Breast Surgery after Primary Systemic Treatment

Thorsten Kuehn

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21.1 Introduction

Primary systemic treatment (PST), most often applied as primary (neoadjuvant) chemotherapy (NACT), has primarily been introduced to allow surgery in locally advanced and inoperable breast cancer patients. Today PST is an established treatment strategy in early breast cancer with steadily raising application. Up to 20% of patients are treated with PST today [1]. The reason for the increasing role of PST is twofold: Primarily systemic treatment can reduce the extent of surgery and increase the rate of breast-conserving surgery (BCS) [2]. In addition, tumour response is an important prognostic factor and a surrogate marker for overall survival at least for some intrinsic subtypes of breast cancer. Surgery following PST is therefore a diagnostic as well as a therapeutic procedure. Furthermore it may improve surgical decision making in patients with suspected BRCA mutation carriage where delaying definitive surgery during PST permits time for gene testing to occur.

21.2 Therapeutic Implications of Breast Surgery After PST (Current Status)

Randomized trials have shown equivalency between adjuvant and neoadjuvant systemic treatment in terms of disease-free and overall survival [2, 3]. In the NSABP-B 18 trial, a significantly higher rate of BCT was achieved for patients who underwent PST without jeopardizing disease-free survival (DFS) or overall survival at a follow-up of 15 years [2]. Downstaging of axillary lymph node status can be achieved in more than 20% of patients according to early randomized trials [4] and may spare these women from full axillary dissection (AD) (see ▶ Chap. 25). Today even higher rates of axillary downstaging are expected [5]. In summary, PST can reduce the extent of surgery and improve quality of life due to higher rates of breast- and axilla-conserving surgeries.

21.3 Diagnostic Implications of Breast Surgery After PST

Clinical response rates are achieved in up to 80% of patients treated with NACT [6, 7]. Histopathologic complete response (pCR) is defined as the absence of any residual cancer on evaluation of the breast specimen and all sampled ipsilateral lymph nodes following completion of neoadjuvant systemic treatment [8]. Pathological CR is associated with improved disease-free survival and overall survival in some intrinsic subtypes of breast cancer [9]. Therefore pCR emerges as a new prognostic surrogate marker with a high potential to tailor future locoregional and systemic treatment decisions. The US Food and Drug Administration (FDA) recently recommended pCR as an endpoint for accelerated approval of new drugs in the neoadjuvant setting [10]. NACT is therefore increasingly used in the context of clinical trials to optimize chemotherapy combinations and integrate targeted therapies.

Tumour biology is highly indicative of the response to PST. In triple negative cancers (TNBC), pCR rates up to 64% can be achieved [11]. The highest rates have been described for ER-negative/HER2-positive tumours (up to 76%) [9, 11 12]. Much lower response rates are observed for luminal tumours even in the presence of a positive HER2 receptor [9, 13]. For this reason the intrinsic subtype can be used as a tool to predict response to PST. Additional use of carboplatin or pertuzumab in combination with transtuzumab in triple negative and HER2-positive breast cancer, respectively, has shown improved response rates compared to the standard regimen [13, 14]. Apart from the stage of the primary tumour and the tumour/breast volume ratio, clinicians increasingly employ the intrinsic subtype as a tool to select patients for PST or primary surgery.

21.4 Neoadjuvant Chemotherapy and Breast Surgery in Suspected BRCA Carriers

Another option for the use of PST is the improvement of surgical decision making in patients with suspected hereditary breast cancer. Women with a family history of breast cancer or patients with suspicious biological features (e.g. triple negative cancers, young age) may be tested for a BRCA mutation during the time of chemotherapy. In case of a positive result, the patient may be a candidate for bilateral mastectomy with primary reconstruction after PST. The time of chemotherapy can be used for counselling and to allow the patient to decide on the surgical approach (conventional surgery vs risk-reducing surgery). Secondary operations can be avoided, and the cosmetic outcome in patients, who primarily would have been treated with BCT and irradiation of the breast and who decide later to have their breast(s) removed, is improved.

21.5 General Remarks: Interdisciplinary Cooperation

PST with subsequent breast surgery requires a close interdisciplinary cooperation between radiologist, surgeon and pathologist. This relates to the pre-PST evaluation of all clinical and imaging procedures regarding the primary tumour size and its growth pattern as well as to the tumour response and the extent of the remission pattern during and after chemotherapy. Regular assessment of tumour response during PST is mandatory and can exclude the rare case of a tumour progression under chemotherapy. In order to assure optimal management for the patient who undergoes PST, some specific measures should be considered.

21.6 Pre- and Post-PST Evaluation of the Tumour

Risk assessment for hereditary breast cancer and determination of the initial tumour stage is important for patients who are candidates for PST. Clinical examination including palpation,

mammography and ultrasound of both breasts and axillae is mandatory for every patient who undergoes breast cancer treatment. In the neoadjuvant setting, the additional role of MRI is controversial at present. According to several trials and a meta-analysis, MRI overestimates the pathologic tumour size after PST. Ultrasound provides comparable results compared to MR. Agreement of palpation and mammography with the definite pathologic findings appears to be poorer than US and MRI. Palpation and ultrasound are therefore the most important clinical tools to evaluate the primary extent of the tumour and its response to PST [15–18].

Assessment of contrast enhancement in MRI may provide additional information regarding the response pattern of the tumour. Since MRI provides a reliable comparability of pre- and post-PST imaging, the technique is preferred by many clinicians to assess response of the tumour under PST.

Image-guided, percutaneous core needle biopsy (CNB) is required to determine the histologic type, tumour grade, oestrogen and progesterone receptor status, HER2 status and the proliferation rate (KI 67). An adequate number of sufficiently thick, nonfragmented cores are needed.

Pretreatment localization of the tumour is strongly recommended to ensure an adequate resection in case of complete clinical response after PST. Clip placement at the time of diagnosis or during the course of treatment represents the standard of care to locate the original tumour bed. Additionally photographs may be helpful to assess tumour location and the response of the tumour to chemotherapy in locally advanced disease.

21.7 Breast Surgery After PST

Randomized trials have shown that PST is associated with higher rates of BCT compared to primary surgery [2, 3]. The improvement of BCT rates does not translate into higher recurrence rates or a higher mortality. In a meta-analysis comparing neoadjuvant with adjuvant systemic treatment, Mauri and colleagues confirmed equivalency between both treatment strategies in terms of survival and overall disease progression [19]. However, neoadjuvant therapy was associated with a higher risk of local recurrence when radiotherapy without surgery was adopted as exclusive local treatment. Therefore it is generally accepted today that breast surgery after PST remains an essential part of locoregional therapy. The target volume for breast surgery after PST is defined as the post-PST tumourload as identified by clinical and imaging techniques. Patients with locally advanced breast cancer who are primarily candidates for mastectomy can be spared from radical surgery when post-PST imaging suggests that BCT is feasible within new (post-PST) margins. No data from prospective trials are available to define the role of margin width with regard to locoregional recurrences or survival. Smaller retrospective studies [20, 21] could not detect a higher rate of margin involvement after PST compared to primary surgery. There was no difference in the rate of tumour involvement in the re-excision specimen. However an association between lobular subtype and higher risk of margin involvement was described. A broad consensus has been reached in international guidelines that the target surgical resection volume is based on postoperative imaging. All residual disease detectable by clinical or imaging techniques should be removed with clear margins [22]. In cases of complete radiologic response, the centre of the original tumour bed should be removed including the marking clips placed prior to or during the course of PST.

For patients who present initially with multifocal or multicentric disease, the impact of the surgical extent (BCT vs mastectomy) after PST on local recurrence and survival has not yet been examined in prospective trials. In a retrospective analysis of 6134 patients from the German GeparTrio, GeparQuattro and GeparQuinto trials with operable or locally advanced tumours receiving anthracycline, taxane and targeted neoadjuvant therapy, the lesions of the participants were classified into unifocal (one lesion), multifocal (>1 lesion in one quadrant) or multicentric (>1 lesion in >1 quadrant) [23]. Local recurrence-free, disease-free and overall survival according to focality stratified by type of surgery and pCR was examined. Patients with multicentric tumours had worse disease-free and overall survival compared to patients with multifocal or unifocal disease. When pCR was achieved, there was no difference in all outcome parameters when breast-conserving therapy was performed. The authors concluded that BCT is feasible in clinically multifocal or multicentric breast cancer patients treated with PST without worsening local relapse-free survival if tumour-free margins can be attained and/or if patients achieved a pathologic complete response.

Close interdisciplinary cooperation between radiologist and breast surgeon is required for patients who undergo PST. This includes a thorough evaluation of all imaging procedures to define the target volume for surgical excision. If this volume does not correspond to the clinical finding (palpation), further measures should be taken to remove all detectable residual disease (imaging and palpation). Wire localization of the clip placed prior to or during the course of PST is widely used to indicate the original tumour site in case of a non-palpable lesion. Additional wires may be used to define a specific target volume. Intraoperative ultrasound is increasingly employed to guide the surgeon to locate the tumour and resect an adequate volume. Specimen imaging (radiography, ultrasound) is mandatory in cases of preoperative image-guided localization of the non-palpable tumour or the clip.

Clear orientation of the specimen is required (template, sutures) (Figs. 21.1., 21.2., 21.3., and 21.4.). This allows an adequate histopathologic evaluation of the resection margins and a targeted reresection in case of incomplete surgery. Intraoperative placement of clips to the tumour bed is strongly encouraged to allow a well-directed boost irradiation for patients who undergo BCT.

In cases of an unfavourable relation between the target resection volume and breast size, oncoplastic techniques can be applied to ensure an adequate resection volume and a good cosmetic outcome (see ▶ Chap. 19). Surgical solutions for eventual reresections and the necessity for unexpected, more extensive surgery should, however, be anticipated.

A close interdisciplinary cooperation between surgeon and pathologist is required to allow a high-quality histopathological evaluation. Ideally patients are discussed in a preoperative conference/multidisciplinary tumour board. The following information should be communicated to the pathologist:

1. The specimen must be clearly marked as a post-PST specimen.
2. Clear orientation of the specimen is mandatory.
3. Results of previous core biopsies should be available.
4. Clinical tumour size before and after chemotherapy (information given in cm or mm, rather than T-stage).
5. Location of the tumour/tumour bed/after chemotherapy (ideally by a diagram or drawing).
6. Information on close margins based on intraoperative findings (specimen radiography).

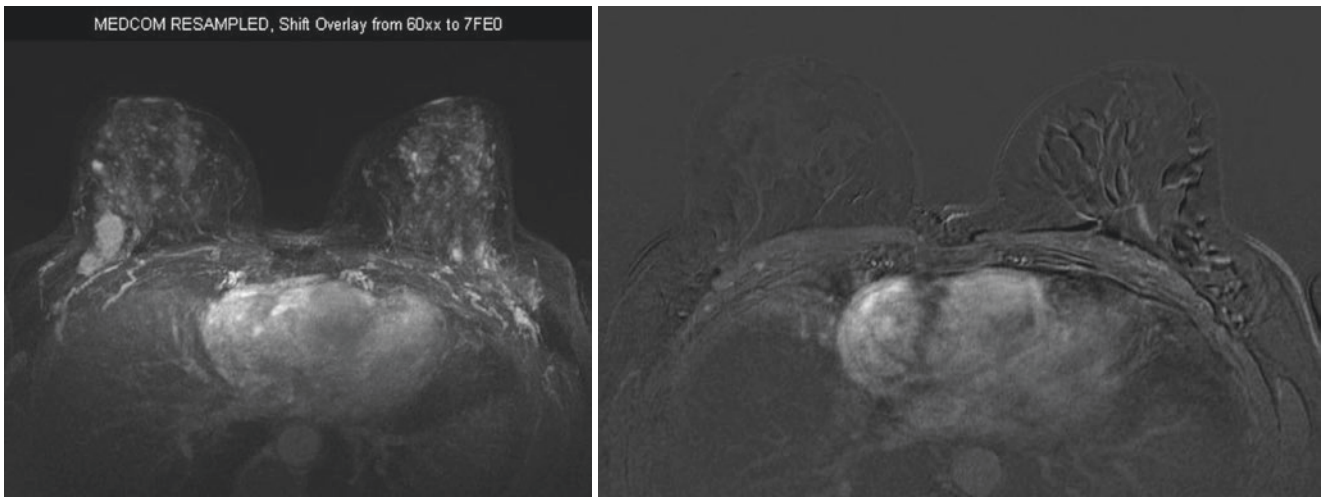

Fig. 21.1 Pre- and post-NACT MRI showing a complete clinical response

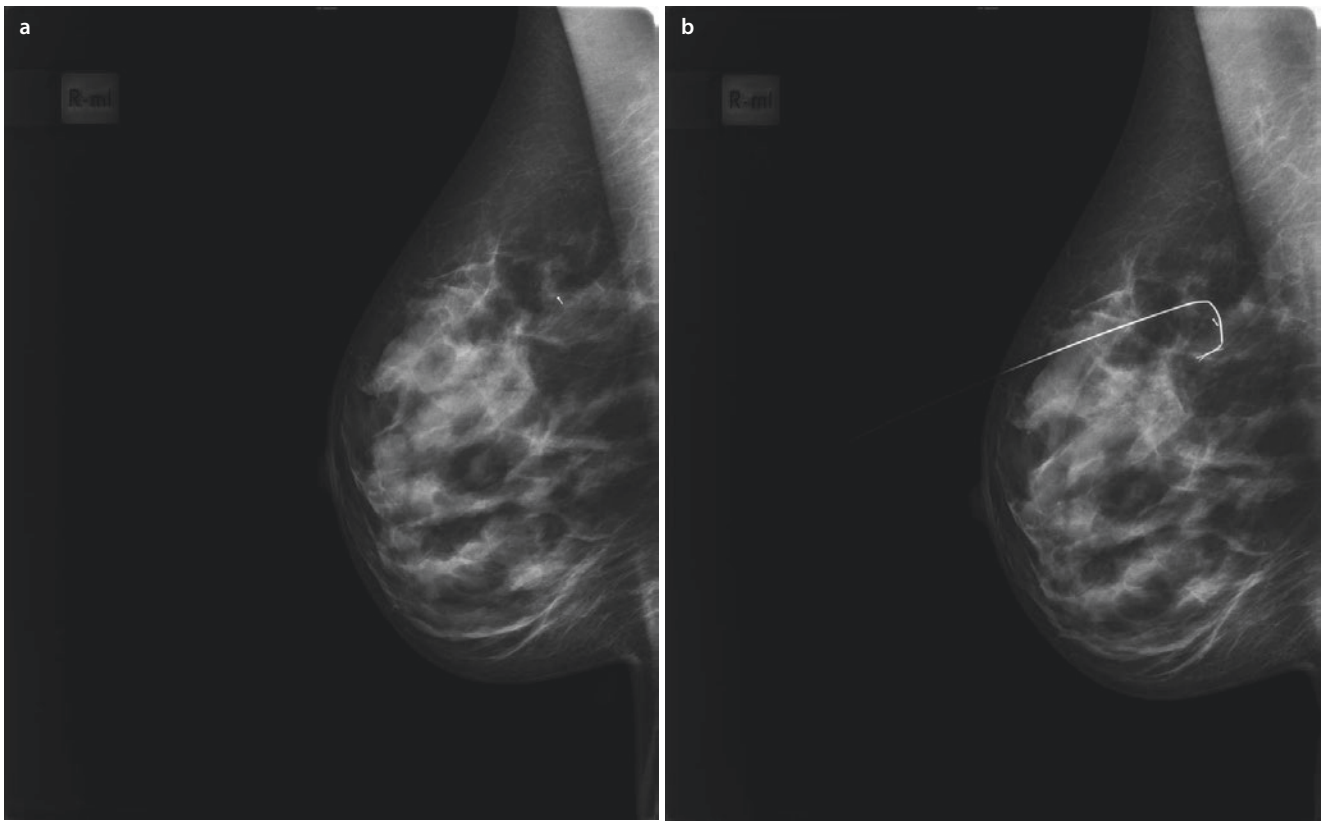

Fig. 21.2 **a** Clip placed in the centre of the original tumour bed and **b** needle localization of the clip

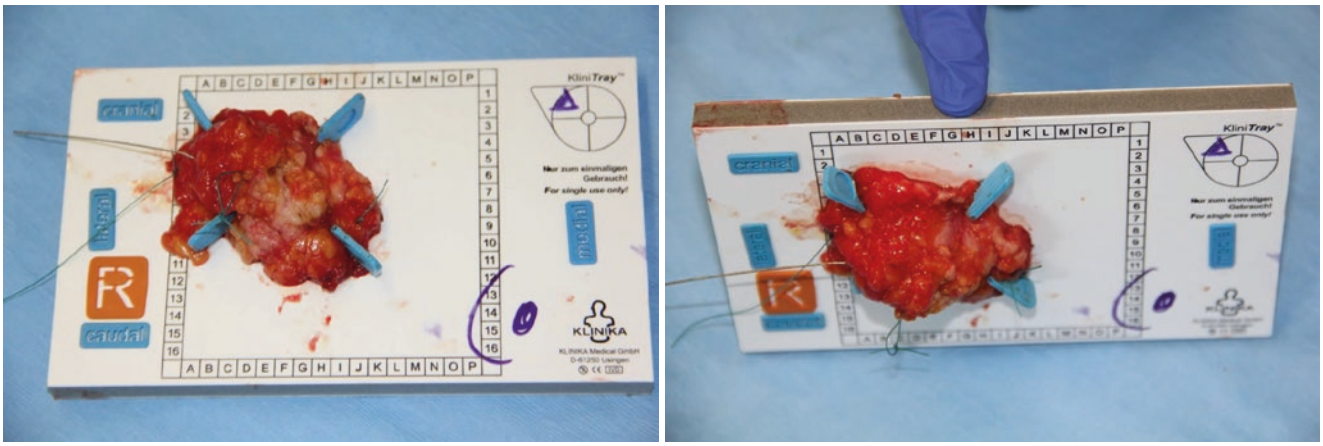

Fig. 21.3 Handling and orientation of the specimen – the specimen is fixed on a template and prepared for radiography in two planes to identify the clip

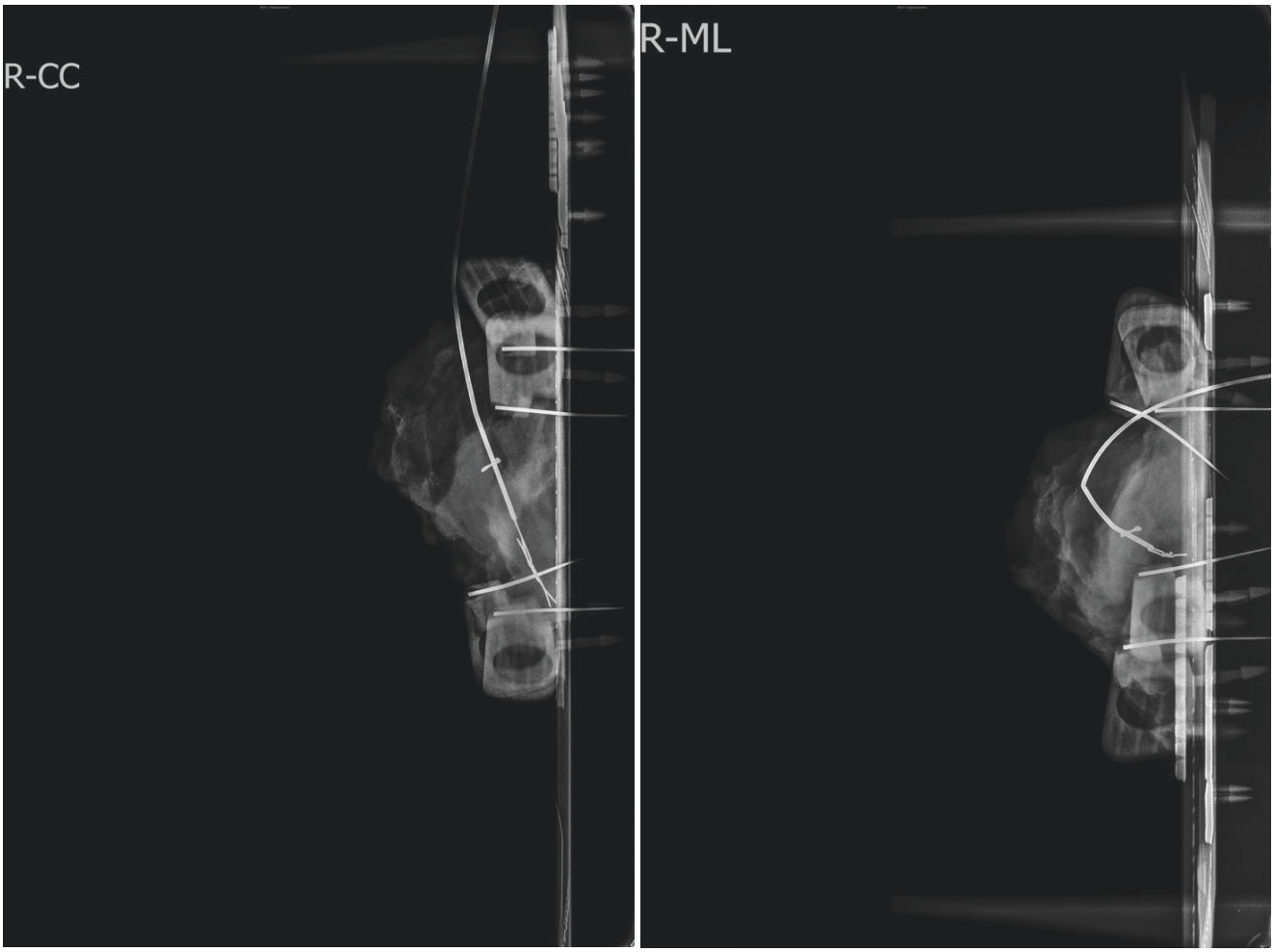

Fig. 21.4 Specimen radiography in two planes. The clip is located in the centre of the specimen with the wire in place

21.8 Pathologic Evaluation

The pathologic evaluation should include information on the adequacy of surgery (identification of the tumour bed) (e.g. clip) and the resection margins. Several reporting systems have been established to allow standardized histopathologic information on tumour response after chemotherapy [24–26]. The residual cancer burden (RCB) that assesses tumour extent, cellularity, size of lymph node metastases and presence of treatment effects in the breast and the lymph nodes after PST is widely used within clinical trials today [27, 28]. The RCB provides a standardized and reproducible tool to define tumour response after PST with a good association with clinical outcome in terms of DFS and overall survival.

21.9 Timing of Surgery and Radiotherapy

Surgery after PST should be planned after the nadir of the leucocyte count, in general 2–4 weeks after the last course of chemotherapy. Radiotherapy should be planned within a timeframe of 2–3 weeks after surgery [29].

21.10 Recent Development of Breast Surgery After PST

Refinements of neoadjuvant regimen and the introduction of targeted therapies such as trastuzumab or pertuzumab have improved pCR rates and outcome after PST considerably. Histopathologic complete response is observed in between 20 and 40% of the patients today, and a pCR rate as high as 74.6% has been achieved for HER-positive and ER-negative patients [12]. Astonishingly, these constantly improving response rates do not translate into a higher rate of BCT which ranges between 13% and 69% [30–31]. The reason for the persisting high mastectomy rates after PST is still unclear. Probably the consensus with regard to the extent of breast cancer surgery after PST is not yet widely accepted by the majority of breast surgeons. However, patients who are candidates for mastectomy prior to PST and whose clinical evaluation after chemotherapy reveals a good response to PST so that BCT appears feasible should be spared by the mutilating procedure of mastectomy wherever possible.

According to a study from the MD Anderson, four factors are associated with an increased recurrence rate in cases of BCT after PST: N2 or 3 disease, the presence of lymphovascular invasion (LVI), residual pathologic tumour size >2 cm and a multifocal residual pattern of disease [33]. These factors were summarized in a prognostic score ranging from 0 to 4 according to the number of risk factors involved. This prognostic index for locoregional recurrence after BCT was evaluated retrospectively in an independent cohort of 551 patients. The 5-year LLR rate was 92%, 92%, 84% and 69% when the index was 0 (no risk factor present), 1 (1 risk factor), 2 (2 risk factors) and 3–4 (3–4 risk factors present). When the prognostic index was 3–4, the 5-year LRR-free survival was significantly lower for patients treated with BCT compared with mastectomy [34].

21.11 Complications for Breast Surgery After NACT

The effect of PST on postoperative complications has not yet been investigated prospectively. In a retrospective analysis of 44,533 patients registered in the American College of Surgeons National Surgical Quality Improvement Programme database, the overall wound complication rate was low (3.4% vs 3.1%) and independent from the use of neoadjuvant chemotherapy. Smoking, functional dependence, obesity, diabetes, hypertension and mastectomy were the main risk factors for wound complications [35].

21.12 Future Perspectives

In view of the constantly improving response rates to systemic treatment regimens (including new targeted drugs) and the increasing sensitivity of imaging techniques to assess the post-PST tumourload, the issue of whether breast surgery is required at all in cases of clinical complete response is a current matter of debate. This relates to the effect of surgery on local control but also to the diagnostic purpose of breast surgery to assess pCR.

Clinical and imaging procedures are not associated with an acceptable sensitivity to assess pCR. Clinical complete response was associated with a 25% sensitivity to predict pCR for physical examination and mammography and 50% for ultrasound and MRI [36]. Shin and colleagues reported an accuracy of pCR prediction of 38% for mammography, 13% for ultrasound and 75% for MRI [37].

Heil and colleagues investigated the false-negative rates (FNR) and the negative predictive values (NPV) (to predict pCR after PST) for core needle biopsy (CNB) and vacuum-assisted biopsy (VAB) in a prospective study of 164 patients [38]. The FNR was, however, as high as 49.3% and the NPV 71.3%. In a small cohort of 16 patients within this study in whom VAB was performed, no FN case was observed. Future studies are being designed to examine the role of minimally invasive procedures to assess pCR.

21.13 Conclusion

Primary systemic treatment is becoming increasingly important in the treatment of breast cancer and has a high potential to tailor future systemic and locoregional treatment decisions. PST allows a more individualized and risk-adapted treatment of the patient. The treatment strategy of PST requires a high standard regarding the radiologic diagnostic

workup, the planning of surgical strategies and the pathologic workup of the specimen. Close interdisciplinary cooperation is an important precondition to ensure that the great potential of a primary systemic treatment strategy can successfully be employed to improve the treatment of an individual patient.

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