm and surgically favorable location; • surgery + WBRT + stereotactic radiosurgery boost [53].	n.a.	n.a.	[Rades et al. 2009]
DEGRO 2010 (Feyer)	Factors in favor of primary radiotherapy: • RPA class II; • no need for rapid decompression; • short recurrence-free interval; • no need for histological verification due to unambiguous medical history (e.g., additional metastatic spread); • high risk of surgery; • tumor location poorly amenable to surgery	n.a.	n.a.	n.a.

Leitlinie	Empfehlung	LoE[32]	GoR[1]	Referenzen
Fernmetastasen – spezifische Diagnostik und Therapie				
DEGRO 2010 (Feyer)	«Solitary Brain Metastasis» WBRT following surgery [41], stereotactic radiotherapy or radiosurgery [56] may improve outcome of patients with a single BM who have favorable prognostic factors and a KPS of at least 70% without extracranial tumor spread (RPA class I) or patients with RPA class II and metastases limited to the skeletal system (Figure 1). Survival free of recurring BM [1 (LoE 2b), 47 (LoE 1b), 49 (LoE 1b) 50 (LoE 1b), 67 (LoE 1b)], as well as overall survival are more favourable in this subgroup [1 (LoE 2b), 47 (LoE 1b), 50 (LoE 1b), 67 (LoE 1b)]. For patients with RPA class III, radiotherapy should be restricted to WBRT.	1b	n.a.	[Noordijk et al. 1994; Patchell et al. 1998; Patchell et al. 1990; Vecht et al. 1993]
		2b		[Andrews et al. 2004]1
		n.a.		[Mintz et al. 1996; Sanghavi et al. 2001]
DEGRO 2010 (Feyer)	«Two or Three Brain Metastases» Resection or stereotactic radiotherapy may be considered [1 (LoE 2b), 35 (LoE 1b)], additional WBRT further improves local tumor control [52] (Figure 1).	1b	n.a.	[Kondziolka et al. 1999]
		2b		[Andrews et al. 2004]
		n.a.		[Rades et al. 2008]
DEGRO 2010 (Feyer)	«Whole-Brain Radiotherapy of More Than Three Brain Metastases» WBRT is the standard treatment (Figure 1). Several RTOG studies investigated different fractionation schedules [10 (LoE 1b), 11 (LoE 1b), 23 (LoE 1b), 37 (LoE 1b), 43] and found a median survival time of 3–6 months irrespective of fractionation. Remission rates and duration of response were comparable between subgroups treated with regimens of 50 Gy/4 w, 40 Gy/3 w, 40 Gy/4 w, 30 Gy/2 w, 30 Gy/3 w, 20 Gy/1 w.	1b	n.a.	[Borgelt et al. 1980; Borgelt et al. 1981; Gelber et al. 1981; Kurtz et al. 1981]
		n.a.		[Murray et al. 1997]
DEGRO 2010 (Feyer)	«Systemic Treatment Option» The role of chemotherapy for BM remains limited.	n.a.	n.a.	n.a.

Leitlinie	Empfehlung	LoE[32]	GoR[1]	Referenzen
Fernmetastasen – spezifische Diagnostik und Therapie				
DEGRO 2010 (Feyer)	«Whole-Brain Radiotherapy of More Than Three Brain Metastases» More hypofractionated regimens like 1 × 10 Gy or 2 × 6 Gy rapidly alleviate symptoms. However, the duration of this effect is short; therefore, these regimens are not recommended.	n.a.	n.a.	n.a.
DEGRO 2010 (Feyer)	«Treatment of Recurrent Brain Metastases» No standard treatment has been established for patients with recurring BM after radiotherapy. Reexcision, radiosurgery [33], or reirradiation of the whole brain may be considered individually as well as systemic treatment options [40]. Retreatment seems reasonable only in cases with a progression-free interval of at least 4 months after initial treatment. The neurologic symptoms, KPS, extracranial tumor control, and the patient's desire are relevant criteria for the treatment decision [72 (LoE 4)].	4 n.a.	n.a.	[Wong et al. 1996] [Jereczek-Fossa et al. 2008; Lin et al. 2009]
DEGRO 2010 (Feyer)	«Radiotherapy and Chemotherapy in Leptomeningeal Carcinomatosis» According to the sparse data, both treatment modalities are effective in LC. Their sequence is determined according to the predominant clinical symptoms. Chemotherapy after irradiation bears an increased risk of leukoencephalopathy [30].	n.a.	n.a.	[Herrlinger et al. 2004]
DEGRO 2010 (Feyer)	«Radiotherapy and Chemotherapy in Leptomeningeal Carcinomatosis» Radiotherapy is an effective palliative treatment for LC [16]. As tumor dissemination affects the whole CSF compartment, basically the complete craniospinal axis should be regarded as target volume. Favorable results have been reported in small series [29]. However, craniospinal irradiation is generally not recommended, as it is assumed to cause substantial myelotoxicity. Instead, besides WBRT, involved-field radiotherapy of bulky disease or symptomatic regions is mostly recommended [18, 27, 39,	n.a.	n.a.	[Chang et al. 2003; Hermann et al. 2001; DeAngelis et al. 2005; Grossman et al. 1999; Deutsche Gesellschaft für Neurologie et al. 2005; National Comprehensive Cancer Network (NCCN) 2008]

Leitlinie	Empfehlung	LoE[32]	GoR[1]	Referenzen
Fernmetastasen – spezifische Diagnostik und Therapie				
	44]. Nevertheless, in defined cases such as multiple circumscript plaques or nodules, radiotherapy of the neuroaxis should be considered.			
DEGRO 2010 (Feyer)	«Radiotherapy and Chemotherapy in Leptomeningeal Carcinomatosis» Chemotherapy may be administered systemically or intrathecally. For intrathecal injection, methotrexate, thiotepa and cytarabine are most commonly applied [15]. Catheters or a ventricular reservoir are used for administration to avoid repeated punctures [13, 34]. Recently, two randomized trials using a liposomal formulation of cytarabine with sustained release had shown promising results in several tumor entities [17, 26]. A subgroup analysis of one of these studies, comprising breast cancer patients only, yielded a median survival of 88 days and a 1-year survival rate of 19%.	n.a.	n.a.	[Chamberlain 2008; Chamberlain et al. 1997; Kim et al. 2001; Cole et al. 2003; Glantz et al. 1999]
DEGRO 2010 (Feyer)	«Radiotherapy and Chemotherapy in Leptomeningeal Carcinomatosis» Intrathecal chemotherapy is effective for diffuse meningeal spread, however, may be ineffective in bulky disease, as drug permeation does not exceed 2–3 mm [12]. This is reflected by the data of the only randomized trial that addressed exclusively breast cancer patients treated for LC. Effectiveness of intrathecal versus systemic treatment was analyzed and no advantage was found for the more invasive method, leading to the conclusion that systemic chemotherapy and irradiation should be preferred because of their lower toxicity [9]. Several other studies confirm the effectiveness of systemic chemotherapy in the treatment of LC [6, 25, 30]. Case studies reported remissions of LC after oral chemotherapy with capecitabine [55] and endocrine treatment [7].	n.a.	n.a.	[Bokstein et al. 1998; Boogerd et al. 2000; Boogerd et al. 2004; Chamberlain 2005; Glantz et al. 1998; Rogers et al. 2004; Herrlinger et al. 2004]
DEGRO 2010 (Feyer)	«Radiotherapy – Technique and Dose: WBRT» In case of leptomeningeal manifestation and infratentorial metastases, the treatment volume should include the spinal cord down to the caudal margin	n.a.	n.a.	[Soffietti et al. 2006; DeAngelis et al. 1989]

Leitlinie	Empfehlung	LoE[32]	GoR[1]	Referenzen
Fernmetastasen – spezifische Diagnostik und Therapie				
	of the second vertebral body. For LC, it is important to cover the meningeal space including the lamina cribrosa and basal cisterns. Three-dimensional planning is useful for optimizing dose distribution. A total dose of 30 Gy in daily fractional doses of 3 Gy and five fractions per week is most commonly used. In patients with a predicted survival exceeding 12 months, reduction of the single fraction to 2 Gy may be preferable (20x2 Gy) [62] in order to reduce brain toxicity [19]. In cases of a more limited prognosis, acceleration of treatment time and single dose may be an alternative (5x4 Gy). These recommendations apply to both, BM and LC.			
DEGRO 2010 (Feyer)	«Radiotherapy – Technique and Dose: LC with spinal manifestations» LC with spinal manifestations: the clinical target volume encompasses the gross tumor volume with a safety margin which is matched to the individual clinical requirements. Dose recommendations are as described above.	n.a.	n.a.	n.a.
DEGRO 2010 (Feyer)	«Radiotherapy – Technique and Dose: Stereotactic radiosurgery» Stereotactic radiosurgery: for stereotactic irradiation, the gross tumor volume in MRI is regarded as clinical target volume, an additional safety margin of 1–2 mm for the planning target volume is recommended, depending on reproducibility and immobilization technique. Single-dose treatment is suitable for lesions up to 3.5 cm in size. A tumor-encompassing dose of 20–25 Gy (80–90% isodose) is recommended, provided no WBRT has recently preceded or is planned consecutively. For tumors with a volume > 4 ml (i.e., diameter > 2 cm), the reference dose should not exceed 18 Gy. When combined with WBRT, the radiosurgical dose should be restricted to 18 Gy and in larger tumors to 15 Gy. Dose prescription refers to the 80–90% isodoses.	n.a.	n.a.	n.a.
DEGRO 2010	«Radiotherapy – Technique and Dose: Fractionated stereotactic	n.a.	n.a.	[International Commission on Radiation

Leitlinie	Empfehlung	LoE[32]	GoR[1]	Referenzen
Fernmetastasen – spezifische Diagnostik und Therapie				
(Feyer)	radiotherapy» Fractionated stereotactic radiotherapy is feasible for tumors > 2 cm and lesions in critical anatomic sites such as the cerebellum with increased risk of incarceration. Moreover, fractionation is preferable for metastases of the brain stem to avoid late reactions with dismal outcome. Depending on the treatment volume, fractionation schedules of 4x8.7 Gy, 5x7 Gy, 6x5 Gy, or 10x4 Gy are in use. In case of additional WBRT, 6x5 Gy are recommended. Dose specification refers to ICRU report 50 [32].			Units and Measurements (ICRU) 1993]

Abkürzungen: MRI = magnetic resonance imaging; CT = computed tomography; Gy = gray (unit); CNS = central nervous system; RPA-class = recursive partitioning analysis class; BM = bone metastases; LC = lung cancer; n.a. = nicht angegeben; KPS = Karnofsky performance status; WBRT = whole brain radiation therapy; CSF = Cerebrospinal fluid; ICRU = International Commission on Radiation Units and Measurements; NHS = national health service; GDG = guideline development group

4.2.15 Empfehlungen zum Thema Psychosoziale Aspekte

4.2.15.1 Eingeschlossene Leitlinien

Zum Thema psychosoziale Aspekte konnten drei Leitlinien der Gruppe 1 extrahiert werden [New Zealand Guidelines Group (NZGG) 2009; National Institute for Clinical Excellence (NICE) 2009; National Institute for Clinical Excellence (NICE) 2009].

Zwei Leitlinien wurden vom National Institute for Health and Clinical Excellence (NICE) aus Großbritannien in 2009 herausgegeben und adressieren umfassend die Therapie der Primärerkrankung einschließlich lokal fortgeschrittener Tumore und die Therapie des fortgeschrittenen Mammakarzinoms. Für die Extraktion dieser Leitlinien (insbesondere der Evidenzklassifikationen [LoE]) wurden zusätzliche Hintergrund- bzw. Methodendokumente ausgewertet [National Institute for Clinical Excellence (NICE) 2009; National Institute for Clinical Excellence (NICE) 2009]. Zu den Empfehlungen haben die Autoren der NICE-Leitlinien sogenannte ‚Qualifying Statements' angeführt. Diese beschreiben zusammenfassend die zugrundeliegende Evidenz der Empfehlungen. Die ‚Qualifying Statements' wurden mit den Empfehlungen extrahiert, um als Ergänzung zu den berücksichtigten Referenzen auch die entsprechenden zusammenfassenden Einschätzungen der Autoren wiederzugeben. Die Leitlinien von NICE enthalten außerdem Empfehlungen für die weitere Erforschung bestimmter Aspekte (Research Recommendations). Diese Empfehlungen wurden extrahiert und entsprechend gekennzeichnet.

Eine Leitlinie wurde von der New Zealand Guidelines Group (NZGG) in 2009 herausgegeben. Diese Leitlinie adressiert umfassend die Therapie der Primärerkrankung. Für die Extraktion dieser Leitlinie wurden keine weiteren Dokumente ausgewertet.

4.2.15.2 In der S3-Leitlinie Mammakarzinom 2008 nicht enthaltene oder diskrepante Empfehlungs-Inhalte

Im Gegensatz zur S3-Leitlinie Mammakarzinom 2008, die keine spezifischen Indikationen für bestimmte therapeutische Verfahren empfiehlt, wird in der NZGG bei PatientInnen mit Vorliegen einer **Angststörung oder Depression eine kognitive Verhaltenstherapie** empfohlen (LoE ++ bis n.a., GoR A). Die NZGG empfiehlt **psychologische Unterstützung auch für Partner und Kinder** und macht auf die **speziellen Bedürfnisse von an Brustkrebs erkankten Männern** aufmerksam („good practice point"). Diese Aspekte werden in der S3-Leitlinie Mammakarzinom 2008 nicht thematisiert.

Tabelle 17: Psychosoziale Aspekte

Leitlinie	Empfehlung	LoE[33]	GoR[1]	Referenzen
Psychosoziale Aspekte				
NICE 2009 early	▪ All members of the breast cancer clinical team should have completed an accredited communication skills training programme. ▪ All patients with breast cancer should be assigned to a named breast care nurse specialist who will support them throughout diagnosis, treatment and follow-up. ▪ All patients with breast cancer should be offered prompt access to specialist psychological support, and, where appropriate, psychiatric services.	1+	n.a.	[Tatrow et al. 2006; Mutrie et al. 2007; Samarel et al. 2002; Gotay et al. 2007; McArdle et al. 1996; Sandgren et al. 2007]
		1	n.a.	[Bantum 2007]
		1-		[Zimmermann et al. 2007; Allard 2007; Allen et al. 2002; Andersen et al. 2004; Antoni et al. 2006; Badger et al. 2007; Burton et al. 1995; Cohen et al. 2007; Dey et al. 2002; Ritz et al. 2000; Sandgren et al. 2003; Stanton et al. 2005]
		2++	n.a.	[Ambler et al. 1999]
		2		[Manne et al. 2007; Classen et al. 2008; Vos et al. 2007; Meneses et al. 2007; Mock et al. 1997]

[33] Für Erläuterungen des Level of Evidence (LoE) und Grade of Recommendation (GoR) siehe Anhang 5.6.

Leitlinie	Empfehlung	LoE[33]	GoR[1]	Referenzen
Psychosoziale Aspekte				
NICE 2009 early	«Research recommendation» ▪ What is the effectiveness of cognitive behavioural therapy compared with other psychological interventions for breast cancer patients?	n.a.	n.a.	n.a.
NICE 2009 advanced	▪ Healthcare professionals involved in the care of patients with advanced breast cancer should ensure that the organisation and provision of supportive care services comply with the recommendations made in 'Improving outcomes in breast cancer: manual update' (NICE cancer service guidance [2002]) and 'Improving supportive and palliative care for adults with cancer' (NICE cancer service guidance [2004]), in particular the following two recommendations: o 'Assessment and discussion of patients' needs for physical, psychological, social, spiritual and financial support should be undertaken at key points (such as diagnosis at commencement, during, and at the end of treatment; at relapse; and when death is approaching).' o 'Mechanisms should be developed to promote continuity of care, which might include the nomination of a person to take on the role of "key worker" for individual patients.' (Qualifying statement: This recommendation is based on anecdotal evidence and experience of GDG members that previous NICE guidance has not been fully implemented and GDG consensus that implementation would improve patients' experience.)	n.a.	n.a.	[National Institute for Clinical Excellence (NICE) 2002; National Institute for Clinical Excellence (NICE) 2004]

Leitlinie	Empfehlung	LoE[33]	GoR[1]	Referenzen
Psychosoziale Aspekte				
NICE 2009 advanced	«Research recommendation» ▪ Research is needed to identify the support needs specific to advanced breast cancer patients who are themselves carers. This research should identify which of these needs are currently met and where additional support resources are required.	n.a.	n.a.	n.a.
NZGG 2009	Psychosocial support should be available to all women with early breast cancer	++	A	[Osborn et al. 2006]
		+		[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Christiaens et al. 2007; Bantum 2007; Chow et al. 2004; Smedslund et al. 2004]
		n.a.		[National Breast Cancer Centre (NBCC) 2003; National Breast Cancer Centre (NBCC) 2001]
NZGG 2009	Cognitive behavioural therapy should be available for women with early breast cancer experiencing an anxiety disorder or depression	++	A	[Osborn et al. 2006]
		n.a.		[Armstrong et al. 1996]
NZGG 2009	Psychosocial support should be available for partners/spouses/children of those with early breast cancer	n.a.	GPP	n.a.
NZGG 2009	Supportive care and psychological therapy offered should reflect the needs of the individual and their social context	n.a.	GPP	n.a.

Leitlinie	Empfehlung	LoE[33]	GoR[1]	Referenzen
Psychosoziale Aspekte				
NZGG 2009	Men diagnosed with breast cancer have particular psychological issues and needs that should be considered	n.a.	GPP	n.a.
Abkürzungen: GDG = guideline development group; n.a. = nicht angegeben				

4.2.16 Empfehlungen zum Thema Supportivtherapie

4.2.16.1 Eingeschlossene Leitlinien

Zum Thema Supportivtherapie konnte eine Leitlinie der Gruppe 1 extrahiert werden [National Institute for Clinical Excellence (NICE) 2009]. Weitere Leitlinien mit spezifischen Empfehlungen zu diesem Thema konnten nicht identifiziert werden. Die extrahierte Leitlinie wurde vom National Institute for Health and Clinical Excellence (NICE) aus Großbritannien in 2009 herausgegeben und adressiert umfassend die Therapie des fortgeschrittenen Mammakarzinoms. Für die Extraktion dieser Leitlinie (insbesondere der Evidenzklassifikationen [LoE]) wurde ein Hintergrund- bzw. Methodendokument ausgewertet [National Institute for Clinical Excellence (NICE) 2009]. Zu den Empfehlungen haben die Autoren der NICE-Leitlinien sogenannte ‚Qualifying Statements' angeführt. Diese beschreiben zusammenfassend die zugrundeliegende Evidenz der Empfehlungen. Die ‚Qualifying Statements' wurden mit den Empfehlungen extrahiert, um als Ergänzung zu den berücksichtigten Referenzen auch die entsprechenden zusammenfassenden Einschätzungen der Autoren wiederzugeben. Die Leitlinien von NICE enthalten außerdem Empfehlungen für die weitere Erforschung bestimmter Aspekte (Research Recommendations). Diese Empfehlungen wurden extrahiert und entsprechend gekennzeichnet.

4.2.16.2 In der S3-Leitlinie Mammakarzinom 2008 nicht enthaltene oder diskrepante Empfehlungs-Inhalte

Die NICE 2009 advanced enthält Empfehlungen zur **Behandlung des Lymphödems bei metastasiertem Brustkrebs** (LoE 1+ bis 3, GoR n.a.) Diese wird im Rahmen der Supportivtherapie in der S3-Leitlinie Mammakarzinom nicht thematisiert. Weiterhin enthält die NICE 2009 advanced Empfehlungen zum Thema **Fatigue,** die spezifischer sind als die in der S3-Leitlinie Mammakarzinom 2008 (unter D5.4 – Diagnostik und Therapie von Neben- und Folgewirkungen der Primär- und Langzeittherapien) getroffenen Aussagen.

Eine Empfehlung zum Vorhalten und zum Einsatz von **„Supportive Care Teams"** bezieht sich auf den Kontext in Großbritannien. „Supportive Care Teams" sind nicht Gegenstand der S3-Leitlinie Mammakarzinom 2008.

Spezifische Empfehlungen zur Behandlung des chemotherapieinduzierten Erbrechens, der Neutropenie oder der Anämie wurden nicht identifiziert.

Tabelle 18: Supportivtherapie

Leitlinie	Empfehlung	LoE[34]	GoR[1]	Referenzen
Supportivtherapie				
Lymphödem bei fortgeschrittenem Brustkrebs				
NICE 2009 advanced	▪ Assess patients with lymphoedema for treatable underlying factors before starting any lymphoedema management programme. ▪ Offer all patients with lymphoedema complex decongestive therapy (CDT) as the first stage of lymphoedema management. ▪ Consider using multi-layer lymphoedema bandaging (MLLB) for volume reduction as a first treatment option before compression hosiery. ▪ Provide patients with lymphoedema with at least two suitable compressiongarments. These should be of the appropriate class and size, and a choice of fabrics and colours should be available. ▪ Provide patients with lymphoedema with clear, written information and the contact details of local and national lymphoedema support groups. (Qualifying statement: These recommendations are based on GDG consensus in the absence of evidence specific to patients with advanced breast cancer. The GDG felt it was appropriate to extrapolate from evidence about physical therapies in patients with early breast cancer to patients with advanced breast cancer with lymphoedema in the absence of locoregional disease.)	1+	n.a.	[Moseley et al. 2007]
		1-		[Sitzia et al. 2002; Didem et al. 2005; Irdesel et al. 2007; Kligman et al. 2004]
		2+		[Vignes et al. 2007]
		2-		[Johansson et al. 2005]
		3		[Fiaschi et al. 1998; Hamner et al. 2007; Kim et al. 2007; Koul et al. 2007]
		4		[Harris et al. 2001; Rinehart-Ayres et al. 2007]
		n.a.		[Badger et al. 2004]

[34] Für Erläuterungen des Level of Evidence (LoE) und Grade of Recommendation (GoR) siehe Anhang 5.6.

Leitlinie	Empfehlung	LoE[34]	GoR[1]	Referenzen
Supportivtherapie				
NICE 2009 advanced	«Research recommendation» • Research is needed to compare the effectiveness of complex decongestive therapy with less intensive interventions in patients with advanced breast cancer. The research should incorporate both objective and quality of life measures.	n.a.	n.a.	n.a.
Fatigue bei fortgeschrittenem Brustkrebs				
NICE 2009 advanced	▪ Offer all patients with advanced breast cancer for whom cancer-related fatigue is a significant problem an assessment to identify any treatable causative factors and offer appropriate management as necessary. ▪ Provide clear, written information about cancer-related fatigue, organisations that offer psychosocial support and patient-led groups. (Qualifying statement: These recommendations are based on GDG consensus and very poor quality evidence.)	1 1- 3	n.a.	[Minton et al. 2007] [Bordeleau et al. 2003] [Carson et al. 2007]
NICE 2009 advanced	▪ Provide information about and timely access to an exercise programme for all patients with advanced breast cancer experiencing cancer-related fatigue. (Qualifying statement: This recommendation is based on a high-quality systematic review and meta-analysis and GDG consensus that this intervention will be of significant benefit to patients.)	1+ 1-	n.a.	[Cramp et al. 2008] [Headley et al. 2004]
NICE 2009 advanced	«Research recommendations» • Randomised controlled trials are needed to assess the value of psychological interventions in the management of fatigue in patients with advanced breast cancer. Both shortand long-term	n.a.	n.a.	n.a.

Leitlinie	Empfehlung	LoE[34]	GoR[1]	Referenzen
Supportivtherapie				
	outcomes should be evaluated. An appropriate validated tool to measure fatigue should be used. • Further research is required into which excercise programmes are most effective for patients with advanced breast cancer and to identify the most efficient way to deliver these in an NHS service.			
NICE 2009 advanced	▪ Healthcare professionals involved in the care of patients with advanced breast cancer should ensure that the organisation and provision of supportive care services comply with the recommendations made in 'Improving outcomes in breast cancer: manual update' (NICE cancer service guidance [2002]) and 'Improving supportive and palliative care for adults with cancer' (NICE cancer service guidance [2004]), in particular the following two recommendations: o 'Assessment and discussion of patients' needs for physical, psychological, social, spiritual and financial support should be undertaken at key points (such as diagnosis at commencement, during, and at the end of treatment; at relapse; and when death is approaching).' o 'Mechanisms should be developed to promote continuity of care, which might include the nomination of a person to take on the role of "key worker" for individual patients.' (Qualifying statement: This recommendation is based on anecdotal evidence and experience of GDG members that previous NICE guidance has not been fully implemented and GDG consensus that implementation would improve patients' experience.)	n.a.	n.a.	[National Institute for Clinical Excellence (NICE) 2002; National Institute for Clinical Excellence (NICE) 2004]

Leitlinie	Empfehlung	LoE[34]	GoR[1]		Referenzen
Supportivtherapie					
NICE 2009 advanced	«Research recommendation ▪ Research is needed to identify the support needs specific to advanced breast cancer patients who are themselves carers. This research should identify which of these needs are currently met and where additional support resources are required.	n.a.	n.a.	n.a.	
Abkürzungen: GDG = guideline development group´; n.a. = nicht angegeben					

4.2.17 Empfehlungen zum Thema Rehabilitation

4.2.17.1 Eingeschlossene Leitlinien

Zum Thema Rehabilitation wurde eine Leitlinie (der Gruppe 1) identifiziert [Deutsche Rentenversicherung (DRV-Bund) 2009]. Die extrahierte Leitlinie wurde 2009 von der deutschen Rentenversicherung herausgegeben. In der Leitlinie werden Standards für eine Rehabilitationsmaßnahme bei Brustkrebs empfohlen. Für die Extraktion dieser Leitlinie (insbesondere der Evidenzklassifikationen [LoE]) wurde ein Hintergrund- bzw. Methodendokument ausgewertet [Deutsche Rentenversicherung (DRV-Bund) 2008]. Die in der Synopse aufgeführten Level of Evidence (LoE) sind ausschließlich dem Leitlinien-Report entnommen. Angaben zur studienübergreifende Einstufung der Evidenz aus den Hintergrundtexten der Leitlinien wurden nicht aufgenommen, weil sie die heterogene Qualität der eingeschlossenen Studien nicht abbilden.

4.2.17.2 In der S3-Leitlinie Mammakarzinom 2008 nicht enthaltene oder diskrepante Empfehlungs-Inhalte

Die DRV-Bund 2009 Leitlinie enthält im Vergleich zur S3-Leitlinie Mammakarzinom zahlreiche **spezifischere Empfehlungen zu Aktivitäten und Schulungsmaßnahmen der Rehabilitation einschließlich ihrer wöchentlich vorgesehenen Dauer.**

Tabelle 19: Rehabilitation

Leitlinie	Empfehlung	LoE[35]	GoR[1]	Referenzen
Rehabilitation				
DRV-Bund 2009	ETM 1: Bewegungstherapie Mind. Anteil Rehabilitanden:75 % Dauer pro Woche: mind. 240 Minuten Häuf. pro Woche: mind. 5 mal	I	n.a.	[Courneya 2003; Stricker et al. 2004]
		II		[Friendenreich et al. 1996; Oldervoll et al. 2004; Pinto et al. 1999; Chlebowski et al. 2002; Box et al. 2002; Wingate et

[35] Für Erläuterungen des Level of Evidence (LoE) und Grade of Recommendation (GoR) siehe Anhang 5.6.

Leitlinie	Empfehlung	LoE[35]	GoR[1]	Referenzen
Rehabilitation				
				al. 1989]
		n.a.		[Segal et al. 2001; Turner et al. 2004; Ebert et al. 2002; Schule 1983]
DRV-Bund 2009	ETM 2: Lymphödemtherapie Mind. Anteil Rehabilitanden: 10 % Dauer pro Woche: mind. 60 Minuten Häuf. pro Woche: mind. 2 mal	II	n.a.	[Box et al. 2002]
		III		[Andersen et al. 2000]
		IV		[Badger et al. 2004; Harris et al. 2001; Johansson et al. 1998; McKenzie et al. 2003; McNeely et al. 2004]
		n.a.		[McKenzie et al. 2003; Szuba et al. 2002; Williams et al. 2002]
DRV-Bund 2009	ETM 3: Patientenschulung Brustkrebs Mind. Anteil Rehabilitanden:80 % Dauer pro Rehabilitation: mind. 180 Minuten	II	n.a.	[Box et al. 2002]
		III		[Andersen et al. 2000]
		IV		[McNeely et al. 2004]
		n.a.		[Watson et al. 1988; Goodwin et al. 2003]
DRV-Bund 2009	ETM 4: Gesundheitsbildung Mind. Anteil Rehabilitanden: 90 % Dauer pro Rehabilitation: mind. 60 Minuten	n.a.	n.a.	[Goodwin et al. 2003; Maunsell et al. 1996; McArdle et al. 1996; Rustoen et

Leitlinie	Empfehlung	LoE[35]	GoR[1]	Referenzen
Rehabilitation				
				al. 2000]
DRV-Bund 2009	ETM 5: Ernährungsschulung – theoretisch Mind. Anteil Rehabilitanden: 75 % Dauer pro Rehabilitation: mind. 45 Minuten	II	n.a.	[Chlebowski et al. 1993; Chlebowski et al. 2002; Djuric et al. 2002; Hebert et al. 2001; Nordevang et al. 1992; Pierce et al. 1997; Rock et al. 2001; Rose et al. 1993; de Waard et al. 1993]
		n.a.		[Rock et al. 2002; Brown et al. 2003]
DRV-Bund 2009	ETM 6: Ernährungsschulung – praktisch Mind. Anteil Rehabilitanden: 10 % Dauer pro Rehabilitation: mind. 180 Minuten	II	n.a.	[Chlebowski et al. 1993; Chlebowski et al. 2002; Djuric et al. 2002; Hebert et al. 2001; Nordevang et al. 1992; Pierce et al. 1997; Rock et al. 2001; Rose et al. 1993; de Waard et al. 1993]
		n.a.		[Rock et al. 2002; Brown et al. 2003]
DRV-Bund 2009	ETM 7: Psychologische Beratung und Therapie Mind. Anteil Rehabilitanden: 40 % Dauer pro Rehabilitation: mind. 180 Minuten	I	n.a.	[Burke et al. 1998; Devine et al. 1995; Edwards et al. 2004; Fawzy et al. 1995; Kissane et al. 1998; Meyer et al. 1995; Rehse et al. 2003; Sellick et al. 1999; Sheard et al. 1999]
		n.a.		[National Health and Medical Research Council (NHMRC) 2003; Kreienberg 2004; Spiegel et al. 1989; Chow et al. 2004; Bourbonniere et al. 2004; Edgar et al. 1992; Zibecchi et al. 2003; Allen

Leitlinie	Empfehlung	LoE[35]	GoR[1]	Referenzen
Rehabilitation				
				et al. 2002; Badger et al. 2001; Arathuzik 1994; Maunsell et al. 1996; McArdle et al. 1996; Watson et al. 1988; Wengstrom et al. 2001]
DRV-Bund 2009	ETM 8: Entspannungstraining Mind. Anteil Rehabilitanden: 40 % Dauer pro Rehabilitation: mind. 180 Minuten Häuf. pro Rehabilitation: mind. 4 mal	I	n.a.	[Luebbert et al. 2001; Devine 2003; Van Kuiken 2004]
		III		[Walker et al. 1999]
		n.a.		[Arathuzik 1994] Zu folgenden Zitaten im Text wurden keine bibliographischen Angaben im Leitlinien-Report identifiziert: Bridge et al. 1988, Gruber et. al. 1993, Kolcaba & Fox 1999, Richardson et a. 1997
DRV-Bund 2009	ETM 9: Künstlerische Therapien Mind. Anteil Rehabilitanden: 15 % Dauer pro Rehabilitation: mind. 270 Minuten	I	n.a.	[Devine et al. 1995]
		III		[Dibbel-Hope 2000; Haun et al. 2001; Reinhardt 1999; Stanton et al. 2002; Walker et al. 1999]
		IV		[Sandel 2004]
		V		[Hampe 1997]
		n.a.		[Burns 2001; Dreifuss 1981; Kreienberg 2004; Serlin 2000; Solheim 2002;

Leitlinie	Empfehlung	LoE[35]	GoR[1]	Referenzen
Rehabilitation				
				Solheim 2004; Specht 1992; National Health and Medical Research Council (NHMRC) 2003]
DRV-Bund 2009	ETM 10: Ergotherapie Mind. Anteil Rehabilitanden: 30 % Dauer pro Rehabilitation: mind. 150 Minuten	n.a.	n.a.	n.a.
DRV-Bund 2009	ETM 11: Sozial- und Sozialrechtliche Beratung Mind. Anteil Rehabilitanden: 50 % Dauer pro Rehabilitation: mind. 30 Minuten	n.a.	n.a.	[Goodwin et al. 2003; Ritz et al. 2000; Watson et al. 1988]
DRV-Bund 2009	ETM 12: Unterstützung der beruflichen Integration Mind. Anteil Rehabilitanden.: 20 % Dauer pro Rehabilitation: mind. 30 Minuten	n.a.	n.a.	n.a.
DRV-Bund 2009	ETM 13: Nachsorge und soziale Integration Mind. Anteil Rehabilitanden: 50 % Dauer pro Rehabilitation: mind. 15 Minuten	n.a.	n.a.	n.a.
Abkürzungen: ETM = Evidenzbasiertes Therapiemodul; n.a. = nicht angegeben				

4.2.18 Empfehlungen zum Thema Nachsorge

4.2.18.1 Eingeschlossene Leitlinien

Zum Thema Nachsorge konnten 3 Leitlinien der Gruppe 1 extrahiert werden [National Institute for Clinical Excellence (NICE) 2009; National Institute for Clinical Excellence (NICE) 2009; New Zealand Guidelines Group (NZGG) 2009; National Breast and Ovarian Cancer Centre (NBOCC) 2010].

Eine Leitlinie wurden vom National Institute for Health and Clinical Excellence (NICE) aus Großbritannien in 2009 herausgegeben und adressiert die Diagnostik und Therapie der Primärerkrankung einschließlich lokal fortgeschrittener Tumore. Für die Extraktion dieser Leitlinie (insbesondere der Evidenzklassifikationen [LoE]) wurden zusätzliche Hintergrund- bzw. Methodendokumente ausgewertet [National Institute for Clinical Excellence (NICE) 2009; National Institute for Clinical Excellence (NICE) 2009]. Zu den Empfehlungen haben die Autoren der NICE-Leitlinien sogenannte ‚Qualifying Statements' angeführt. Diese beschreiben zusammenfassend die zugrundeliegende Evidenz der Empfehlungen. Die ‚Qualifying Statements' wurden mit den Empfehlungen extrahiert, um als Ergänzung zu den berücksichtigten Referenzen auch die entsprechenden zusammenfassenden Einschätzungen der Autoren wiederzugeben. Die Leitlinien von NICE enthalten außerdem Empfehlungen für die weitere Erforschung bestimmter Aspekte (Research Recommendations). Diese Empfehlungen wurden extrahiert und entsprechend gekennzeichnet.

Eine extrahierte Leitlinie wurde vom National Breast and Ovarian Cancer Centre (NBOCC) aus Australien in 2010 herausgegeben. Diese Leitlinie gibt Empfehlungen zur Nachsorge bei primärem Mammakarzinom. Für die Extraktion dieser Leitlinie wurde kein weiteres Dokument ausgewertet. Die Leitlinie des NBOCC enthält Statements, in denen evidenzbasierte Aussagen zusammengefasst werden und Empfehlungen, die eine Handlungsanweisung enthalten. Sowohl Statements als auch die Empfehlungen wurden für die Synopse extrahiert.

Eine Leitlinie wurde von der New Zealand Guidelines Group (NZGG) in 2009 herausgegeben. Diese Leitlinie adressiert umfassend die Diagnsotik und Therapie der Primärerkrankung. Für die Extraktion dieser Leitlinie wurden keine weiteren Dokumente ausgewertet.

4.2.18.2 In der S3-Leitlinie Mammakarzinom nicht enthaltene oder diskrepante Empfehlungs-Inhalte

In der NBOCC 2010 wird ausgeführt, dass **asymptomatisch entdeckte Rezidive eine bessere Prognose** (in Bezug auf das Gesamtüberleben) haben als symptomatische entdeckte, diese Information ist in der S3-Leitlinie Mammakarzinom 2008 im Kapitel Nachsorge nicht enthalten.

Die **Mammographie** wird in der NBOCC 2010 und in der NICE 2009 early grundsätzlich **jährlich** empfohlen, in der S3-Leitlinie Mammakarzinom 2008 dagegen in den ersten 3 Jahren ipsilateral halbjährlich.

Die NBOCC 2010 empfiehlt im Gegensatz zur S3-Leitlinie Mammakarzinom 2008 das **Durchführen einer Mammasonographie** in der Nachsorge nur bei begründeter Indikationsstellung (LoE IV).

Die NBOCC enthält weiterhin eine Reihe von Evidenzstatements und Empfehlungen zu **Umfang, Art der Durchführung und Dauer der Nachsorge**, die im Vergleich zur S3-Leitlinie Mammakarzinom spezifischer sind. Mit einem Evidenzgrad von II wird beispielsweise angemerkt, dass die Profession des nachsorgenden Betreuers das Überleben der Patienten nicht beeinflusst. Dies wird in der S3-Leitlinie Mammakarzinom 2008 nicht thematisiert.

Tabelle 20: Nachsorge

Leitlinie	Empfehlung	LoE[36]	GoR[1]	Referenzen
Nachsorge				
NBOCC 2010	Statement: Breast cancer recurrence or new primary or contralateral breast cancers may be self-detected or detected by breast imaging or clinical examination	n.a.	n.a.	[Montgomery et al. 2007; de Bock et al. 2004]
NBOCC 2010	Statement: Some recurrences are detected at routine appointments while others are detected when patients present with symptoms between appointments	IV	n.a.	[de Bock et al. 2004; Donnelly et al. 2001; Hiramanek 2004]
NBOCC 2010	Statement: Clinical breast examination and mammography can identify asymptomatic recurrences	IV	n.a.	[Perrone et al. 2004; te Boekhorst et al. 2001; Donnelly et al. 2001]

[36] Für Erläuterungen des Level of Evidence (LoE) und Grade of Recommendation (GoR) siehe Anhang 5.6.

Leitlinie	Empfehlung	LoE[36]	GoR[1]	Referenzen
Nachsorge				
NBOCC 2010	Statement: Ipsilateral breast cancer recurrences detected by mammography have better overall survival compared with those detected by clinical breast examination alone	IV	n.a.	[Montgomery et al. 2007]
NBOCC 2010	Statement: Contralateral breast cancers detected by mammography have better prognostic characteristics (Kollias) (tumour size, lower grade and lymph node status) and overall survival (Robinson) compared with those detected by clinical breast examination alone	IV	n.a.	[Kollias et al. 2000; Robinson et al. 2007; Kaas et al. 2001]
NBOCC 2010	Statement: No primary studies were identified which addressed the use of ultrasound, PET or MRI in routine follow-up care	n.a.	n.a.	n.a.
NBOCC 2010	Statement: No primary studies were identified which addressed how long follow-up care should continue after diagnosis or treatment	n.a.	n.a.	n.a.
NBOCC 2010	Statement: Increased frequency of follow-up does not improve disease free survival or overall survival	II IV	n.a.	[Kokko et al. 2005] [Kaas et al. 2001]
NBOCC 2010	Statement: Treatment-related side effects may occur long after completion of active treatment	n.a.	n.a.	n.a.
NBOCC 2010	Statement: The profession of the health professional who is responsible for follow-up care does not influence survival outcomes (Grunfeld, Koinberg) or psychosocial or quality of life outcomes	II	n.a.	[Grunfeld et al. 2006; Koinberg et al. 2004; Brown et al. 2002; Koinberg et al. 2006]
NBOCC 2010	Statement: The health professional who is responsible for follow-up care may include a medical oncologist, radiation oncologist, surgeon, breast care	n.a.	n.a.	[National Breast Cancer Centre (NBCC) 2001]

Leitlinie	Empfehlung	LoE[36]	GoR[1]	Referenzen
Nachsorge				
	nurse and general practitioner (GP)			
NBOCC 2010	Statement: For multidisciplinary follow-up to be effective, good communication and effective referral options between team members is required	n.a.	n.a.	[National Breast Cancer Centre (NBCC) 2005]
NBOCC 2010	Statement: Not every clinician involved in the treatment of a woman will be closely involved in her follow-up	n.a.	n.a.	NBCC Clinical practice guidelines 2001
NBOCC 2010	Statement: Psychosocial issues, anxiety and depression are common following diagnosis and treatment for breast cancer and individual needs may change over time. Appropriate referral may alleviate depression and anxiety	I	n.a.	[National Health and Medical Research Council (NHMRC) 2000]
NBOCC 2010	Statement: Follow-up care includes managing the expectations of women and empowering them to request or seek what they need	I	n.a.	[National Health and Medical Research Council (NHMRC) 2003]
NBOCC 2010	Statement: Some women may find regular checkups psychologically reassuring (Gaudine, Kelly) and/or associate them with increased anxiety (Jiwa, Renton, Pennery)	IV	n.a.	[National Health and Medical Research Council (NHMRC) 2003; McCaughan et al. 2007; Kelly et al. 2006; Beaver et al. 2005; Gaudine et al. 2003; Allen 2002; Jiwa et al. 2006; Renton et al. 2002; Pennery et al. 2000]
NBOCC 2010	Statement: Intensive follow-up, such as chest X-ray, bone scan, computed tomography (CT), PET or MRI scans, and/or blood tests including full blood count, biochemistry or tumour markers, does not confer any survival benefit or increase in quality of life compared to a standard follow-up schdedule	I	n.a.	[Rojas et al. 2000]

Leitlinie	Empfehlung	LoE[36]	GoR[1]	Referenzen
Nachsorge				
NBOCC 2010	Recommendation: A history should be taken at each follow-up visit for symptoms of locoregional or systemic relapse, long-term treatment-related side effects or psychosocial distress	IV	n.a.	[Montgomery et al. 2007; de Bock et al. 2004]
NBOCC 2010	Recommendation: At each follow-up visit clinical examination should be performed. This includes the breast(s) or chest wall, regional lymph nodes and the arm on the treated side. Where appropriate, the examination may also include other organs such as the liver and lungs	IV	n.a.	[Montgomery et al. 2007; de Bock et al. 2004]
NBOCC 2010	Recommendation: Mammography should be performed annually to detect ipsilateral recurrence (Montgomery) or new primary, or contralateral breast cancer (Kollias, Robinson, Kaas)	IV	n.a.	[Montgomery et al. 2007; Kollias et al. 2000; Robinson et al. 2007; Kaas et al. 2001]
NBOCC 2010	Recommendation: Ultrasound may be used in addition to mammography when indicated on clinical or radiological grounds	n.a.	n.a.	n.a.
NBOCC 2010	Recommendation: The routine use of PET or MRI is not recommended as part of follow-up. However, the use of MRI may be considered in specific high risk groups	n.a.	n.a.	n.a.
NBOCC 2010	Recommendation: Women should be advised that between visits they should be aware of the normal look and feel of their breasts, and if changes are detected, to make immediate contact with their GP or the health professional identified as responsible for their follow-up care	IV	n.a.	[Montgomery et al. 2007; de Bock et al. 2004]
NBOCC 2010	Recommendation: A standard follow-up schedule is recommended (see NBOCCrecommended follow-up schedule Appendix A)	I	n.a.	[Rojas et al. 2000]
NBOCC 2010	Recommendation: Patient history and clinical examination should occur	IV	n.a.	[Montgomery et al. 2007]

Leitlinie	Empfehlung	LoE[36]	GoR[1]	Referenzen
Nachsorge				
	every 3-6 months for the first 2 years, every 6-12 months for the next 3 years and annually after 5 years			
NBOCC 2010	Recommendation: Mammography (and ultrasound if indicated) should be conducted annually following breast cancer diagnosis	IV	n.a.	[Montgomery et al. 2007]
NBOCC 2010	Recommendation: There is no evidence to indicate the optimal duration of follow-up. This should be discussed between the patient and the health professionals involved in the woman's care	n.a.	n.a.	n.a.
NBOCC 2010	Recommendation: Intensive follow-up, such as chest X-ray, bone scan, CT, PET or MRI scan, tests including full blood count, biochemistry or tumour markers, are not part of standard follow-up and are recommended only if clinically indicated	I	n.a.	[Rojas et al. 2000]
NBOCC 2010	Recommendation: The selection of the provider of follow-up care should be a decision made by the multidisciplinary team and the woman, and be based on the purpose of follow-up and the individual woman's needs. This decision should be reviewed over time	n.a.	n.a.	n.a.
NBOCC 2010	Recommendation: The multidisciplinary team, including the GP and the woman should be informed of the health professional(s) designated to provide follow-up care, and the schedule for follow-up	n.a.	n.a.	[National Breast Cancer Centre (NBCC) 2005]
NBOCC 2010	Recommendation: A patient-held follow-up schedule should be provided to assist with coordination of the patient care plan	n.a.	n.a.	[National Institute for Clinical Excellence (NICE) 2008]
NBOCC 2010	Recommendation: The provider of follow-up care should assess psychosocial distress, the impact of the disease and its treatment, and	n.a.	n.a.	[National Health and Medical Research Council (NHMRC) 2000]

Leitlinie	Empfehlung	LoE[36]	GoR[1]		Referenzen
Nachsorge					
	provide appropriate support and referral				
NBOCC 2010	Recommendation: Other disease, treatment and patient factors may influence the requirements for follow-up and should be considered. These include: ▪ long-term hormonal therapy ▪ age and hormonal status ▪ genetic factors ▪ accessibility of services ▪ clinical trial participation or data collection and audit ▪ long-term effects of systemic therapy ▪ side effects of active treatment such as secondary lymphoedema ▪ patient preference ▪ co-morbidities and their management ▪ management of interval presentation for investigation of symptoms ▪ bone health ▪ sexuality and body image ▪ fertility ▪ advice about lifestyle factors which may reduce risk of recurrence	n.a.	n.a.	n.a.	
NBOCC 2010	Recommendation: When sufficient evidence does not exist to guide definitive recommendations for follow-up, patients should, if possible, be offered entry into clinical trials	n.a.	n.a.	n.a.	

Leitlinie	Empfehlung	LoE[36]	GoR[1]	Referenzen
Nachsorge				
NICE 2009 early	▪ Offer annual mammography to all patients with early breast cancer, including DCIS, until they enter the NHSBSP/BTWSP. Patients diagnosed with early breast cancer who are already eligible for screening should have annual mammography for 5 years. (Qualifying statement: This recommendation is based on evidence from observational studies and GDG consensus.)	3	n.a	[Liberman et al. 1997; Weng et al. 2000]
NICE 2009 early	▪ Do not offer ultrasound or MRI for routine post-treatment surveillance in patients who have been treated for early invasive breast cancer or DCIS. (Qualifying statement: There is insufficient evidence to support the routine use of ultrasound or MRI imaging modalities in post-treatment surveillance.)	n.a.	n.a.	n.a.
NICE 2009 early	«Research recommendation» ▪ For patients who have been treated for early invasive breast cancer or ductal carcinoma in situ (DCIS), what is the optimal frequency and length of surveillance of follow-up mammography	n.a.	n.a.	n.a.
NICE 2009 early	▪ Patients with early invasive breast cancer should have a baseline dual energy X-ray absorptiometry (DEXA) scan to assess bone mineral density if they: o are starting adjuvant aromatase inhibitor treatment	n.a.37	n.a.	[Reid et al. 2008]

[37] Der Evidence Review zu dieser Leitlinie enthält eine Bewertung der Leitlinie von Reid et al. 2008 mit dem AGREE-Instrument

Leitlinie	Empfehlung	LoE[36]	GoR[1]	Referenzen
Nachsorge				
	○ have treatment-induced menopause ○ are starting ovarian ablation/suppression therapy. ▪ Do not offer a DEXA scan to patients with early invasive breast cancer who are receiving tamoxifen alone, regardless of pretreatment menopausal status. (Qualifying Statement: These recommendations are based on guidance produced by Reid et al. (2008) and GDG consensus.)			
NICE 2009 early	▪ Offer bisphosphonates to patients identified by algorithms 1 and 2 in 'Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK expert group' (2008) (see Appendix 2). (Qualifying statement: This recommendation is based on evidence from RCTs and guidance produced by Reid et al. (2008)).	1++	n.a.	[Pavlakis et al. 2005; Wu et al. 2007]
		1+		[Brufsky 2006; Fuleihan et al. 2005; Gnant et al. 2007; Greenspan et al. 2007; Ha et al. 2007; Saarto et al. 2004; Vehmanen et al. 2004]
		1-		[Bundred et al. 2008]
		n.a.[16]		[Mystakidou et al. 2005; Reid et al. 2008]
NZGG 2009	Regular mammography should be used in order to detect recurrence or new breast cancers at an early stage in patients who have undergone previous treatment for breast cancer	++	A	[Lu et al. 2009; Rojas et al. 2000]
		+/-		[Barnsley et al. 2007]
NZGG 2009	A woman should have her first post-treatment mammogram one year after her first diagnostic mammogram or 6 months after radiotherapy, and annually thereafter	++	A	[Rojas et al. 2000]
		+		[Khatcheressian et al. 2006]

Leitlinie	Empfehlung	LoE[36]	GoR[1]	Referenzen
Nachsorge				
		n.a.		[National Breast Cancer Centre (NBCC) 2001; Grunfeld et al. 2002]
NZGG 2009	For a woman at high risk of contralateral breast cancer (eg, BRCA1 or BRCA2 gene carriers) mammography of the contralateral breast should be performed no later than 12 months after the post-diagnostic mammogram and other imaging modalities may also be considered	n.a.	GPP	n.a.
NZGG 2009	Continuity of care for those with breast cancer is encouraged and should be undertaken by a clinician (eg, breast specialist, breast physician, nurse practitioner) experienced in the surveillance of breast cancer and in breast examination, including the examination of irradiated breasts	++	B	[Rojas et al. 2000]
		+ +/-		[Montgomery et al. 2007]
		+		[Scottish Intercollegiate Guidelines Network (SIGN) 2005; Khatcheressian et al. 2006]
		+/-		[Nissen et al. 2007]
NZGG 2009	Continuity of care may be shared with a general practitioner in appropriate circumstances (ie, ready access to specialist support)	++	C	[Rojas et al. 2000]
		+ +/-		[Montgomery et al. 2007]
NZGG 2009	Where patients are discharged to follow-up in primary care, guidance to general practitioners on appropriate management and referral back to secondary care should be provided	n.a.	GPP	n.a.
NZGG 2009	Provision of follow-up care should endeavour to avoid known barriers to patient care and follow-up such as financial, geographic and linguistic	n.a.	GPP	n.a.

Leitlinie	Empfehlung	LoE[36]	GoR[1]	Referenzen
Nachsorge				
	barriers			
Abkürzungen: CT = computed tomography scan; DEXA = dual energy X-ray absorptiometry ; GDG = Guideline development group; GPP = Good practice point; MRI = magnetic resonance imaging; n.a. = nicht angegeben; NHS = National Health Service; PET-CT = Positron emission tomography fused with computed tomography; UK = United Kingdom				

5. Anhänge

5.1 Suchstrategie und Trefferzahlen der Recherche in Medline (PubMed) vom 18.11.2010

Suchschritt	Details	Treffer.
#1	"Breast Neoplasms"[MeSH]	176228
#2	"Breast Neoplasm*" TI] OR "Breast Tumor*"[TI] OR "Breast Cancer*"[TI] OR "Cancer* of Breast"[TI] OR "Cancer* of the Breast"[TI] OR "Mammary Carcinoma*"[TI] OR "Mammary Neoplasm*"[TI]	88424
#3	(#1) OR (#2)	183909
#4	"Guidelines as Topic"[MeSH]	85337
#5	"Practice Guidelines as Topic"[MeSH]	58080
#6	"Consensus Development Conferences as Topic"[MeSH]	1714
#7	"Consensus Development Conferences, NIH"[MeSH]	296
#8	"Guideline"[Publication Type]	20042
#9	"Practice Guideline"[Publication Type]	14575
#10	"Consensus Development Conference"[Publication Type]	7168
#11	"Consensus Development Conference, NIH"[Publication Type]	657
#12	guideline*[TI] OR recommendation*[TI] OR consensus[TI] OR standard*[TI] OR "position paper"[TI] OR "clinical pathway*"[TI] OR "clinical protocol*"[TI] OR "good clinical practice"[TI]	121229
#13	(#4) OR (#5) OR (#6) OR (#7) OR (#8) OR (#9) OR (#10) OR (#11) OR (#12)	193257
#14	(#3) AND (#13)	2919
#15	(#3) AND (#13) Limits: Publication Date from 2006, English, French, German	878

5.2 Ausgeschlossen Leitlinien der Recherche in Medline (PubMed) nach Vollextsichtung

Referenz	Grund für Ausschluss[38]
Chalasani P, Downey L, Stopeck AT. Caring for the breast cancer survivor: a guide for primary care physicians. Am J Med 2010;123(6):489-95.	A1
AIUM practice guideline for the performance of a breast ultrasound examination. J Ultrasound Med 2009;28(1):105-9.	A1
Reid DM, Doughty J, Eastell R, Heys SD, Howell A, McCloskey EV, Powles T, Selby P, Coleman RE. Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK Expert Group. Cancer Treat Rev 2008;34 Suppl 1:S3-18.	A7
Dowsett M, Hanby AM, Laing R, Walker R. HER2 testing in the UK: consensus from a national consultation. J Clin Pathol 2007;60(6):685-9.	A1
McNaught J, Reid RL, Provencher DM, Lea RH, Jeffrey JF, Oza A, Swenerton KD. z Society of Obstetricians and Gynaecologists of Canada and the Society of Gynecologic Oncologists of Canada. J Obstet Gynaecol Can 2006;28(7):616-39.	A1
Kaufmann M, Hortobagyi GN, Goldhirsch A, Scholl S, Makris A, Valagussa P, Blohmer JU, Eiermann W, Jackesz R, Jonat W, Lebeau A, Loibl S, Miller W, Seeber S, Semiglazov V, Smith R, Souchon R, Stearns V, Untch M, von MG. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: an update. J Clin Oncol 2006;24(12):1940-9.	A4
Collie K, Bottorff JL, Long BC, Conati C. Distance art groups for women with breast cancer: guidelines and recommendations. Support Care Cancer 2006;14(8):849-58.	A1
Cataliotti L, de WC, Holland R, Marotti L, Perry N, Redmond K, Rosselli Del TM, Rijken H, Kearney N, Ellis IO, Di LA, Orecchia R, Noel A, Andersson M, Audretsch W, Bjurstam N, Blamey RW, Blichert-Toft M, Bosmans H, Burch A, Bussolati G, Christiaens MR, Colleoni M, Cserni G, Cufer T, Cush S, Damilakis J, Drijkoningen M, Ellis P, Foubert J, Gambaccini M, Gentile E, Guedea F, Hendriks J, Jakesz R, Jassem J, Jereczek-Fossa BA, Laird O, Lartigau E, Mattheiem W, O'higgins N, Pennery E, Rainsbury D, Rutgers E, Smola M, Van LE, von SK, Wells C, Wilson R. Guidelines on the standards for the training of specialised health professionals dealing with breast cancer. Eur J Cancer 2007;43(4):660-75	A1
Delaloye JF, Wight E, Fink D, Otto R, Steiner R. [A practice guideline for diagnosis and treatment of ductal in situ carcinoma of the breast]. Gynakol Geburtshilfliche Rundsch 2006;46(1-2):64-7.	A3
Huang KE, Baber R. Updated clinical recommendations for the use of tibolone in Asian women. Climacteric 2010;13(4):317-27.	A1
Muller-Schimpfle MP, Heindel W, Kettritz U, Schulz-Wendtland R, Bick U. [Consensus Meeting of Course Directors in Breast Imaging, 9 May 2009, in Frankfurt am Main - Topic: Masses]. Rofo 2010;182(8):671-5.	A7

[38] Erläuterung: A1 = Leitlinie ist nicht spezifisch für die Zielgruppe; A3 = Die Leitlinie ist nicht in deutscher oder englischer Sprache verfügbar; A4 = Die Leitlinie ist vor 2006 publiziert; A7 = Publikation ist keine Leitlinie

Umemura S, Kurosumi M, Moriya T, Oyama T, Arihiro K, Yamashita H, Umekita Y, Komoike Y, Shimizu C, Fukushima H, Kajiwara H, Akiyama F. Recommendations for 'adequate evaluation of hormone receptors' a report of the task force of the Japanese Breast Cancer Society. Oncol Rep 2010;24(2):299-304.	A7
Dawood S, Merajver SD, Viens P, Vermeulen PB, Swain SM, Buchholz TA, Dirix LY, Levine PH, Lucci A, Krishnamurthy S, Robertson FM, Woodward WA, Yang WT, Ueno NT, Cristofanilli M. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 2010.	A7
Bergren T, Heuberger R. Vitamin D and breast cancer prevention: practical guidelines for clinicians. Nurs Womens Health 2010;14(5):368-75.	A1
Belkacemi Y, Gligorov J, Chauvet MP, Tsoutsou PG, Boussen H, Bourgier C. [Radiotherapy and combined therapy in breast cancer: Standards and innovations in the adjuvant setting.]. J Gynecol Obstet Biol Reprod (Paris) 2010.	A3

5.3 Übersicht der berücksichtigten Leitlinien-Datenbanken und Leitlinien-Anbieter

AWMF ▪ Gynäkologie Geburtshilfe ▪ Onkologie
Nationale VersorgungsLeitlinien
Leitlinien der Selbstverwaltungskörperschaften ▪ BÄK ▪ AkdÄ
Leitlinien-Programme ausgewählter Fachgesellschaften und Berufsverbände □ Allgemeinmedizin (DEGAM) □ Brusterkrankungen (Dt. Gesellschaft für Senologie) □ Geburtshilfe und Gynäkologie (Dt. Ges. für Gynäkologie und Geburtshilfe) □ Onkologie (Arbeitsgemeinschaft Gynäkologische Onkologie)
Leitlinien aus dem ambulanten Bereich ▪ Leitliniengruppe Hessen

Leitlinien aus Universitäten, Klinikverbünden usw. ▪ Uniklinik Köln ▪ Univ. Witten-Herdecke ▪ Tumorzentrum Berlin ▪ Tumorzentrum Brandenburg ▪ Tumorzentrum Freiburg ▪ Tumorzentrum Heidelberg ▪ Tumorzentrum München ▪ Das Tumorzentrum Süd-Ost-Niedersachsen ▪ Tumorzentrum Tübingen
Leitlinien zur Rehabilitation ▪ Dt. Rentenvers. Bund
Pflegestandards und Pflegeleitlinien ▪ Dt. Gesellschaft für Palliativmed.
Australien ▪ Medical Journal of Australia ▪ Nat. Health and Med. Res. Council ▪ NSW Health
Finnland ▪ Finish Medical Society Duodecim
Frankreich ▪ Haute Autorité de Santé
Großbritannien ▪ National Library of Health – Guidelinesfinder (Suchbegriff “Breast Cancer”) ▪ National Institute for Health and Clinical Excellence ▪ Scottish Intercollegiate Guidelines Network
Irland ▪ Guidelines and Audit Implementation Network (GAIN + CREST Guidelines)
International ▪ Guidelines International Network (Suchstrategie: MeSH Term: Breast Neoplasms, Languages: Englisch, Deutsch, Französisch, Publication Status: Published,

Publication Type: Guideline) ▪ World Health Organisation
Kanada ▪ Alberta Medical Association ▪ British Columbia Council on Clinical Practice Guidelines ▪ Canadian Medical Association ▪ Guidelines Advisory Committee
Neuseeland ▪ New Zealand Guidelines Group
USA ▪ AHRQ ▪ American Medical Directors Association ▪ Colorado Clinical Guidelines Collaborative ▪ Health Services/Technology Assessment Text ▪ Institute for Clinical Systems Improvement ▪ National Guidelines Clearinghouse (Suchbegriffe: Diseases - Neoplasms - Neoplasms by Site - Breast Neoplasms) ▪ National Institutes of Health
Allgemeinmedizin ▪ American Academy of Family Physicians ▪ American College of Physicians ▪ Royal Australian College of General Practicioners ▪ Royal Australasian College of Physicians ▪ Royal College of General Practitioners ▪ Royal College of Physicians ▪ Royal New Zealand College of General Practitioners
Geburtshilfe und Gynäkologie ▪ Royal College of Obstetricians and Gynaecologists ▪ Geneva Foundation for Medical Education and Research ▪ Society of Obstetricians and Gynaecologists of Canada
Onkologie

- Australian Cancer Network
- American Society of Clinical Oncology
- BC Cancer Agency
- Cancer Care Ontario
- Cancer Council Australia
- European Cancer Organisation
- European Society for Medical Oncology
- European Society of Breast Cancer Specialists
- Fédération Nationale des Centres de Lutte Contre le Cancer
- National Breast and Ovarian Cancer Centre
- National Comprehensive Cancer Network

5.4 Ausgeschlossen Leitlinien der Recherche in Leitlinien-Datenbanken und bei Leitlinien-Anbietern

Leitlinien-Anbieter oder Fachrichtung	Titel	Grund für Ausschluss[39]
Arbeitsgemeinschaft Gynäkologische Onkologie	Adjuvante endokrine Therapie prämenopausaler Patientinnen	A7
	Adjuvante endokrine Therapie postmenopausaler Patientinnen	A7
	Adjuvante Chemotherapie + Trastuzumab, Optimale Substanzen / Dosierung / Trastuzumab	A7
	Neoadjuvante (Primäre) systemische Therapie	A7
	Operative Therapie des Mammakarzinoms unter onkologischen Aspekten	A7
	Plastisch- rekonstruktive Aspekte nach Mastektomie	A7

[39] Erläuterung: A1 = Leitlinie ist nicht spezifisch für die Zielgruppe; A3 = Die Leitlinie ist nicht in deutscher oder englischer Sprache verfügbar; A4 = Die Leitlinie ist vor 2006 publiziert; A5 = Die Leitlinie wurde bereits in der S3-Leitlinie zur Diagnostik, Therapie und Nachsorge des Mammakarzinoms (2008) als Quell-Leitlinie zitiert; A6 = A7 = Publikation ist keine Leitlinie

	Läsionen mit unsicherem biologischen Potenzial (B3, inkl. "Precursor Lesions")	A7
	Duktales Carcinoma in situ (DCIS)	A7
	Adjuvante Strahlentherapie (RT)	A7
	Pathologie	A7
	Nebenwirkungen der Therapie	A7
	Brustkrebs: Spezielle Situationen	A7
	Supportive Therapie	A7
	Brustkrebs Nachsorge	A7
	Früherkennung und Diagnostik	A7
	Brustkrebsrisiko und Prävention	A7
	Loko- regionäres Rezidiv	A7
	Prognostische und prädiktive Faktoren	A7
	Endokrine Therapie des metastasierten Mammakarzinoms	A7
	Chemotherapie des metastasierten Mammakarzinoms	A7
	Besondere Situationen und Lokalisationen in der metastasierten Situation	A7
	Knochenmetastasen und Osteoporose	A7
	ZNS Metastasen beim Mammakarzinom	A7
	Zielgerichtete Substanzen	A7
	Komplementäre Therapie, Hormontherapie nach Mammakarzinom und (pflanzliche) Alternativen, "Survivorship"	A7
	Bisphosphonate und der RANKL-Antikörper Denosumab	A7
Tumorzentrum Brandenburg	Tumorzentrum Land Brandenburg: Empfehlungen zur Nachsorge von Patienten mit onkologischen Erkrankungen (2005)	A4
Tumorzentrum Tübingen	Aufklärung von Tomorpatienten (2008)	A1
	Schmerztherapie bei Tumorpatienten (2009)	A1
	Pflegestandard: Pflege eines onkologischen Patienten mit tumorbedingten Schmerzen (2009)	A1

Leitlinien zur Rehabilitation	Leitlinien zur sozialmedizinischen Beurteilung der Leistungsfähigkeit bei Mamma Karzinom (2006)	A6
Pflegestandards und Pflegeleitlinien	Leitlinien Palliativpflege zu: Dyspnoe (2006)	A1
	Situation nach dem Versterben (2008)Dt. Gesellschaft für Palliativmed. (23.07.2010)	A1
Medical Journal of Australia	Clinical practice guidelines for communicating prognosis and end-of-life issues with adults in the advanced stages of a life-limiting illness, and their caregivers (2007)	A1
Haute Autorité de Santé - Frankreich	ALD n 30 – Cancer du sein (2010)	A 3
National Library of Health (UK) – Guidelinesfinder	Royal College of Pathologists: Tissue pathways for breast pathology (2009)	A7
	CKS: Tamoxifen – managing adverse effects (2009)	A6
National Institute for Health and Clinical Excellence	Endoscopic axillary lymph node retrieval for breast cancer (IPG147) (2005)	A4
	Appraisals Bevacizumab for the first-line treatment of metastatic breast cancer (TA147) (2008)	A7
	Doxetaxel for the adjuvant treatment of early node-positive breast cancer (TA109) (2006)	A7
	Gemzitabine for the treatment of metastatic breast cancer (TA116) (2007)	A7
	Hormonal therapies for the adjuvant treatment of early oestrogen-receptor-positive breast cancer (TA112) (2006)	A7
	Paclitaxel for the adjuvant treatment of early node-positive breast cancer (TA108) (2006)	A7
	Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer (TA107) (2006)	A7
Scottish Intercollegiate Guidelines Network	Management of breast cancer in women (2006)	A 4
British Columbia Council on Clinical Practice Guidelines	Palliative Care for the Patient with Incurable Cancer or Advanced Disease (2010)	A1
AHRQ (USA)	Core-Needle Biopsy for Breast Abnormalities: Clinician’s Guide (2010)	A7
Health Services/Technology Assessment Text (USA)	Evidence Reports: HER2 Testing to Manage Patients With Breast Cancer or Other Solid Tumors (2008)	A7
	Impact of Gene Expression Profiling Tests on Breast Cancer Outcomes (2008)	A7
Institute for Clinical Systems Improvement	Palliative Care (2009)	A1

(USA)		
National Guidelines Clearinghouse (USA)	ACR Appropriatness Criteria: palpable breast masses (2009)	A7
	stage I breast carcinoma (2009)	A7
	bone metastases (2008)	A7
	conservative surgery and radiation-stage I and II breast carcinoma (2008)	A7
	locally advanced breast cancer (2007)	A7
	postmastectomy radiotherapy (2008)	A7
American College of Physicians (USA)	Palliative Care at the End of Life (2008)	A1
Royal College of Obstetricians and Gynaecologists (UK)	Breast health Global Initiative: Guidelines for International Breast Health and Cancer Control – Implementation (2008)	A1
American Society of Clinical Oncology (USA)	ASCO Update of the Breast Cancer Follow-up and Management in the Adjuvant Setting (2006)	A5
	ASCO/CAP Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer (2006)	A5
BC Cancer Agency (Kanada)	Staging (2006)	A7
	Follow up (2006)	A7
	Upper Extremity Rehab after Axillary Dissection (2007)	A7
	Pathology requisitions (2008)	A7
Cancer Care Ontario (Kanada)	Management of Ductal Carcinoma In Situ of the Breast (2006)	A5
	The Role of HER2/neu in Systemic and Radiation Therapy for Women with Breast Cancer (2006)	A5
European Society for Medical Oncology (EU)	Erythropoiesis-stimulating agents in the treatment of anaemia in cancer patients (2010)	A1
	Hematopoietic growth factors (2010)	A1
	Management of febrile neutropenia (2010)	A1
	Management of cancer pain (2010)	A1
	Management of oral and gastrointestinal mucositis (2010)	A1
	Venous thromboembolism in cancer patients (2010)	A1

European Society of Breast Cancer Specialists (EU)	The role of complementary and alternative medicine in the management of early breast cancer: Recommendations of the European Society of Mastology (2006)	A1
	The management of lobular carcinoma in situ (LCIS). Is LCIS the same as ductal carcinoma in situ (DCIS)? (2006)	A1
	The requirements of a specialist breast unit (2010)	A1
National Breast and Ovarian Cancer Centre (Australien)	Breast imaging: a guide for practice (2007)	A1
	The investigation of a new breast symptom: a guide for general practitioners (2006)	A1
	The use of sentinel node biopsy in early (operable) breast cancer: a guide for general practitioners (2009)	A1
	Multidisciplinary care for advanced disease: a guide for cancer health professionals (2008)	A1
National Comprehensive Cancer Network (USA)	Adult Cancer Pain V.2 2010	A1
	Antiemesis	A1
	Cancer- and Chemotherapy-Induced Anemia	A1
	Cancer-Related Fatigue	A1
	Distress Management	A1
	Myeloid Growth Factors	A1
	Palliative Care	A1
	Prevention and Treatment of Cancer-Related Infections	A1
	Senior Adult Oncology	A1
	Venous Thromboembolic Disease	A1
Fédération Nationale des Centres de Lutte Contre le Cancer (Frankreich)	Recommendations pour la pratique clinique: Saint Paul de Vence 2007: cancer du sein	A3

5.5 Ausgeschlossene Leitlinien aufgrund methodischer Kriterien

Referenz	Einschlusskriterium 5a) Bei der Generierung und Formulierung der Leitlinie kam eine methodische Systematik zur Anwendung (systematische Recherche nach Primär- bzw. Sekundärliteratur)	Einschlusskriterium 5b) Die Kernempfehlungen der Leitlinie sind in ihrer Mehrheit mit den Referenzen der ihnen zugrunde liegenden Primär- / Sekundärliteratur hinterlegt
29. Climent F, Soler MT, Catala I, Castella E, Corominas JM, Walsh PM. Breast Cancer OncoGuia: surgical pathology report guidelines. Clin Transl Oncol 2010;12(2):138-41.	Nein	Nein
30. Manchon P, Borras JM, Ferro T, Espinas JA. Breast Cancer OncoGuia. Clin Transl Oncol 2010;12(2):113-38	Nein	Ja
31. Kaufmann M, Morrow M, von MG, Harris JR. locoregional treatment of primary breast cancer: consensus recommendations from an International Expert Panel. Cancer 2010;116(5):1184-91.	Nein	Nein
32. Beslija S, Bonneterre J, Burstein HJ, Cocquyt V, Gnant M, Heinemann V, Jassem J, Kostler WJ, Krainer M, Menard S, Petit T, Petruzelka L, Possinger K, Schmid P, Stadtmauer E, Stockler M, Van BS, Vogel C, Wilcken N, Wiltschke C, Zielinski CC, Zwierzina H. Third consensus on medical treatment of metastatic breast cancer. Ann Oncol 2009;20(11):1771-85.	Ja	Nein
33. Albanell J, Andreu X, Calasanz MJ, Concha A, Corominas JM, Garcia-Caballero T, Lopez JA, Lopez-Rios F, Cajal S, Vera-Sempere FJ, Colomer R, Martin M, Alba E, Gonzalez-Martin A, Llombart A, Lluch A, Palacios J. Guidelines for HER2 testing in breast cancer: a national consensus of the Spanish Society of Pathology (SEAP) and the Spanish Society of Medical Oncology (SEOM). Clin Transl Oncol 2009;11(6):363-75.	Nein	Nein
34. Surgical guidelines for the management of breast cancer. Eur J Surg Oncol 2009;35 Suppl 1:1-22.	Nein	Nein
35. Jones AL, Barlow M, Barrett-Lee PJ, Canney PA, Gilmour IM, Robb SD, Plummer CJ, Wardley AM, Verrill MW. Management of cardiac health in trastuzumab-treated patients with breast cancer: updated United Kingdom National Cancer Research Institute	Nein	Nein

recommendations for monitoring. Br J Cancer 2009;100(5):684-92.		
36. Sturgeon CM, Duffy MJ, Stenman UH, Lilja H, Brunner N, Chan DW, Babaian R, Bast RC, Jr., Dowell B, Esteva FJ, Haglund C, Harbeck N, Hayes DF, Holten-Andersen M, Klee GG, Lamerz R, Looijenga LH, Molina R, Nielsen HJ, Rittenhouse H, Semjonow A, Shih I, Sibley P, Soletormos G, Stephan C, Sokoll L, Hoffman BR, Diamandis EP. National Academy of Clinical Biochemistry laboratory medicine practice guidelines for use of tumor markers in testicular, prostate, colorectal, breast, and ovarian cancers. Clin Chem 2008;54(12):e11-e79.	Nein	Ja
37. Mann RM, Kuhl CK, Kinkel K, Boetes C. Breast MRI: guidelines from the European Society of Breast Imaging. Eur Radiol 2008;18(7):1307-18.	Nein	Nein
38. Seifart U, Albert US, Heim ME, Hubner J, Jungkunz W, Prokein R, Rick O, Hoffmann M, Engenhart-Cabillic R, Kopp I, Wagner U, Kalder M. [Lymphedema in patients with breast cancer--a consensus regarding diagnostics and therapy in patients with postoperative lymphedema after primary breast cancer]. Rehabilitation (Stuttg) 2007;46(6):340-8.	Nein	Nein
39. Wildiers H, Kunkler I, Biganzoli L, Fracheboud J, Vlastos G, Bernard-Marty C, Hurria A, Extermann M, Girre V, Brain E, Audisio RA, Bartelink H, Barton M, Giordano SH, Muss H, Aapro M. Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology. Lancet Oncol 2007;8(12):1101-15.	Ja	Nein
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52. American College of Radiology ACR Appropriateness Criteria® Clinical Condition: Palpable Breast Masses	Ja	Nein
53. American College of Radiology ACR Appropriateness Criteria: Bone Metastases 2009	Nein	Nein
54. American College of Radiology ACR Appropriateness Criteria® Clinical Condition: Stage I Breast Carcinoma 2009	Nein	Nein
55. ACR–ACS–CAP–SSO PRACTICE GUIDELINE FOR THE MANAGEMENT OF DUCTAL CARCINOMA IN-SITU OF THE BREAST (DCIS) 2006	Nein	Nein

56. BRCA in breast cancer: ESMO Clinical Practice Guidelines 2010	Nein	Nein
57. Cardiotoxicity of chemotherapeutic agents and radiotherapy-related heart disease: ESMO Clinical Practice Guidelines 2010	Nein	Nein
58. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up 2010	Nein	Nein
59. Cancer, fertility and pregnancy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up 2010	Nein	Nein
60. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference 2010	Ja	Nein
61. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up 2010	Nein	Nein
62. The role of complementary and alternative medicine in the management of early breast cancer: Recommendations of the European Society of Mastology (EUSOMA) 2006	Nein	Nein
63. Magnetic resonance imaging of the breast: Recommendations from the EUSOMA working group 2010	Nein	Nein
64. Diagnosis of Breast Disease, ICSI 2010	Nein	Nein
65. BNMS Procedure Guidelines for Radionuclide Lymphoscintigraphy for Sentinel Node Localisation in Breast Carcinoma 2009	Nein	Nein
66. RECOMMENDATIONS FOR Aromatase inhibitors as adjuvant endocrine therapy for post-menopausal women with hormone receptor-positive early breast cancer 2006	Nein	Ja
67. RECOMMENDATIONS FOR USE OF Trastuzumab (Herceptin®) for the treatment of HER2-positive breast cancer 2007	Nein	Ja
68. NCCN Breast Cancer 2010	Nein	Nein
69. NCCN: Breast Cancer Screening and Diagnosis 2010	Nein	Nein
70. NZ: Suspected Cancer in Primary Care: Guidelines for investigation, referral and reducing ethnic disparities 2009	Nein	Ja
71. The pathology reporting of breast cancer A guide for pathologists, surgeons, radiologists and oncologists National Breast and Ovarian Cancer Centre and Australian Cancer Network 3rd edition 2008	Nein	Nein
72. Supportive Therapie bei Tumorerkrankungen 2008	Nein	Nein

5.6 Evidenzklassifikationen und Empfehlungsgrade

5.6.1 National Institute for Clinical Excellence (NICE)

Leitlinien:

- Early and locally advanced breast cancer: diagnosis and treatment (2009)
- Advanced breast cancer: diagnosis and treatment (2009)

Evidenzklassifikation

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs) or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias
1−	Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies; high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2−	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies (for example case reports, case series)
4	Expert opinion, formal consensus

Empfehlungsgraduierung

In den Leitlinien von NICE konnte keine systematische Graduierung der Empfehlungen identifiziert warden.

5.6.2 New Zealand Guidelines Group (NZGG)

Leitlinie:

- Management of early breast cancer (2009)

Evidenzklassifikation

++	Very high quality: assigned when all or most validity criteria met
+	High quality: assigned when some criteria met and where unmet criteria are not likely to affect the validity, magnitude or precision, or applicability of the results markedly
–	Low quality: assigned when few or none of the criteria met.
++, +	Intermediate grades: were assigned when the overall study quality fell between the three categories listed above.

Study appraisal was conducted as follows:

- for study designs where formal quantitative appraisal is not possible (eg, case-series) a brief narrative overview was prepared
- relevant guidelines were assessed using the AGREE instrument and the individual relevant sections of each guideline were appraised as for a systematic review (see below)
- diagnostic accuracy studies were appraised for quality using the QUADAS tool which was designed for this purpose. QUADAS consists of 14 questions. The number of items (out of 14) that were judged as valid on the QUADAS scoring list are given for each study
- all other studies (eg, meta-analyses, systematic reviews and randomised controlled trials) that met the inclusion criteria for each clinical question were appraised and graded for quality, using relevant checklists developed by SIGN.381 These were modified to incorporate summary levels of evidence for the validity, magnitude or precision of effect, and applicability of each study.

Empfehlungsgraduierung

A	The recommendation is supported by good evidence (based on a number of studies that are valid, consistent, applicable and clinically relevant)

B	The recommendation is supported by fair evidence (based on studies that are valid, but there are some concerns about the volume, consistency, applicability and clinical relevance of the evidence that may cause some uncertainty but are not likely to be overturned by other evidence)
C	The recommendation is supported by international expert opinion
I	The evidence is insufficient, evidence is lacking, of poor quality or opinions conflicting, the balance of benefits and harms cannot be determined
Good practice points (GPP)	Where no evidence is available, best practice recommendations are made based on the experience of the Guideline Development Team, or feedback from consultation within New Zealand
Grades indicate the strength of the supporting evidence rather than the importance of the evidence	

5.6.3 Nice/Saint-PauldeVence

Leitlinie:

- Belkacemi Y, Fourquet A, Cutuli B, Bourgier C, Hery M, Ganem G, Marsiglia H, Namer M, Gligorov J, Azria D. Radiotherapy for invasive breast cancer: Guidelines for clinical practice from the French expert review board of Nice/Saint-Paul de Vence. Crit Rev Oncol Hematol 2010.

Evidenzklassifikation

Niveau 1	Essais comparatifs randomisés de forte puissance Méta-analyse d'essais comparatifs randomisés Analyse de décision basée sur des études bien menées
Niveau 2	Essais comparatifs randomisés de faible puissance Etudes comparatifs non randomisées bien menées Etudes de cohorte

Niveau 3	Etudes cas-témoins Essais comparatifs avec série historique
Niveau 4	Etudes comparatives comportant des biais importants Etudes rétrospectives Séries de cas Etudes épidémiologiques descriptives (transversale, longitudinale)
Die Autoren der Leitlinien führen zu einigen Empfehlungen in Klammern an 'expert agreement'. Diese Darlegung der zugrundeliegenden Evidenz wurde in die Synopse bei den Level of Evidence (LoE) zusätzlich aufgenommen.	

Empfehlungsgraduierung

Grade A	Preuve scientifique établie
Grade B	Présomption scientifique
Grade C	Faible niveau de preuve scientifique

5.6.4 National Breast and Ovarian Cancer Centre (NBOCC)

Leitlinien:

- Taxane-containing chemotherapy regimens for the treatment of early (operable) breast cancer (2008)
- Endocrine therapy for the treatment of hormone receptor-positive advanced breast cancer (2008)

- Chemotherapy for the treatment of advanced breast cancer (2010)
- Follow-up of women with early breast cancer (2010)

Evidenzklassifikation

I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly designed randomised controlled trial.
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group.
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series with a parallel control group.
IV	Evidence obtained from case series, either post-test or pre-test and post-test.

Empfehlungsgraduierung

In den Leitlinien von NBOCC konnte keine systematische Graduierung der Empfehlungen identifiziert warden.

5.6.5 DRV Bund

Leitlinie:

- Reha-Therapiestandards Brustkrebs. Leitlinie für die medizinische Rehabilitation der Rentenversicherung

Evidenzklassifikation

Level I	Meta-Analyse von randomisierten kontrollierten Studien mit Homogenität der Ergebnisse oder eine randomisierte kontrollierte Studie mit engem Konfidenzintervall
Level II	Meta-Analyse von Kohortenstudien oder RCT geringer Qualität oder Kohortenstudie

Level III	Meta-Analyse von Fallkontrollstudien mit Homogenität der Ergebnisse oder einzelne Fallkontrollstudien
Level IV	Fallserien, Fallkontrollstudien geringer Qualität
Level V	Expertenmeinung

Empfehlungsgraduierung

In der Leitlinie von DRV-Bund konnte keine systematische Graduierung der Empfehlungen identifiziert warden.

5.6.6 DEGRO

Leitlinien:

- Feyer P, Sautter-Bihl ML, Budach W, Dunst J, Haase W, Harms W, Sedlmayer F, Souchon R, Wenz F, Sauer R. DEGRO Practical Guidelines for palliative radiotherapy of breast cancer patients: brain metastases and leptomeningeal carcinomatosis. Strahlenther Onkol 2010;186(2):63-9.
- Souchon R, Wenz F, Sedlmayer F, Budach W, Dunst J, Feyer P, Haase W, Harms W, Sautter-Bihl ML, Sauer R. DEGRO practice guidelines for palliative radiotherapy of metastatic breast cancer: bone metastases and metastatic spinal cord compression (MSCC). Strahlenther Onkol 2009;185(7):417-24

Evidenzklassifikation

Es wird das Schema des Centre for Evidence-based Medicine-Oxford angewendet (Anfrage bei Autoren).

Tabelle 21: Oxford - Levels of Evidence

Level **1A**	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	1a SR (with homogeneity*)of RCTs SR (withhomogeneity*) of inception cohort studies; CDR† validated in different populations SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres SR (with homogeneity*) of prospective cohort studies SR (with homogeneity*) of Level 1 economic studies
Level **1b**	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis	Individual RCT (with narrow Confidence Interval‡) Individual inception cohort study with > 80% follow-up; CDR† validated in asingle population Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre

	Differential diag/symptom prevalence Economic and decision analyses	Prospective cohort study with good follow-up**** Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
Level **1c**	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	All or none§ All or none case series Absolute SpPins and SnNouts†† All or none case-series Absolute better-value or worse-value analyses ††††
Level **2a**	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	SR (with homogeneity*) of cohort studies SR (withhomogeneity*) of either retrospective cohort studies or untreated control groups in RCTs SR (with homogeneity*) of Level >2 diagnostic studies SR (with homogeneity*) of 2b and better studies SR (withhomogeneity*) of Level >2 economic studies
Level **2b**	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	Individual cohort study (including low quality RCT; e.g., <80% followup) Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR† or validated on split sample §§§ only Exploratory** cohort study with good††† reference standards; CDR† after derivation, or validated only on split-sample§§§ or databases Retrospective cohort study, or poor follow-up Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
Level **2c**	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	"Outcomes" Research; Ecological studies "Outcomes" Research Ecological studies Audit or outcomes research
Level **3a**	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	SR (with homogeneity*) of case-control studies SR (with homogeneity*) of 3b and better studies SR (with homogeneity*) of 3b and better studies SR (with homogeneity*) of 3b And better studies
Level **3b**	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	Individual Case-Control Study Non-consecutive study; or without consistently applied reference standards Non-consecutive cohort study, or very limited population Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses IIncorporatingclinically sensible variations.
Level **4**	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	Case-series (and poor quality cohort and casecontrol studies§§) Case-series (and poor quality prognostic cohort studies***) Case-control study, poor or nonindependent reference standard Case-series or superseded reference standards Analysis with no sensitivity analysis

Level 5	Therapy/Prevention, Aetiology/Harm	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"
	Prognosis	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"
	Diagnosis	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"
	Differential diag/symptom prevalence	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"
	Economic and decision analyses	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"
NOTES Users can add a minus-sign "-" to denote the level of that fails to provide a conclusive answer because: EITHER a single result with a wide Confidence Interval OR a Systematic Review with troublesome heterogeneity. Such evidence is inconclusive, and therefore can only generate Grade D recommendations.		

*	By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
†	Clinical Decision Rule. (These are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category.)
‡	See note above for advice on how to understand, rate and use trials or other studies with wide confidence intervals.
§	Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available,but none now die on it.
§§	By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and nonexposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.
§§§	Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.
††	An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules out the diagnosis.
‡‡	Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.
†††	Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference

	standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.
††††	Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the equally or more expensive.
**	Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.
***	By poor quality prognostic cohort study we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.
****	Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (for example 1-6 months acute, 1 - 5 years chronic).

Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009)
(for definitions of terms used see glossary at http://www.cebm.net/?o=1116)

Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Updated by Jeremy Howick March 2009

Empfehlungsgraduierung

A	consistent level 1 studies
B	consistent level 2 or 3 studies or extrapolations from level 1 studies
C	level 4 studies or extrapolations from level 2 or 3 studies
D	level 5 evidence or troublingly inconsistent or inconclusive studies of any level

.

6. Literatur

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