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Neoadjuvant therapy for breast cancer patients and its impact on surgical treatment and radiotherapy (part 2.)

Zbigniew I. Nowecki[1], Agnieszka Jagiełło-Gruszfeld[1], Katarzyna Pogoda[1], Anna Niwińska[1], Wojciech P. Olszewski[2], Paweł Winter[1], Rafał Matkowski[3, 4], Wojciech M. Wysocki[5, 6, 7]

[1]*Department of Breast Cancer & Reconstructive Surgery, M. Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*
[2]*Department of Pathology and Laboratory Diagnostics, M. Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*
[3]*Department of Oncology, Wroclaw Medical University, Wroclaw, Poland*
[4]*Breast Unit, Wrocław Comprehensive Cancer Center, Wroclaw, Poland*
[5]*General, Oncological and Vascular Surgery Clinic, 5th Military Hospital with Polyclinic in Cracow, Cracow, Poland*
[6]*Chair of Surgery, Faculty of Medicine and Health Science, A. Frycz Modrzewski Krakow University, Cracow, Poland*
[7]*Scientific Editing, M. Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*

Neoadjuvant therapy (NAT) is increasingly applied in patients with initially inoperable breast cancers and, frequently, in those with tumours that are initially operable, too. In most cases, the response to the applied NAT affects the scope of surgical treatment and radiotherapy, and in some situations also the complementary systemic postoperative treatment. The available studies indicate importance of response to NAT within the breast and regional lymph nodes. Assessment of response to treatment allows personalization of treatment and in some cases a change of therapy, which improves long-term outcomes.

This article summarizes the current rules of conduct in patients with early breast cancer qualified for neoadjuvant therapy, paying attention to the practical aspects and possibilities of national health insurance-covered therapies in Poland. It discusses in detail the applied regimens of systemic therapy, surgical techniques, eligibility rules and complementary radiotherapy. Systems for assessing response to neoadjuvant treatment are also presented.

Key words: breast cancer, surgery, systemic therapy, neoadjuvant therapy, adjuvant therapy

Surgical treatment

The canon of surgical treatment outlined by W. Halsted in 1894 consists in treatment of the mammary gland and axillary lymphatic drainage. Despite numerous modifications, the standard of surgical treatment of cancer patients is as follows:

- in the breast area:
  - sparing treatment (various methods) or
  - mastectomy (various methods with / without simultaneous reconstruction),
- in the axillary area:
  - sentinel lymph node biopsy (SLNB), or
  - axillary lymph node dissection (ALND) [1].

Mammary gland surgery

There are five forms of response of the breast tumour to systemic neoadjuvant therapy:

1. complete disappearance of neoplastic changes,
2. reduced size,

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3. multifocal atrophy of neoplastic tissue without a change of the tumour contour (tumour fragmentation, the tumour resembles a honeycomb),
4. no response to treatment,
5. progression during treatment [2].

There are different definitions of pathological complete response (pCR) to NAT, therefore the post-operative histopathology report should always describe presence or absence of a residual component of the DCIS (ductal carcinoma *in situ*). Progression during NAT in the case of inoperable lesions (cT4N2/3, inflammatory breast cancer) is observed in about 3% of cases. Patients with symptoms of disease progression during NAT have a poor prognosis regardless of whether a surgery can be performed [2].

Size of the tumour, along with the biological subtype is one of the eligibility criteria for NAT. The Livingstone-Rosanoff study analysed 38,864 cases of patients who had had neoadjuvant therapy. Pathological complete response was recorded in 19% of the patients, including 15% of those with tumours above 5 cm (cT3) and 20–21% of those with tumours up to 5 cm (cT1–2). The effect of the biological subtype on response to the treatment was much higher. The highest rates of clinical response were observed with HER2+ and TNBC cancers [3].

Microcalcifications are found in some patients after NAT with or without a tumour visible on imaging studies. In 38.5% of patients, the extent of microcalcifications assessed by mammography after NAT does not correlate with the extent of the remaining tumour. Patients who initially had steroid receptors present (HR+) have more malignant microcalcifications after NAT as compared to patients with no such receptors in the tumour (HR–) (48.9% *vs.* 13.5%, $p = 0.019$) [4]. Within microcalcifications, only 24–50% of pathological complete responses to NAT are found. Further, microcalcifications often indicate the presence of a residual DCIS component. Therefore, considering lack of efficient imaging methods (digital mammography and magnetic resonance mammography) in assessing response (pCR) to NAT, surgery should involve complete removal of microcalcifications [5].

For various reasons, not all patients undergo surgical treatment of the primary lesion after NAT. In an assessment of 350 patients who had not undergone surgery after NAT (they had only had external beam irradiation [XRT] applied) in comparison to a group of patients who had been operated on (breast conserving treatment [BCT]) no statistical differences were found with respect to OS (95.7% *vs.* 86.9%, $p = 0.26$) [6]. It may be a very tempting option for patients to forego a surgery, in the case of clinical and radiological response to NAT, confirmed as pCR by a vacuum-assisted biopsy (VAB). At the San Antonio Breast Cancer Symposium 2019, results were presented of 4 trials assessing effectiveness and accuracy of VAB in the case of clinical and imaging complete response in breast MRI after NAT. False-negative rate (FNR) ranged between 17.8 and 39%, while negative predictive value (NPV) was between 75 and 84%. No residual neoplastic disease was identified in 2/3 of patients. Thus, there is no scientific evidence to justify foregoing resection of the primary breast cancer focus after NAT, even in the case of clinical and imaging complete response [7–10]. However, it should be stressed that sensitivity of VAB in identification of the residual disease after NAT depends on thickness of the applied needle and number of samples – the best results can be obtained with 7–8 G needles and large number of samples.

There is a discussion about the problem of potential local recurrence after NAT in patients who had a breast-conserving surgery. A meta-analysis by Early Breast Cancer Trialists Collaborative Group, based on data from a follow-up of patients treated in 1983–2002, revealed higher rates of local recurrences after pre-operative chemotherapy as compared to post-operative chemotherapy: 21.4% *vs.* 15.9% ($p = 0.0001$) [11]. A more recent study by the German Breast Group brought opposite results. This organisation's meta-analysis covered more than 10,000 patients with NAT, who had participated in 9 clinical trials applying systemic neoadjuvant therapy between 199 and 2013. It proved that the 5-year rate of locoregional recurrence (LRR) was 7.8% for breast-sparing treatment, 11.3% for mastectomy, 4.1% in the case of pathological complete response (pCR), and 9.5% in the case of pathological partial response (pPR) (HR – 3.33, $p < 0.001$). Depending on the biological subtype, LRR was: for LA / LB – 6.9%, HER2-LB – 7.6%, Her2-NL – 10.5% and 14.4% for TNBC. The multivariate analysis showed that it was the patients' young age, clinically changed lymph nodes, G3 grade, and not the type of surgery, that influenced the partial response to treatment (pPR) [12].

The period of neoadjuvant systemic therapy allows for further diagnostics, enabling identification of patients with hereditary predisposition to breast cancer. If such changes are found and upon consultation with the patient, the planned scope of the surgery can be changed, e.g. to plan a bilateral mastectomy with reconstruction instead of a breast-sparing surgery.

In breast surgery, the dominating approach can be described as breast-contour-preserving procedure (BCPP). After a surgery, the patient's silhouette should be preserved, including breast prominence. In the Netherlands, the percentage of BCPP is steadily increasing. In 2015, BCPP made 71% of surgeries, mostly due to the increasing number of breast-conserving surgeries (BCS) – a significant part of them after NAT – with immediate breast reconstruction (IBR) after mastectomy. BCS is dominant in the 50-60 age group (57-63% of surgeries), BCS after NAT among patients under 50 years of age (12–14% of surgeries), and IBR mastectomies among patients under 40 years of age (26-44% of all surgeries in this age group). Depending on the hospital, BCPP procedures are performed in 47–88% of operated patients in the Netherlands [13]. In women with operable breast cancer, a decreasing trend is observed in performance of BCS, while the percentage of

mastectomy is growing (mostly nipple sparing mastectomy [NSM]) with immediate breast reconstruction – direct to implant (IBR-DTI) [14].

Kołacińska analysed surgeries at 8 centres in Poland. At 7 wards, BCS was performed in 50–70% of patients and only at 1, it made 24% of surgeries. IBR mastectomy was performed in 6–42% of patients, including 5 oncology centres performing surgeries after systemic neoadjuvant therapy [15].

A very important criterion for selecting the type of surgery is patient satisfaction. The BREST-Q questionnaire (a tool measuring patients' satisfaction after surgical treatment) enables estimation that satisfaction with the physical effect of the surgery decreases with time elapsing after its performance, while satisfaction in psycho-social aspect and sexual satisfaction increases. However, patients after BCT display higher satisfaction in all aspects as compared to patients after SSM / NSM ($p < 0.001$). Probably it also matters for satisfaction that BCS, in contrast to NSM, allows for retaining sensation in the nipple, areola and skin and for natural "aging" of the spared breast, similar to the natural process. Radiotherapy leads to lower BREST-Q results throughout the observation period and in all analysed aspects ($p < 0.05$) [16].

Breast-sparing treatment

Breast-sparing treatment remains a standard in surgical therapy, also after the systemic neoadjuvant therapy [17]. The surgical resection margin must be free of any tumour infiltration, i.e. it should be assessed as R0 (no-ink-on-tumour) in the post-operative histopathology test. That's why after NAT, a surgeon removes the mammary gland tissue in the "new range", removing also the residual fragment of the tumour or only the site marked before the surgery (if the tumour is not identified clinically or in pre-operative imaging). The resection does not involve the mammary gland covering the area originally affected by the tumour, i.e. within the "prior" boundaries before NAT [18–21]. It is used only in the case of pPR and numerous diffuse changes reaching the borders of surgical cuts within the entire bed (the tumour resembles a honeycomb). Resection of the tumour bed can be considered then [22].

Depending on the centre's practices, re-surgeries performed in the case of non-radical resection of the tumour at the first surgery concern 10–50% of cases, and BCS after NAT – 6–36% [23]14/40 (35%). Resection of mammary gland tissue with oncoplastic breast-conserving surgery (OBCS) allows for oncological safety and aesthetic acceptability surgery, especially in the case of more locally advanced breast tumours. Due to the non-radical nature of the OBCS, re-surgery was required in 6% of cases after NAT and 4.3% after primary surgery. Complications were found in 23% of patients after NAT and 27% of those without neoadjuvant therapy [17]. OBCS is a safe and aesthetically acceptable option for a breast-conserving treatment after NAT.

In a three-year follow-up of patients after NAT and breast-sparing surgery for unifocal, multifocal and multicentric breast cancers, locoregional failure risk (LRFR) survival rate after a radical surgery (R0 margin) were: 92.9%, 95.1% and 90.4% respectively ($p = 0.002$) [24]. No difference was found in 10-year LRR after NAT between the BCT group and the mastectomy group (9.2% *vs.* 10.7%, $p = 0.8$). The OS was 63% *vs.* 60%, respectively ($p = 0.8$). In this group, all patients underwent postoperative radiotherapy [21].

Mastectomy

Non-reconstructive mastectomy is still the standard option in patients with inflammatory breast cancer (IBC) and cT4 staging [18, 19, 25]. In the case of complete remission after NAT, some expert recommendations allow conservative surgery or NSM + IBR [24, 26]. For women after mastectomy, simultaneous reconstruction allows for psychological benefits: it improves self-esteem and appearance, and reduces anxiety and depression associated with cancer treatment [27]. Skin-sparing mastectomy (SSM) described by Toth and Lappert (1991) and mastectomy sparing the skin and nipple-areola complex (NSM) originally performed by Freeman (1962) have become the standard surgical treatment of invasive breast cancer [28]. The European Society of Breast Cancer Specialists recommends a simultaneous reconstruction in a minimum of 40% of patients who underwent mastectomy [27]. In an analysis held in France in 2012, 27.4% of primary mastectomies were associated with reconstructions. These operations were more often performed in women under 65 (42.1%) than in older women (7.7%, $p < 0.001$). Reconstructions were performed more often at university hospitals and oncology centres than at public hospitals [29]. According to a report by the American Society of Plastic Surgeons (ASPS), the most common form of simultaneous post-mastectomy reconstruction is implant reconstruction. In 2017, over 80% of patients had 1-stage (direct-to-implant – DTI) or 2-stage (initially expander, then final breast prosthesis) reconstructions [30]. NAT had no effect on postoperative complications after IBR, regardless of the method of reconstruction (1- or 2-stage) [31].

Even if BCT treatment after NAT is possible, more and more young women choose mastectomy with simultaneous reconstruction [14]. In an analysis by the European Institute of Oncology in Milan, among 1,711 patients who underwent NSM, as many as 48.4% patients had cancers up to 2 cm (pT1) [32]. In Europe and Asia, in the case of TNBC cancers without BRCA mutation, a breast-sparing surgery is chosen by 55% of patients, and by 80% in the USA [33]. It should be highlighted, however, that there is no evidence of improved oncological results after application of broader procedures (uni- or bilateral mastectomy) instead of breast-sparing surgery in patients who are not diagnosed as carriers of mutations associated with increased risk of breast cancer. Further, most evidence suggests that the sparing therapy is associated with better

prognosis and better quality of life; therefore in cases where breast-sparing surgery is possible, mastectomy is not recommended or considered as an optimal option in management [34–41]. Moreover, many studies reveal worse outcomes in terms of local recurrence in patients with selected subtypes of breast cancer after mastectomy as compared to breast-sparing surgeries [42]. Therefore, a mastectomy should not be proposed or performed, if less radical treatment is feasible [43].

According to the analysis of National Cancer Database data (for 2010–2014) concerning almost 0.25 million women with T1–3N0–3 stage cancers who had had combined treatment (surgery and chemotherapy), NAT was provided to 25.3% of the patients. Pathological complete response (pCR) increased from 33.3% to 46.3% (p = 0.22). Lower frequency of unilateral mastectomies was observed (43.3% *vs.* 34.7%), while the rate of bilateral mastectomies without reconstruction remained on the same level (11.7% *vs*. 11.%, p = 0.82), with an increase in BCS (37.0% *vs.* 40.8%, p = 0.02) and bilateral mastectomies with IBR (8.0% *vs.* 13.1%, p = 0.02) [33].

In Poland simultaneous reconstructions were analysed by Kołacińska et al. Depending on the centre, IBR was performed in 6–42% breast cancer surgeries, including 70% with NAT at certified oncology centres [15]. Local recurrence rate is similar for SSM and NSM after NAT as in the case of mastectomy. LRR depends on the original tumour stage and is not correlated with the type of surgery [44].

NSM is the type of mastectomy preferred by women. Despite the fact that in a vast majority of cases the range of superficial sensation within the skin of the breast, and especially the nipple, is disturbed, this method enables a very good aesthetic, but also oncological effect, if patients are correctly qualified for surgery [32]. The NSM reconstruction success after one-year follow-up was 96.7% [45]. The major problem in performance of NSM involves ensuring a cancer-free surgical margin on the nipple side. In one study, neoplastic infiltration of the nipple-areola complex (NAC) was found in 13.3% of NSM surgeries without NAT and in 9.8% with NAT. Tumour infiltration of NAC was associated with the size and multifocality of the tumour [44]. Postoperative nipple necrosis was found in 3.3% of patients after a surgery [32, 46]. Complications after NSM / SSM and IBR occurred in 7.5–47.3% of treated patients [51, 68–70], while local recurrence was found in 3.2–5.3% of cases [32, 46]. Postoperative complications were not associated with NAT but with body mass index (BMI), smoking, adjuvant radiotherapy, and concurrent ALND [28, 45–47].

Currently, prepectoral breast reconstructions, popular in the 1960s, are regaining importance with improved production technology of implants and meshes applied in breast reconstruction – biological ones (acellular dermal matrix – ADM) or synthetic ones, fully or partially absorbable. This type of reconstruction is frequently applied by surgeons who reconstruct defects after mastectomy and it's popular among patients, too. Maintaining unchanged anatomy of the chest wall (muscles), acceptable rate of complications and very good aesthetic effect are the factors contributing to its popularity. In an analysis of 6 prospective clinical studies, "capsular contracture" in the case of ADM in prepectoral reconstruction was found in only 1.2% of patients [48, 49]. Another study assessed frequency of all complications of prepectoral ADM reconstructions at 28.6%. Skin necrosis occurred in 5.2% of operated patients and infection in 3.2%. According to the univariate analysis, serious complications were related to the body mass index (BMI), ALND performed, weight of the operated breast and size of the implants used [50]. Complications were found in 25% of overweight women and in 10% of women of normal weight. In patients with BMI of 30–35, complications rate was at the level of 18%, and those with BMI> 35 – at 41% [51].

Recommendations by the international team of surgeons led by Vidya which concern prepectoral reconstructions describe the following counterindications against NSM: BMI > 40, diabetes which is difficult to control, smoking, chronic immunotherapy, previous radiotherapy of the chest wall, tumour infiltration of the skin and the chest wall. The authors of these recommendations state that the 1-step technique (DTI) is more frequent in Europe and the 2-step technique in the United States. In the second stage of treatment, expander is exchanged for a permanent prosthesis, and frequently fat cells are additionally transplanted. The authors of the recommendations approve various techniques of covering the implant with a mesh: complete, only partial from the side of the skin pocket, and combined technique: mesh with a stripped skin flap from the bottom. They indicate also that it is possible to perform NSM with a prepectoral mesh technique if the patient is eligible for postoperative radiotherapy [48], but they stress that in addition to the mentioned contraindications, the patient's skin flaps must be sufficiently thick [34]. Finally, they highlight that previous observations are based on short-term follow-up (as compared to follow-up of patients with submuscular reconstructions), and there are no randomised trials to compare oncological outcomes and distant cosmetic results of pre- and retropectoral techniques.

Before applying prepectoral techniques, especially in patients who will undergo radiation therapy, it is important to bear in mind these conditions and the fact that previous observations concern selected groups of women, most often with very favourable parameters determining good quality of the skin flaps. So far, there have been no randomised trials considering surgery technique, scope of the surgery, radiotherapy design (changing in recent years), disease stage, subcutaneous tissue thickness and other factors which affect the rate of lost implants and the risk of formation of a fibrous pouch around the implant. The authors stress that qualification for surgery should be careful and balanced and the patient should be informed that the prepectoral technique is quite new and there are no long-term observations on its outcomes. Undoubtedly, frequency of prosthesis rippling at the neckline should be

mentioned, as it requires procedures of filling the defects with fat transfer. The cost of ADM meshes is important, too, and in Poland the procedure of filling defects with free fat transfer is not reimbursed by the state insurance.

Prepectoral location of the implant and adjuvant radiation therapy are new methods that are observed very closely. Initial results of simultaneous prepectoral reconstructions are very promising and they suggest favourable surgical and cosmetic outcomes. In Sigalow's study (52 patients), during 25 months' follow-up complications occurred in 5.9% of patients with post-operative radiation therapy, and the implant had to be removed in 2.9% of the patients. No case of "capsular contracture" was recorded [30, 52].

Sinnott et al. assessed the incidence of complications after prepectoral and retropectoral reconstructions in patients after radiotherapy. Prepectoral reconstructions were performed using Wise technique, i.e. the "pocket" for the prosthesis was the lower, deepithelialized lobe of the mammary gland with an ADM mesh sewn from above. "Capsular contracture" occurred in the non-radiotherapy group in 3.5% of the patients and after radiotherapy in 16.1% of the cases ($p = 0.0008$). In patients after radiotherapy, complications were three times more frequent after retropectoral reconstruction (52.2% *vs.* 16.1%, $p = 0.0018$) and they were more intensive ("capsular contracture", 3–4 grade in Baker scale: 83.3% *vs.* 22.2%, $p = 0.0092$) as compared to patients with prepectoral reconstruction. However, the authors stressed the short follow-up time and the increased incidence of prosthesis rippling [53].

With the increasing use of NSM technology, both in surgeries in patients with diagnosed invasive cancers, and in cases of mastectomy in women with indications for surgery to reduce the risk of breast cancer (prophylactic mastectomy), increasing attention has been paid to radicality of the surgery and possibility to leave residual breast tissue (RBT) on the skin "envelope" (NSM and SSM surgeries). In a survey, 550 doctors (radiotherapists and surgeons) were asked about frequency of RBT after SSM/NSM. The answer "never" or "rarely" was chosen by 69.4% radiotherapists and 75.8% of surgeons. Meanwhile the question whether 10 mm of RBT was acceptable in terms of oncological safety, was answered affirmatively by 39.2% of radiation therapists and 59.9% of surgeons [54].

In the SKINI-Trial (10 to 14 envelope skin points were studied after NSM/SSM), RBT was identified in 51.3% of mastectomies. In the case of SSM, RBT was found in 40.4% of the operated patients and for NSM – In 68.9% ($p < 0.001$). Residue varied depending on the surgeon from 26.2% to 100%. Flap necrosis was found in 28% of NSM surgeries and 15% of SSM surgeries ($p = 0.051$). It was emphasized that the heterogeneous anatomical structure of the gland surface could affect radicality of the removal of glandular tissue. When performing subcutaneous excision of the mammary gland and generating even very thin skin flaps for the "skin envelope", the surgeon may leave intact vascular system, allowing for radical and uncomplicated mastectomy [55, 56]. In their study, Gianotti et al. found RBT in 29.9% of mastectomies performed. RBT was found at 2.8% of the studied points after a radical mastectomy, 13.2% after SSM and 73.8% after NSM. The presence of RBT correlated with flap thickness ($p < 0.001$), patient weight ($p < 0.001$), mastectomy type ($p < 0.012$ for SSM, $p < 0.001$ for NSM/MRM) and breast reconstruction with a flap ($p < 0.019$). In 9 out of 11 measurement points, the thickness of the flap exceeded 5.5 mm [57]. The clinical significance of residual breast tissue (RBT) after NSM/SSM is unknown, so further patient follow-up and prospective studies are necessary [56].

In some patients after mastectomy with reconstruction and radiation therapy, autologous transplant of fat tissue to the surgery site is necessary for aesthetical reasons. This method is widely applied by oncologic surgeons and plastic surgeons and it is safe in the oncological aspect [58].

Lymph node surgery

Historically, after systemic neoadjuvant therapy, axillary lymph node resection was performed, regardless of the condition of the nodes. Introduction of the sentinel lymph node biopsy (SLNB) has changed the standard procedures in diagnosis and management of patients with breast cancer. SLNB is the only verified and reliable method of diagnosing regional lymph drainage. Patients with clinically unchanged lymph nodes (cN0) are eligible for SLNB. If systemic neoadjuvant therapy is applied, cN0 is diagnosed in two situations:

1. initially cN0,
2. initially cN1 with conversion to cN0 after NAT (ycN0).

Both national and international guidelines recommend SLNB after NAT. This allows the following benefits:

- performance of only one surgery within the lymph node drainage system (in cases of ypN0), i.e. breast cancer surgery with SLNB,
- evaluation of the response to the applied systemic treatment, both within the breast tumour, and regional lymph nodes,
- achieving successful pCR within the axillary lymph node (conversion from pN1 to ypN0) in order to avoid ALND [18,19, 59, 60].

Pilewski et al. found that personalisation of the therapeutic sequence is a way to reduce the number of ALND procedures performed. The decision whether to start the treatment with a surgery or NAT should depend not only on the biological subtype of the cancer, but also on the scope of surgery within the breast (BCS *vs.* MT). These authors strongly recommend primary systemic treatment (NAT) for: HER2-positive cancers and TNBC, as such a treatment strategy reduces the proportion of performed ALNDs [61]. Depending on the biological subtype of the breast cancer, response of nodal metastases to NAT varies. Complete response to neoadjuvant therapy was achieved in lymph nodes in approximately 20% of patients with LA/LB biological subtype of cancer, and in 48–70% of

patients with HER2-LB, 60–97% of patients with HER2-NL and in 47% of cases with TNBC [62, 63].

The study by Samiei et al. compared the response to preoperative chemotherapy in breast tumours metastasising to regional lymph nodes. For initially cN0 cancers (with pCR within the breast itself), 97.7% had ypN0 stage, while in cases with pPR within the breast, only 71.6% were ypN0 stage. For initially cN1 cancers, if pCR occurred in the breast, 45% of patients had ypN0 stage, while with pPR in breasts only 9.4% had ypN0 stage [64, 65]. Experience of multiple centres which perform sentinel lymph node biopsies after the systemic treatment shows that NAC changes SLNB outcomes by reducing identification of sentinel lymph nodes and increasing FNR [66]. Based on an analysis of NSABP B-18 and B-27 studies, Mamaunas et al. concluded that the most important predictor for LRR after NAT involves the residual lymph node metastasis (ypN+) [67].

When qualifying a patient for SLNB after NAT, the therapeutic team should determine accuracy of the method used (SLNB) and its oncological safety [66].

Initially cN0 lymph nodes

Multiple studies and meta-analyses show that SLNB performed according to the given centre's standard (usually this a radioisotope +/− stain) is equally effective in patients assessed at cN0 before the systemic treatment as for those without the primary systemic therapy. SLN identification is assessed at >90%, and FNR at <10% (method reference values). No differences were observed in loco-regional recurrence, DFS and OS in patients with cN0 cancer (pN0) who underwent only SLNB as compared to those qualified for ALND. The rate of regional recurrences was at 1% [66, 68]. Therefore, for cN0 patients, SLNB is recommended after NAT [18, 19, 60, 69, 70]. Genea2 study showed that about 25% of clinically suspicious lymph nodes contain metastases after NAT (cN0 ypN1). The initial size of the tumour at T2–3, G3 feature and luminal subtype of breast cancer correlate with frequency of identified metastases to sentinel lymph nodes after NAT (tab. I) [71].

The standard SLNB procedure in patients with cN0 tumour who begin oncological treatment with systemic therapy should include:

Table I. Metastases to SLN after NAT, depending on the stage of breast cancer and its biological subtype [71]

Stage	Biological subtype	Drainage of SLN containing metastases (%)
cT1–3N0	LA/LB (ER+HER–)	23.8–41.7%
	HER2-LB (ER+HER+)	7.2–11.5%
	HER2-NL (ER–HER+)	0–6.3%
cT1–2N0	TNBC	2.9–6.2%
cT3–N0	TNBC	30.4%

- SLNB performed after NAC,
- application of SLNB technique which is standard at the given centre, as in the case of primary surgical treatment ("isotope", "dual technique", or another one, e.g. SentiMag),
- identification of the number of sentinel lymph nodes (SLN) according to the surgery technique (although some institutions recommend sampling 2 SLN).

Patients should be referred for ALND if:

- SLN are not identified,
- there are metastases to SLN (including ITC).

Initially cN1 lymph nodes

The increased rate of referrals for systemic neoadjuvant therapy affects surgical management of some patients with primary metastases to axillary lymph nodes – cN1/pN1. After NAT, frequency of ALND performed decreases, while there are more SLNB procedures. At Mayo Clinic in 2009–2017, a decrease of 60% was observed in the case of ALND after NAT, and an increase of 60% in the case of SLNB, while an Italian centre recorded an increase of SLNB procedures from 9.1% in 2011 to 46.5% in 2017 [72, 73]. A prospective study by Mamtani et al. showed that after NAT, it is possible to perform SLNB in approximately 70% of patients with initial cN+ cancer and in 48% it is possible to forego ALND [64].

Currently, international and national guidelines recommend:

- SLNB in patients with ycN0 cancer after systemic treatment,
- ALND in any case of ycN1 or ypN+ cancers [18, 19, 59, 60, 70].

So far, there have been organised four multi-centre prospective clinical trials to assess possibility of performing SLNB after a conversion from cN+ to cN0 after the systemic oncological treatment (tab. II).

As shown in table IV, SLNB performed in such a group of patients carries relatively low identification index below 90% and quite high FNR – above 10%. These values are inacceptable, if the method should be recommended as a reference.

To improve SLNB outcomes in patients with initial cN1/pN1 cancer and conversion to ycN0 stage after NAT, two variants of the surgery have been developed.

Option 1. Classical biopsy of sentinel nodes. In these patients, it is required to apply the "dual method" (staining and isotope) for identification of SLN and sampling of at least 3 lymph nodes corresponding to SLN criteria.

It was noted that SLNB after NAT performed analogically to the group without NAT (single biopsy with a radioisotope and identification of 1–2 sentinel lymph nodes), bears an unacceptably high FNR rate. In GENEA2 study, FNR was 19.3%, when only 1 SLN was identified, and in ACOSOG Z1071 it was 21%, when at least 2 SLN were identified. Meanwhile, the SENTINA study (C arm) revealed FNR of 24.3% for a single SLN and 18.5% for 2 SLN. In four meta-analyses which assessed SLNB in 9,266 patients, FNR ranged from 13–17% (14.8% on average) and

Table II. Prospective clinical trials concerning SLNB performed after NAT in the case of conversion from cN1/pN1 to ycN0 [74, 75]

Trial		SENTINA	ACOSOG Z1071	SN FAC	Genea 2
number of patients		592	689	153	307
stage		N1–2	T0–4 N1–2	T0–4 N1–2	
identification of SLNs (%)		80.1	92.3	87.6	80.0
FNR (%)		14.2	12.6	13.4	11.9
number of SLNs (average)		2	2	2.7	1.9
SLN FNR (%)	1 SLN	24.3	31.5	18.2	19.3
	2 SLN	18.5	21	4.9*	7.8*
	≥3 SLN	7.3	9.1	NR	NR
	sngle technique	16	20.3	16	
	dual technique	8.6	10.8	5.2	
	FNR with IHC in pathology	NA	8.7	8.4	
definition of a metastasis		ITC	>2 mm	ITC	

* reported ≥2 SLN; NR – no data

fell to 10.4% with application of isotope and staining in biopsy and sampling of 2 SLN.

Analysis of study results presented in table II allowed a conclusion that application of the dual method in SLNB and identification of at least three lymph nodes corresponding to SLN criteria allow for reduction of FNR below 10% and improve SLN identification within drainage of the biopsied nodes. Therefore, in order to reduce FNR (below 10%), and thus to increase a chance of identification of the residual disease in the regional lymph nodes, international and national organisations recommend application of the dual method in patients with ycN0 disease and identification of at least three SLN (some organisations suggest even four SLN) [18, 19, 74, 75, 59, 70]. Meanwhile, guidelines by the American Society of Breast Surgeons provide for necessary identification of at least two SLN, or preferably three of them. The guidelines are based on expertise of American surgeons who participated in the I-SPY study, in which SLN biopsy techniques after NAT were developed [63, 70].

Histopathology testing with immunohistochemistry (IHC) staining is not a routinely recommended method of histopathology diagnostics of sentinel lymph nodes in breast cancer, although it has been applied in some prospective studies with randomised patient selection. Application of IHC allows for identification of isolated tumour cells (ITC) and reduces FNR to 8.4–8.7% [62]. Identification of ITCs and micro-metastases in SLN after NAT may result from partial response of the micro-metastasis to the applied treatment or else they may be a pool of tumour clones refractory to systemic treatment [76]. If a metastasis to SLN (of any size) is found in the post-operative histopathology test, probability of metastases to other axillary lymph nodes increases by 17–69%. This is why any size of metastasis to SLN after NAT is an indication to ALND [77–79]. It seems that an intra-operational test of sampled SLNs would be interesting. Unfortunately, this is not a way to find ITCs or micro-metastases, but it allows good identification of macro-metastases. Intraoperative tests have FNR above 10%: 30% of the false negative results concern ITCs, and 46% – micro-metastases [80, 81]. A. Barrio argues that identification of 88% of drainage ≥3 SLN after NAT allows for resignation of labelling of the lymph node that was metastatically changed before NAT, this is why the Memorial Sloan Kettering Cancer Centre prefers SLNB with dual marking and sampling of ≥3 SLN (four SLN on average). This centre does not apply TAD technique in SLN biopsy after NAT [64, 82]. Other centres' experience shows that in about 2/3 of patients with ypN0 cancer after NAT (conversion from pN+), ≥3 lymph nodes can be identified [83].

Option 2. TAD biopsy of sentinel lymph nodes. It involves sampling within SLNB of a lymph node labelled before NAT, where a metastasis was found before the systemic therapy. The following methods of labelling nodes are used:

- attaching a marker to the metastatic lymph node,
- performing a tattoo of the metastatic node with carbon particles,
- application of a marker with radioactive isotope ^{125}I to the metastatic node,
- application of an electromagnetic marker to the node, analogically to the SentiMag biopsy method.

Each of the above methods improves effectiveness of SLNB. However, depending on the centre, its technical and financial capabilities, different node marking techniques are used [84]. Attaching the marker to the metastatic lymph node before the start of NAT, analogically to the breast tumour, allows precise labelling of the lymph node containing metastasis. The problem is its identification during SLNB.

One of the identification techniques is the intraoperative ultrasound of the axillar cavity and identification of the SLN containing the marker. After NAT, the marker was identified in an ultrasound study in 72–83% of patients [85, 86]. Another

method to facilitate identification of a labelled lymph node is to establish an "anchor" on the day of surgery, similar to the location of the cancer in the mammary gland. This technique is applied by the team of the Department of Breast Cancer & Reconstructive Surgery of the National Research Institute of Oncology in Warsaw. Meanwhile, some centres before the surgery apply the ^{125}I isotope marker to the lymph node.

A single-centre study of MD Anderson in the United States concerned biopsies of sentinel lymph nodes with subsequent ALND. For SLNB using staining and isotope, FNR was 10.1%. Sampling of stained SLN/SLN collecting the isotope and necessary sampling of the node labelled before NAT with the ^{125}I isotope marker allowed reduction of FNR down to 2.0, and in the case of the labelled node itself – to 4.2%. Meanwhile, with intraoperative sampling of lymph nodes which corresponded to the sentinel lymph node criteria (isotope uptake and staining), and no identification of the node with a marker among them, FNR was 23% [2].

Multiple studies confirm the value of TAD technique in SLNB [17, 24]. The problem of identifying the right lymph node may arise from marker migration outside the labelled node due to its involution caused by chemotherapy. However, these inconveniencies do not affect benefits perceived by multiple oncological associations which recommend this technique of SLNB [18, 19, 59, 75].

Tattooing of the metastatically changed lymph node with carbon particles or injecting the node with an electromagnetic marker, analogically as in the SentiMag breast biopsy method, is another type of TAD biopsy. However, tattooing the node with carbon particles may be inaccurate, as there have been reports of migration of the staining to other nodes in the region. During SLNB procedure, in 45% of cases of drainage, more tattooed SLN were found than were actually tattooed before NAT [87]. Thus, tattooing is a less accurate alternative method to application of a marker [18, 19, 59, 74, 75]. Injection of an electromagnetic marker, analogically as in the case of SentiMag breast biopsy method, is performed by very few institutions, experienced in SLNB with application of this carriers. In the Netherlands, it is recommended to apply a marker containing a radioactive ^{125}I isotope (MARI clinical trial), allowing for reduction of FNR down to 7%. However, this is not a typical SLNB method, because a colloid containing ^{99}Tc or stain is not administered preoperatively. Meanwhile, in the ACOSOC 1071 trial and one-centre MD Anderson study, sentinel lymph node biopsy with ^{125}I isotope marking enabled reduction of FNR below 2% [2].

According to a 2017 survey of members of the American Society of Breast Surgeons – ASBrS, 67% of surgeons use markers for lymph nodes. The most common markers used intraoperatively in SLN were "anchors" (52%) and isotopic markers (9%). After a biopsy, 82% of surgeons performed an intraoperative mammography of the preparation to confirm presence of the marker in SLNB. According to this survey, still, 21.9% of surgeons routinely performed ALND after NAT without attempting to perform SLNB [80, 88]. It appears that "extended SLNB" (endoscopic sentinel lymph node biopsy – ESLNB), i.e.:

- biopsy using staining and isotope,
- removal of at least 3 SLN (including nodes with a metastasis diagnosed before NAT and a marker attached), and
- ALND, if no pCR in sampled SLN (including even ITC),

is an oncologically safe method and allows avoiding ALND in patients with initially cN1 cancer and conversion to ycN0 after NAT [72, 62].

Axillary lymphadenectomy without attempting to perform SLND after NAT is recommended in patients:

- with clinically altered axillary nodes at presentation – cN2/3 (or >2 suspicious lymph nodes in ultrasound),
- with any histopathologically confirmed metastasis to SLN after preoperative therapy (ypN+ – including ICT and micro-metastases),
- if there are fewer than three SLN identified (in some institutions the threshold is two SLN) in the case of application of the "dual" technique in SLNB,
- if the lymph nodes with a marker affixed are not identified in the TAD method [18, 19, 59, 70].

In the case of patients with cN2-3 disease after NAT, the effect of ALND on improved survival in this groups has not been determined. The trial by Park et al. suggests a positive effect of lymphadenectomy in this group of patients (HR – 0.68, $p < 0.0010$) [73]. The authors listed multiple limitations of the study, including inability to assess the patients' overall condition, inability to assess LFR and DFR, inability to unequivocally identify patients who underwent SLNB and ALND beside the arbitrarily assumed number of removed lymph nodes. It should be stressed that most flagship studies, including NSABP B-04, indicate no benefit from ALND as compared to SLNB in patients with N2–N3 at presentation [89]. Bonneau et al. found no differences in survival between patients with 3 or more metastatic lymph nodes, whether or not these patients had SLNB or ALND [90].

Pathomorphological assessment of response to systemic treatment in breast cancer

Evaluation of postoperative material after systemic treatment is an important issue in pathomorphological diagnostics, considering the lack of a single, broadly accepted method of its reporting. The following terms are used the most frequently in pathomorphological analysis of the response to treatment:

- the system associated with the TNM classification (tumour-node-metastasis) by the American Joint Committee on Cancer (AJCC),
- system for describing residual cancer burden (RCB),
- Pinder system.

Post-treatment surgical procedures – a tumorectomy or mastectomy with sentinel nodes sampling or lymphadenec-

tomy – are primarily of therapeutic nature, but they also allow determination how the cancer responded to the applied systemic treatment. Thus, the likely future development of the disease can be forecasted, too.

The pathomorphological assessment of cancer after systemic treatment has been standardised in recent years. Sampling is key for getting comparable results. It is recommended to harvest samples containing the entire cross-section through the tumour bed. Tumour bed is the area within the breast that was originally occupied by cancer. In the case of little response to treatment, there is no difficulty in finding, measuring and sampling this area. In cases of complete or near-complete response, sampling must be correlated with the tumour's radiological description (its location, size, potential multifocality) and involves finding the marker placed in the tumour during the diagnostic biopsy. However, in cases of significant pathomorphological response, finding the metastatically changed lymph nodes is sometimes difficult in the process of harvesting diagnostically reliable samples.

For many years, pathomorphology reports described the degree of damage to tumour cells after the treatment (significant, insignificant, none) and occurrence of necrosis (percentage of necrotic tissue). However, it is difficult to define the degree of damage. This type of assessment is subjective and difficult to use clinically. The assessment methods described below use more measurable response parameters and their results are more objective and comparable. Their value is documented by clinical studies. In the proposed systems, it is important to refer to changes both within the primary tumour and in metastases to lymph nodes. The system proposed by the VIII edition of AJCC (TNM) is better adapted to non-pathomorphological diagnostic techniques, but it should be included in the pathomorphology report, too. It suffices to determine T and N parameters and compare them to respective results before the treatment (tab. III).

Table III. Classification of breast cancer after neoadjuvant therapy according to AJCC (VIII edition of 2018)

Category of response to treatment	Definition	Sample entry
CR complete response	no tumour infiltration or metastases	ypTisypN0cM0 pCR
PR partial response	reduced T and/or N parameter and no increase in T or N parameter	ypT1ypN0cM0 pPR
NR no response	unchanged T and/or N parameter or increase in T and/or N parameter	ypT2ypN1cM0 pNR

The system to describe the residual cancer burden (RCB) (tab. IV) applies easily defined parameters which can be assessed in microscopic evaluation of H-E staining. The mathematical formula of RCB is complicated, but it can be calculated within several seconds with an online calculator (RCB calculator) (tab. V), available at: http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3

If there is no internet connection, only its components required for its calculation can be defined:

- 2 dimensions of the initial tumour,
- tumour cellularity,
- *in situ* tumour tissue,
- number of metastases to lymph nodes,
- size of the largest metastasis to a lymph node.

Due to inclusion of more parameters and the numerical, easily compared form of the result, RCB seems more valuable for an oncologist analysing a post-operative pathomorphology report. From the point of view of people and organisations involved in analysing efficiency of breast cancer treatment, this system with no additional financial expanses allows for objective and reproducible assessment of response to cancer treatment.

Table IV. Calculating the residual cancer burden (RCB)

Components required for assessment of the residual cancer burden (RCB)			
tumour	1.	size of the original tumour (2 dimensions) – the largest tumour in the case of multinodular breast cancer (mm)	$d_{prim} = d_1 d_2$
	2.	tumour cellularity after treatment – percentage of the area covered by neoplastic cells (%)	$f_{inv} = (1 - (\%\ CIS/100) \times (\%\ CA/100)$
	3.	percentage of ***in situ*** tumour tissue after treatment (%)	% CIS
lymph nodes	4.	number of metastatic lymph nodes	LN
	5.	diameter (largest dimension) of the largest metastasis (mm)	d_{met}
Method of calculation of the RCB Index and definition of RCB categories [91]			
RCB index		$RCB = 1.4\ (f_{inv}\ d_{prim})^{0.17} + [4(1-0.75^{LN})\ d_{met}]^{0.17}$	
RCB groups		RCB 0 = RCB 0 index or pCR	complete remission (pCR)
		RCB I = index above 0 to 1.36	minimal residual disease
		RCB II = index above 1.36 to 3.28	moderate residual disease
		RCB III = index above 3.28	massive residual disease

RCB evaluation with online calculator (RCB calculator) http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3

Table V. Describing residual cancer burden (RCB) [91]

www.mdanderson.org/breast-cancer_RCB	
RCB 0 (pCR)	no cancer in the breast or lymph nodes (pCR)
RCB 1	partial response, minimal residual cancer
RCB 2	partial response, moderate residual cancer
RCB 3	chemoresistance, massive residual cancer

A report in the case of tumorectomy or mastectomy after systemic treatment includes the same elements as a routine pathomorphology report. Additional elements to be specified:

- cellularity,
- presence of changes in the breast resulting from the treatment applied,
- presence of changes in lymph nodes resulting from the treatment applied,

The Pinder scale (tab. VI) is recommended in the European Union's guidelines as a method of presenting response to treatment, although it is not referred to in literature as frequently as the RCB system.

Application of neoadjuvant therapy in breast cancers affects also other parameters, including predictive factors. The status of the steroid receptors, estrogen ER and progesterone PgR, as well as HER2, may be altered. It concerns from a few to over ten percent of cases, depending on the parameter. There may also be a change in the mitotic index of cancer, determined by immunohistochemical expression of the Ki-67 protein, which most often decreases compared to before treatment. Therefore, if a complete pathomorphological response has not been achieved, it is advisable to repeat the assessment of predictors in the section containing the residual infiltrating cancer tissue. A pathomorphological report of these parameters after systemic treatment is analogous to that of an untreated tumour.

Radiotherapy after systemic neoadjuvant treatment

Table VI. Assessment of response to systemic treatment in breast cancer according to the Pinder scale [92]

Breast
1. pCR: (1) no residual cancer or (2) no residual infiltrative cancer but cancer *in situ* present
2. partial response (1) minimal residual disease (<10% of the residual tumour) or (2) evidence of response with 10-50% persistent cancer, or (3) >50% of persistent cancer with evidence of post-treatment damage
3. no evidence of response to treatment.
Lymph nodes
1. no metastases and no evidence of response to treatment
2. no metastases, but evidence of treatment response present
3. metastases present but with evidence of response to treatment
4. metastases present and no evidence of response to treatment

Changed rules of proceeding in clinical oncology and breast cancer surgery, introduced in recent years, have led to changes in radiotherapy. Currently, in consideration of referral for adjuvant therapy, the following should be taken into account:

1. initial clinical stage of the disease,
2. application of the systemic neoadjuvant therapy and degree of response to treatment,
3. type of breast surgery performed (breast-conserving surgery vs. mastectomy),
4. type of axillary surgery (sentinel node biopsy *vs.* axillary lymphadenectomy),
5. final result of postoperative histopathological examination.

Currently, two groups of patients undergo preoperative systemic treatment: those with initially operable breast cancer, mainly (TNBC or HER2-positive) of cT1–2N0–1 clinical stage, and those with locally advanced, initially inoperable breast cancer, regardless of biological type.

Irradiation of patients with initially operable cT1–2N0–1 HER2-positive or TNBC breast cancer after systemic neoadjuvant treatment and after surgery

Breast irradiation

In all cases of invasive breast cancer, the remaining mammary gland is irradiated after the conserving surgery, but the extent of irradiation within the breast depends on the risk of local and regional recurrence.

In patients at high risk of recurrence – i.e. under 50 years of age, with a biological type of triple-negative or HER2-positive cancer, histological G3 grade, with invasion of lymphatic and blood vessels by cancer cells or with a narrow / questionable margin of healthy tissue around the excised tumour – the entire remaining mammary gland is irradiated and the dose to the bed after the excised cancer has to be increased (boosted).

In patients at average risk of recurrence – that is, at the age of 60 and more, with biological type of luminal cancer, histological grade of G1, G2 – irradiation to the tumour bed can be foregone after irradiation of the entire breast, provided that the patients receive hormone therapy.

The technique of choice in treatment of patients after a breast-sparing surgery is 3D conformal radiotherapy (3D CRT) with application of a computer-aided treatment planning system. A modification of this technique involves 3D irradiation with simultaneous integrated boost (SIB) in the tumour bed [93]. In exceptional cases, when the 3D CRT treatment plan is unacceptable due to the unsatisfactory distribution of the radiation dose in the treated breast or too high radiation dose to critical organs (heart, lung, other breast), the patient after a breast-sparing surgery is irradiated with a technique using modulation of beam intensity (intensity modulated radiation therapy – IMRT) from static fields or using dynamic

techniques (e.g. arc technique [volumetric intensity modulated arc therapy – V-MAT]). By using a multileaf collimator (MLC), a three-dimensional dose distribution is obtained, adapted to the shape and size of the irradiated area [94]. In order to reduce the exposure of the heart to radiation, in patients who have undergone surgery on the left breast, the technique of irradiation in deep breath hold (deep inspiration breath hold – DIBH, 4D radiotherapy) is used. Thus, the average dose to the heart and coronary vessels can be reduced [95] .

Based on the Ontario Trial, START A and START B studies, in which fractional doses (hypofractionation) higher than 2 Gy were tested, irradiation in 15–16 fractions of 2.5–2.67 Gy is a standard in breast-sparing treatment and after mastectomy, irrespective of the patient's age and applied neoadjuvant chemotherapy [32, 96–98]. Basing on its own results [99, 100], the National Research Institute of Oncology in Warsaw applies mild hypofractionation in a fractional dose to the whole breast of 2.25 Gy up to a total dose of 45 Gy and a fractional dose per tumour bed: 2.7–2.8 Gy up to a total dose of 54–56 Gy.

Nodal area irradiation

Indications for nodal irradiation are a much bigger problem in patients with initially operable breast cancer after systemic neoadjuvant treatment. In this group of patients, the principles of radiotherapy for patients after the primary surgery do not apply, because the radiotherapist has no information on the number of axillary lymph nodes initially involved by metastases. Before starting systemic neoadjuvant treatment, only a biopsy of the breast tumour and axillary lymph nodes is performed, obtaining information only about the presence or absence of neoplastic cells in the lymph nodes, without precise determination of the number of nodes affected by metastases (1–3 *vs.* 4 and more).

In patients with clinical features of cN0 stage (no palpable lymph nodes) at presentation, if the sentinel lymph node procedure after neoadjuvant chemotherapy confirms the absence of pN(sn)0 lymph node metastases, there is no indication for radiotherapy in the nodal area.

In patients with the initial clinical features of cN0 stage, if the sentinel node procedure after neoadjuvant chemotherapy confirms the presence of axillary lymph node metastases (pN1), then axillary lymphadenectomy should be performed, followed by irradiation of all nodal regions, especially if there are additional risk factors for recurrence (TNBC cancer, age <40 years, G3, poor response to systemic therapy) [75, 101].

In patients with the initial clinical features of cN1 stage (palpable metastases to axillary lymph nodes, confirmed in fine-needle biopsy), if the sentinel node procedure performed after neoadjuvant chemotherapy still confirms the presence of lymph node metastases (pN1), then after axillary lymphadenectomy all nodal areas should be irradiated [101].

In patients with the initial clinical features of cN1 stage (palpable metastases to axillary lymph nodes, confirmed in fine-needle biopsy), if the sentinel node procedure performed after neoadjuvant chemotherapy reveals no lymph node metastases (pN0) and axillary lymphadenectomy has not been performed, then nodal areas should be irradiated.

In patients with initial clinical features of cN1 stage (palpable metastases to axillary lymph nodes, confirmed in fine-needle biopsy), if no metastases to lymph nodes are found after neoadjuvant chemotherapy and axillary lymphadenectomy, then additional recurrence risk factors should be assessed (especially the patient's age, G stage, Ki-67, response to the therapy within the breast) and the team should decide on irradiation of all nodal areas [32, 98, 101]. A pending clinical trial NSABP B51 assessed the role of radiotherapy in patients with cN1–>pN0 features after the systemic neoadjuvant therapy of an initially operable breast cancer [75, 101].

Irradiation of patients with locally advanced, inoperable breast cancer after systemic neoadjuvant treatment and mastectomy

Patients with locally advanced breast cancer (in clinical stage III, with T4 and/ or N2/ N3 features), after systemic neoadjuvant treatment and mastectomy with lymphadenectomy, always have indications for postoperative radiotherapy of the chest wall and regional lymph nodes, regardless of the achieved clinical and pathological response after systemic treatment. This applies even to patients with complete pathological regression of lesions (pCR), in whom the risk of local and locoregional recurrence without radiotherapy is 33%. The decision about radiotherapy in this group of patients is influenced by the initial stage of the cancer [102].

Irradiation after mastectomy covers the area of the chest wall after the removed breast and the area of supraclavicular nodes, three levels of the axillary and parasternal nodes. Controversies concerning advisability of irradiation of parasternal nodes concern low risk of recurrence in this nodal group, associated with high risk involved in relatively high-dose irradiation of main coronary arteries which supply both the left and right heart ventricle. According to current recommendations, post-operative irradiation of parasternal lymph nodes is applied in patients with cancer located in medial chest quadrants, with multiple metastases to axillary lymph nodes, upon confirmation that the heart will not be irradiated with too high a dose [101].

In irradiation of the chest wall and regional lymph nodes, 3D photon techniques, IMRT photon techniques (static or V-MAT) are applied, and so are photon-electron techniques, but less frequently. Usually a total dose of 50 Gy is administered in 25 fractions. Hypofractionation is also allowed at a fractional dose of 2.67 Gy, although the scientific evidence of safety of such treatment in patients after mastectomy is lesser than in the case of patients after breast-sparing treatment [75, 96]. In Poland, most radiotherapy centres irradiate patients after mastectomy with a fractional dose of 2.25 Gy and a total dose

of 45 Gy – according to the results of a clinical trial carried out at the Oncology Centre in Warsaw [99].

In patients with features of T3N1 after neoadjuvant chemotherapy with significant regression within the breast, a sparing surgery may be considered, however, in all cases, postoperative irradiation of the breast and regional lymph nodes is necessary.

Supplementary irradiation of patients with pT3N0 stage was a subject of controversy due to the lack of randomized clinical trials on this issue. However, the analysis of 4,291 patients with pT3N0 breast cancer showed a clinical benefit from irradiation of the chest wall and regional lymph nodes - reducing the risk of recurrence and prolonging survival of patients, especially <75 years of age [103, 104].

Benefits of the systemic neoadjuvant treatment in patients treated for breast cancer

Neoadjuvant systemic therapy in patients treated for breast cancer:

- facilitates surgery in cases of inoperable breast cancer,
- facilitates performance of a breast-sparing surgery instead of radical mastectomy,
- enables obtaining information on the individual response to the applied systemic treatment,
- allows modification of adjuvant treatment in the case of partial pathological response (pPR) after systemic treatment,
- provides the necessary time to perform genetic testing and a possible change in the scope of the operation,
- enables development of a reconstructive surgery plan - in patients who choose to undergo mastectomy [19].

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Wojciech M. Wysocki
5. Wojskowy Szpital Kliniczny z Poliklinika w Krakowie
Klinika Chirurgii Ogólnej, Onkologicznej i Naczyniowej
ul. Wrocławska 1–3
30-901 Kraków, Poland
e-mail: wwysocki@mp.pl

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