Breast Cancer

A Guide to Clinical Practice

Adnan Aydiner
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Editors

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Preface

This guidebook is focused on providing a practical approach to the allocation of available diagnostic procedures and therapies to individual patients in light of the most recent and reliable information from clinical trials and international guidelines. It reviews substantial new evidence on locoregional and systemic therapies for early and advanced breast cancer and in situ carcinoma. In breast cancer, the treatment strategy is chosen based on the features and biology of the tumor and on the patient's age, general health status, and personal preferences. The decision options in this edition of the book are based on the best evidence-based recommendations available. The majority of breast cancer deaths now occur in less developed regions of the world. The gold standard for breast cancer care includes an integrated multidisciplinary team approach comprising pathologists, radiologists, surgical oncologists, medical oncologists, radiation oncologists, oncology nurses, and plastic surgeons. The first chapter comprises decision pathways outlining the step-by-step clinical decision-making process for patient management. In the subsequent chapters, the recommendations are discussed in light of randomized trials.

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Part VIII Treatment of Metastatic Breast Cancer

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Part I
Review of the Breast Cancer Management

Chapter 1
Decision Pathways in Breast Cancer Management

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Introduction

The decision options in this edition of the book are based on the best evidence-based recommendations available. This chapter is focused on providing a practical approach to the allocation of available diagnostic procedures and therapies to individual patients in light of the most recent and reliable information from clinical trials and international guidelines. As new information is obtained from randomized clinical trials, the decision options will change over time. In this chapter, the proposal 1 and proposal 3 recommendations are noted. Unless otherwise stated, the level of evidence for the other recommendations is generally 2.

Recommendation level	Definition
Proposal 1	There is a common consensus based on level 1 evidence
Proposal 3	There is no consensus based on level III evidence

Level of Evidence

Level I Evidence from at least one *well-designed controlled clinical randomized trial* and/or *meta analyses* and/or *systematic reviews*.

Level II (1) Evidence from a single randomized trial and/or well-designed non-randomized clinical trials. (2) Evidence from well-designed cohort or case-control studies (studies conducted by more than one research group or center are preferred). (3) Evidence obtained from case series with or without intervention.

Level III Descriptive studies, expert committee reports, or *respected authority opinions* based on clinical experience.

Breast Disease: Management (*Fig. 1.1*)

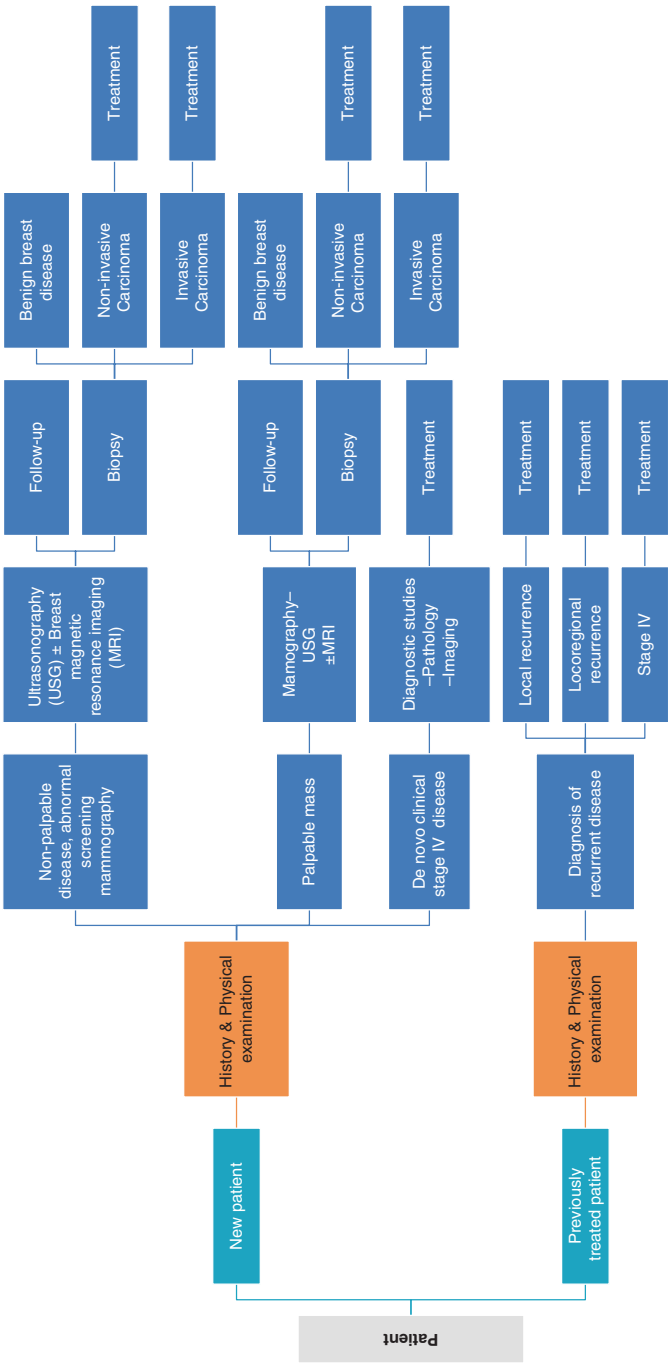

Fig. 1.1 Summary of the step-by-step clinical decision-making process in patient management (see Table 1.1)

Breast Disease: Approach to Benign Disease of the Breast
(Fig. 1.2)

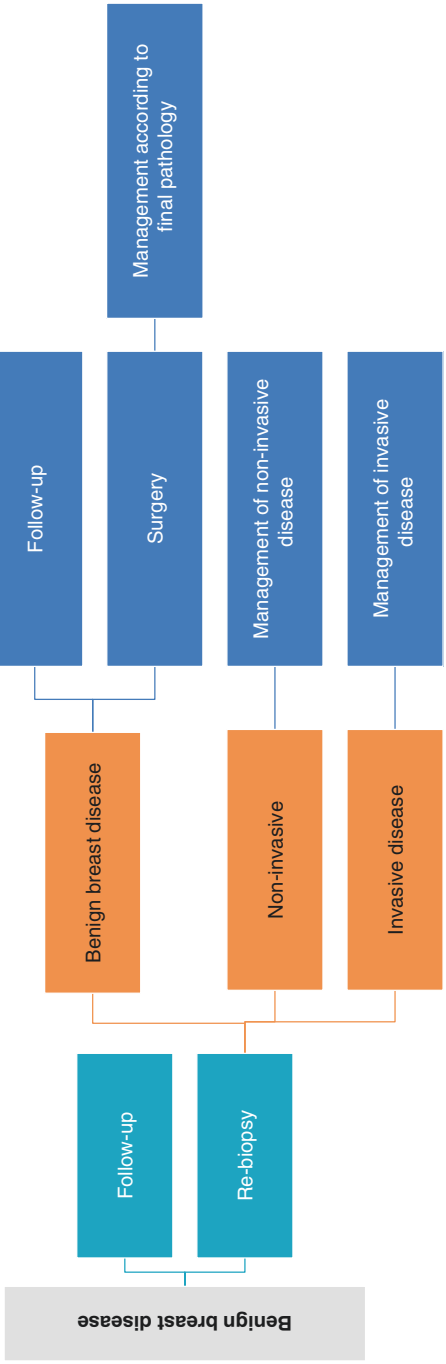

Fig. 1.2 Approach to benign breast disease after biopsy

Breast Disease: Diagnosis and Staging

Table 1.1 Diagnostic procedures for non-invasive (in situ) and invasive breast carcinoma

	In situ carcinoma	Invasive breast cancer		Inflammatory breast cancer
	Stage 0	Stage I, IIA, IIB, IIIA	Stage IIIA (N2), IIIB, IIIC	Stage T4d, N0–N3, M0
Medical history and physical examination	☑	☑	☑	☑
Mammography (MMG)	☑	☑	☑	☑
Ultrasonography (USG)		☑	If necessary ☑	If necessary ☑
Breast magnetic resonance imaging (MRI)	If necessary ☑	☑ Optional[a]	☑ Optional[a]	☑ Optional[b]
Pathological evaluation	☑	☑	☑	☑
Hormone receptors (HR) [Estrogen receptor (ER) and progesterone receptor (PgR)] determination	☑	☑	☑	☑
Assessment of tumor HER2 status		☑	☑	☑
Genetic counseling for patients at high risk for hereditary breast cancer	☑	☑	☑	☑
If required, fertility counseling	☑	☑	☑	☑
Blood tests (complete blood count, liver function tests, renal function tests, alkaline phosphatase (ALP), calcium, glucose)		☑	☑	☑
Serum tumor markers: CEA, CA153			☑	☑
Serum tumor marker: Ca125 (for young patients)		☑	☑	☑
In the case of localized bone pain or high ALP: bone scintigraphy (if PET/CT scan is not necessary)		☑	☑	☑
In the presence of high ALP, abnormal liver function tests, abdominal symptoms, or abnormalities upon abdominopelvic physical examination: abdomen ± pelvic computed tomography (CT) or MRI (or PET/CT scan)		☑	☑	☑
In the presence of pulmonary symptoms: CHEST CT		☑	☑	☑
FDG positron emission tomography (PET/CT)		☑ Optional[c]	☑	☑

[a]Density on mammography, <35 years of age, multifocality/multicentricity suspicion, evaluation for neoadjuvant chemotherapy (i.e., if treatment change is considered)
[b]If a treatment change is considered in neoadjuvant chemotherapy evaluation
[c]Tumor biology (i.e., triple-negative breast cancer) or according to stage (stage II–III); PET-CT may be required in patients with suspicious findings in conventional imaging modalities

Non-Invasive Breast Cancer: In Situ Carcinoma

STAGE 0 (Tis, N0, M0) (diagnosis established pathologically with biopsy or surgical excision specimen) (Fig. 1.3)

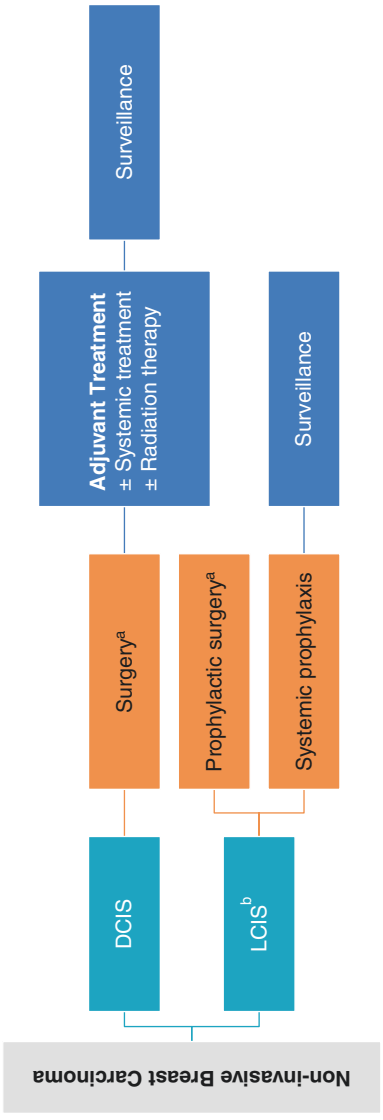

Fig. 1.3 Non-invasive breast cancer treatment. [a]Reconstruction is recommended if mastectomy is planned. [b]For the pleomorphic subtype of lobular carcinoma in situ (LCIS), ductal carcinoma in situ (DCIS) treatment alternatives should be administered. Surgical treatment is performed in high-risk patients or if there are familial risk factors for lobular carcinoma LCIS; chemoprevention is the choice in other patients. Patients with LCIS lesions detected by imaging methods are generally considered as higher-risk LCIS. DCIS treatment options should be applied in cases with the pleomorphic subtype of LCIS. Florid LCIS is a newly defined subtype that is suggested to be managed like pleomorphic LCIS. Multifocal LCIS (>4 terminal ductal lobular unit involvement) may be associated with higher risk for recurrence and invasive cancer. Tamoxifen, raloxifene or aromatase inhibitors may be preferred for chemoprevention

Non-Invasive Breast Cancer: In Situ Carcinoma: Ductal Carcinoma In Situ

Locoregional Therapy (*Fig. 1.4*)

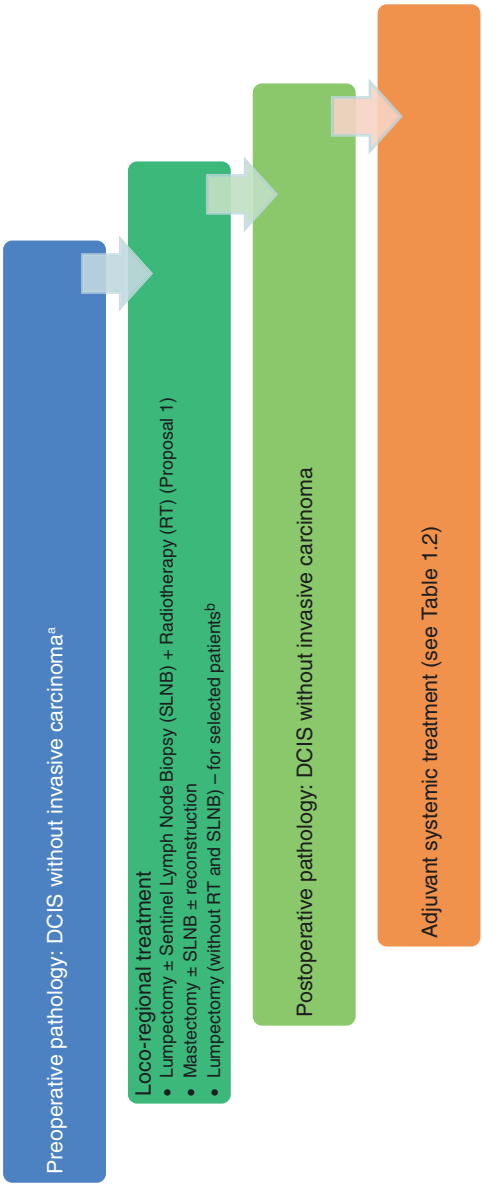

Fig. 1.4 Management of patient with ductal carcinoma in situ (DCIS). [a]Preoperative MR imaging is recommended in DCIS. The specimen should be evaluated with X-ray imaging. Radiation therapy (RT) after breast-conserving surgery is the standard treatment in DCIS. The disease-free surgical margin should be adequate (≥2 mm) [1–3]. At the St Gallen 2017 consensus meeting, a few researchers stated that "no ink on margin" may be considered sufficient in selected cases, whereas a surgical margin of 2 mm and above is considered safe in patients with DCIS undergoing breast-conserving surgery (BCS). In cases undergoing BCS, a surgical margin of 2 mm or above is considered safe only in those with DCIS. If the invasive tumor is <1 mm in DCIS, the surgical border safety is evaluated according to DCIS. If the invasive focus is >1 mm in DCIS, the surgical margin width should be evaluated according to the invasive cancer. A sufficient surgical margin should be decided together with clinical, radiological and pathological findings. The decision regarding the "sufficient surgical margin" should be made according to findings such as additional radiological foci (multiple foci, microcalcification), invasive lobular carcinoma, presence of more than one surgical margin and persistence of surgical marginal proximity in re-excision. [b]ER-positive, postmenopausal case, advanced age, low-grade tumors

Adjuvant Systemic Therapy (*Table 1.2*)

Table 1.2 Adjuvant systemic therapy of ductal carcinoma in situ

Risk reduction treatment for the ipsilateral breast after breast-conserving surgery
Tamoxifen for 5 years:
–For ER- or PgR-positive patients who have undergone breast-conserving surgery (BCS) and RT
–Benefit of tamoxifen is not definite for ER-negative patients
–Patients treated with excision only
Aromatase inhibitor for 5 years[a]:
–For ER-positive or PgR-positive postmenopausal (<60 years) patients who have undergone BCS and RT
Risk-mitigating treatment for the contralateral breast
Counseling for risk reduction (see Figs. 1.45, 1.46, and 1.47 and Table 1.9)

[a]The primary endpoint of NSABP B-35, a phase III trial comparing anastrozole to tamoxifen for DCIS after breast-conserving surgery, each given for 5 years, was breast cancer-free interval (BCFI), defined as the time from randomization to any breast cancer (BC) event including local, regional, or distant recurrence or contralateral disease, invasive or DCIS. Postmenopausal women with ER- or PgR-positive (by IHC analysis) DCIS and no invasive BC who had undergone a lumpectomy with clear resection margins were randomly assigned. Stratification was by age (<60 v ≥60). There were 198 BCFI events, 114 in the tamoxifen group and 84 in the anastrozole group (hazard ratio, 0.73; $p = 0.03$). There was a significant interaction between treatment and age group (p = 0.04); the benefit of anastrozole was observed only in women <60 years old. There were 63 cases of invasive breast cancer in the tamoxifen group and 39 in the anastrozole group (hazard ratio, 0.61; p = 0.02). There was a non-significant trend for a reduction in breast second primary cancers with anastrozole (hazard ratio, 0.68; p = 0.07). In conclusion, anastrozole provided a significant improvement compared to tamoxifen for BCFI, which was seen later in the study, primarily in women <60 years old [7]. In the IBIS-II DCIS trial, anastrozole was shown to reduce recurrence, similar to tamoxifen [8]. The non-inferiority of anastrozole was well-established but its superiority to tamoxifen was not

Monitoring and Follow-Up (*Table 1.3*)

Table 1.3 DCIS—monitoring and follow-up[a]

Medical history and physical examination
–Every 6 months for 5 years
–Once a year thereafter
Mammography
–Once a year (If BCS is performed, at months 6–12 following RT)

[a]If treated with tamoxifen monitor according to breast cancer risk mitigation guidelines

Non-Invasive Breast Cancer: In Situ Carcinoma: Lobular Carcinoma In Situ

Diagnosis and Management

Medical History
Physical Examination
Mammography

Pathology: Lobular carcinoma in situ (without DCIS or invasive carcinoma). For the pleomorphic subtype of lobular carcinoma in situ, DCIS treatment alternatives should be administered.
Counseling for risk-mitigating approaches (see Figs. 1.45, 1.46, and 1.47)
Follow-up

Invasive Breast Cancer (IBC)

Clinical Staging (Fig. 1.5)

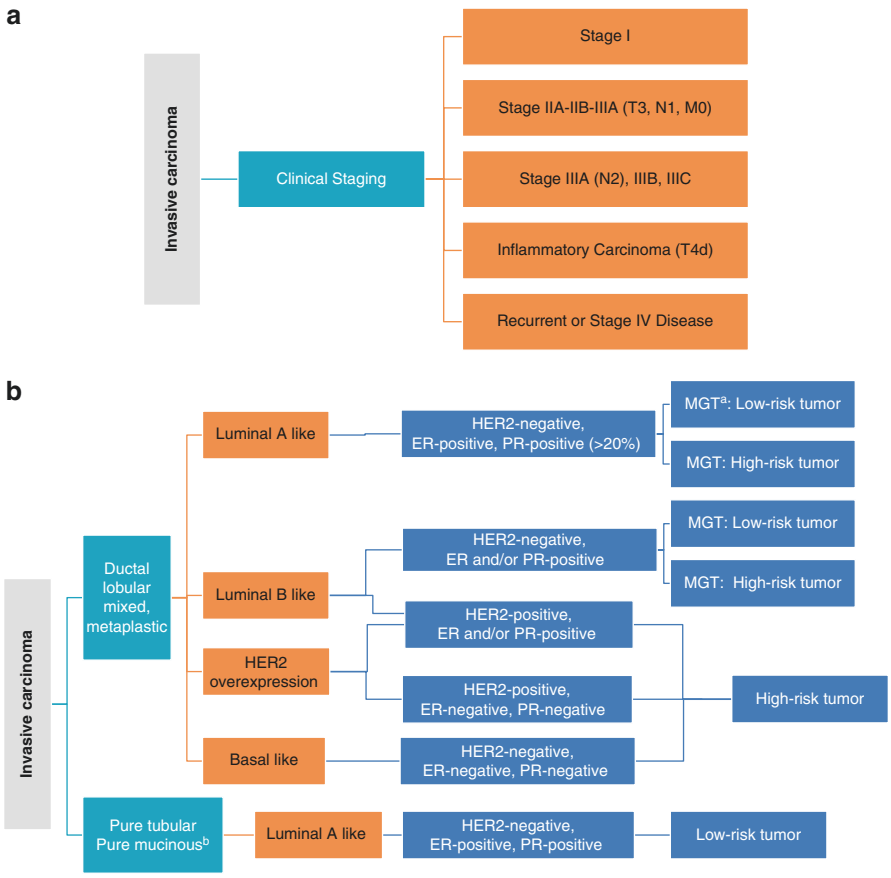

Fig. 1.5 (**a**) Clinical stages of invasive breast cancer. (**b**) Intrinsic subtype and clinicopathological surrogate definitions of invasive carcinoma. [a]*MGT* multigene tests. *Oncotype DX* (Genomic Health); *EndoPredict* (Sividon Diagnostics, Germany); *MammaPrint* (Agendia, Irvine, CA); *PAM50 ROR score* (Prosigna Breast Cancer Prognostic Gene Signature Assay; NanoString Technologies, Seattle, WA); *Breast Cancer Index* (Biotheranostics); *uPA and PAI-1*. [b]Very rarely (1%) mucinous invasive cancer can be a "non-luminal A" type

Invasive Breast Cancer: Clinical Stage I, II, IIIA (T3N1M0)

Axillary Evaluation (*Fig. 1.6*)

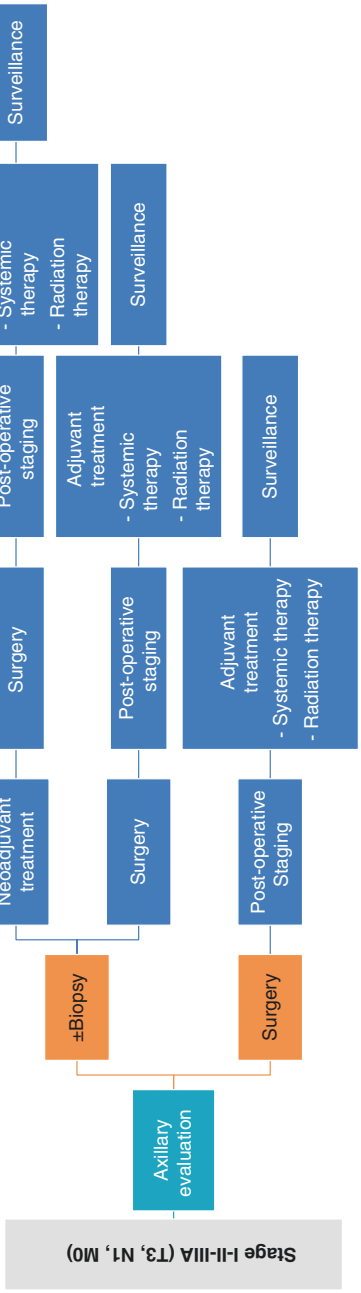

Fig. 1.6 Axillary evaluation and management of patients with clinical stages I, II or IIIA (T3, N1, M0)

Invasive Breast Cancer: Clinical Stage[1] I, II, IIIA (T3N1M0)

Surgical Axillary Staging and Management (Fig. 1.7)

[1] Stage I (T1, N0, M0); Stage IIA (T0, N1, M0; T1, N1, M0; T2, N0, M0); Stage IIB (T2, N1, M0; T3, N0, M0); Stage IIIA (T3, N1, M0).

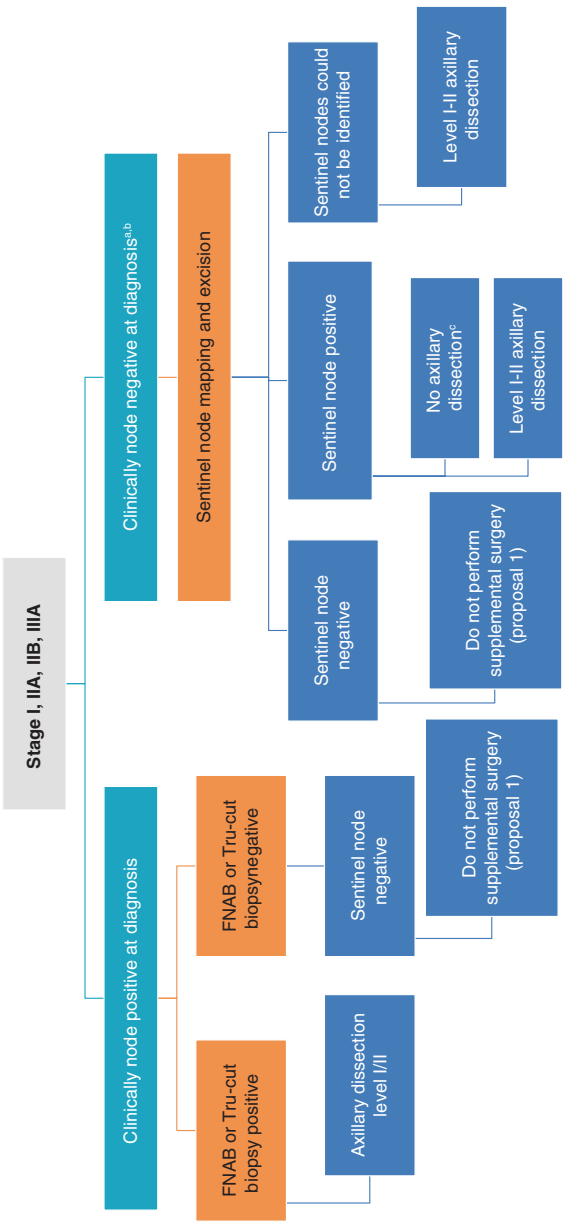

Fig. 1.7 Axillary management of patients with clinical stages I, II or IIIA (T3, N1, M0). *FNAB* fine-needle aspiration biopsy, *SLN* sentinel lymph node, *BCS* breast-conserving surgery. [a]For BCS: In patients with macrometastases in 1–2 sentinel lymph nodes, complete axillary dissection can be safely omitted when "conservative resection with RT" is performed [1, 3, 9–11]. [b]For mastectomy: In patients with macrometastases in 1–2 sentinel lymph nodes, complete axillary dissection must be performed when 'no adjuvant RT is planned'; however, in patients for whom RT is planned, no consensus exists for omitting axillary dissection [1, 3, 9]. [c]In patients with T1 or T2 tumors with BCS and 1–2 positive SLNs, if there is no neoadjuvant chemotherapy and whole-breast irradiation is planned, axillary dissection is not needed [1, 3, 9–17]. Axillary dissection is considered for SLN-positive patients with triple-negative breast cancer

Invasive Breast Cancer: Clinical Stage[2] II, IIIA (T3N1M0)

Axillary Management After Neoadjuvant Therapy (Fig. 1.8)

[2] Stage IIA (T0, N1, M0; T1, N1, M0; T2, N0, M0); Stage IIB (T2, N1, M0; T3, N0, M0); Stage IIIA (T3, N1, M0).

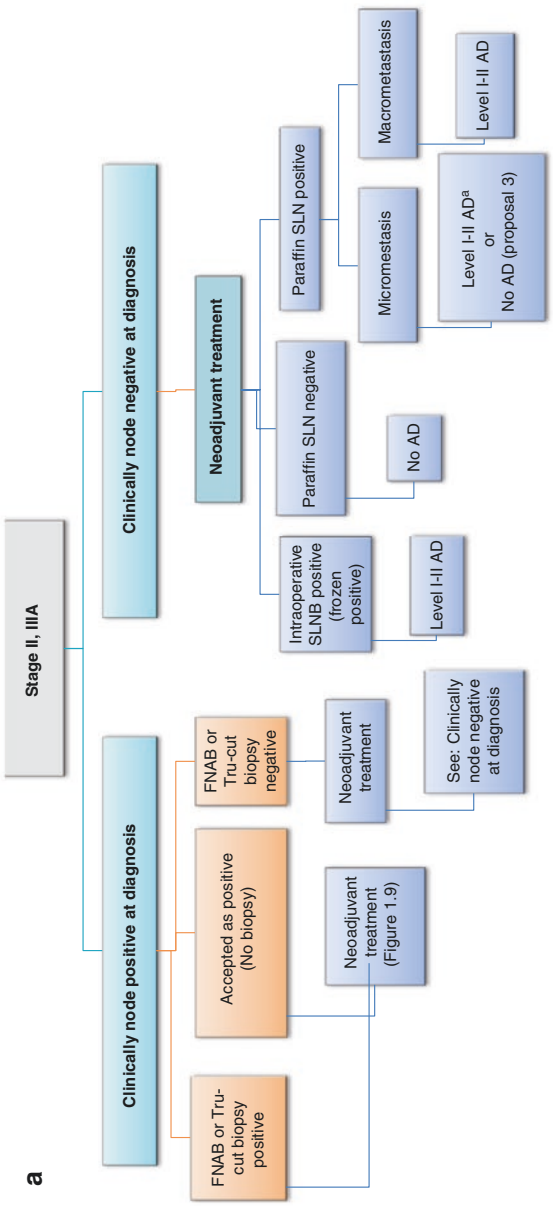

Fig. 1.8 Axillary management of patients with clinical stage II or IIIA (T3, N1, M0) invasive breast cancer. FNAB: fine-needle aspiration biopsy, *SLN* sentinel lymph node biopsy, *AD* axillary dissection. [a]Moo et al. examined the false-negative rate of frozen section after neoadjuvant chemotherapy (NAC) and the association between size of SLN metastasis and residual axillary disease at axillary dissection (ALND) [18]. A total of 702 patients underwent SLN biopsy after NAC. Overall, 17% patients with isolated tumor cells and 50% with micrometastases had additional nodal metastases at ALND. The authors concluded that low-volume disease in the SLN after NAC is not an indicator of a low risk of additional positive axillary nodes. These tumor cells are potentially drug resistant and are an indication of ALND, even when not detected on intraoperative frozen section

Invasive Breast Cancer: Clinical Stage[3] II, IIIA (T3N1M0)

Axillary Management After Neoadjuvant Therapy (Fig. 1.9)

[3] Stage IIA (T0, N1, M0; T1, N1, M0); Stage IIB (T2, N1, M0); Stage IIIA (T3, N1, M0).

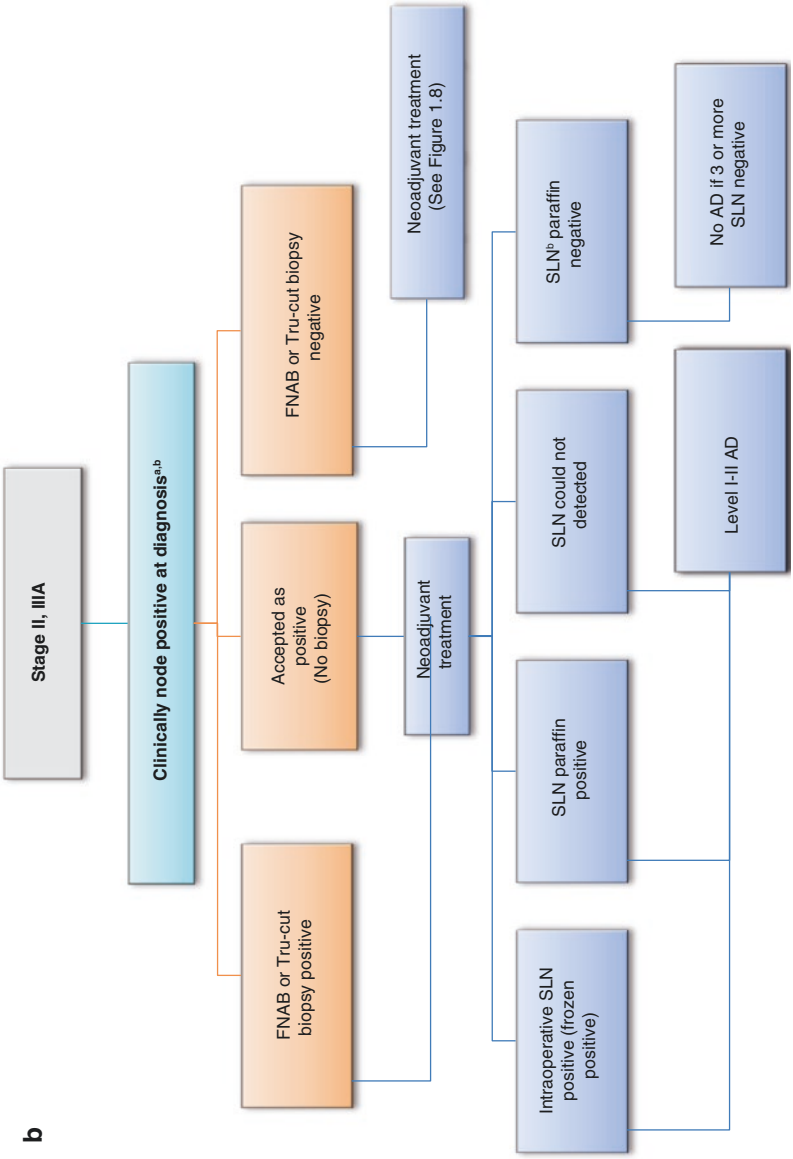

Fig. 1.9 Axillary management of patients with clinical node-positive stage II or IIIA (T3, N1, M0) invasive breast cancer. *FNAB* fine-needle aspiration biopsy, *SLN* sentinel lymph node biopsy, *AD* axillary dissection. [a]After neoadjuvant therapy, if the SLN is positive in frozen or paraffin sections, level I–II axillary dissection is recommended [1, 3, 9–17]. [b]At least 3 SLNs should be assessed in patients receiving neoadjuvant treatment

Invasive Breast Cancer: Clinical (T1–2N0M0) Disease

Box 1.1 Summary of approach to axilla—*no neoadjuvant treatment*—clinically node negative

Clinical T1–T2N0 patients:

Paraffin block examination after primary surgery:

–SLN negative: Axillary dissection is NOT performed

–SLN positive:

Micrometastasis only:

Axillary dissection is NOT performed

If *all of the following* are present, axillary dissection is NOT performed:

T1–T2 tumour;

1 or 2 positive SLNs;

BCS;

RT is planned for the entire breast;

No preoperative treatment.

–Undetermined SLN: Perform level I–II axillary dissection

Invasive Breast Cancer: Clinical Stage[4] I, II, IIIA (T3N1M0)

Surgical Approach (*Fig. 1.10*)

[4] Stage IA (T1, N0, M0); Stage IB (T0, N1mi; M0; T1, N1mi, M0); Stage IIA (T0, N1, M0; T1, N1, M0; T2, N0, M0); Stage IIB (T2, N1, M0; T3, N0, M0); Stage IIIA (T3, N1, M0).