Current Oncology Reports
https://doi.org/10.1007/s11912-019-0850-y

BREAST CANCER (B OVERMOYER, SECTION EDITOR)

When Can We Avoid Postmastectomy Radiation Following Primary Systemic Therapy?

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Abstract

Purpose of Review Postmastectomy radiation therapy (PMRT) has been shown to reduce the risk of locoregional recurrences (LRR) and of distant metastases (DM) and to improve breast cancer–specific survival (BCSS) as well as overall survival (OS) in patients with locally advanced breast cancer who are considered high risk because of large tumors (> 5 cm) and/or presence of axillary lymph node involvement.

Recent Findings Controversy is still ongoing with respect to the indication of PMRT in the case of earlier stage invasive tumors in the presence of risk factors including young age, premenopausal status, presence of lymphovascular invasion (LVI), high tumor grade, or tumor size 2–5 cm. Simultaneously, the evolution of our understanding of breast cancer biology has led us to better identify patients for whom the administration of systemic treatment prior to surgery reduces tumor load, not only in the case of locally advanced tumors but also for earlier stages, namely in the case of unfavorable molecular subtypes. The role of PMRT in the context of these patients treated with primary systemic therapy (PST), especially after a good tumor response, is under evaluation by various studies.

Summary This review identifies factors that may permit PMRT omission in a selected group of patients after PST.

Keywords Breast cancer · Mastectomy · Postmastectomy radiation therapy · Primary systemic therapy · Lymph node irradiation

Introduction

Locoregional treatment of breast cancer has evolved remarkably over the last decades. Modified radical mastectomy has been traditionally the primary treatment for women presenting with locally advanced breast cancer or for those who present challenges for breast-conserving surgery. There is a consensus for postmastectomy radiation therapy (PMRT) for patients presenting with more advanced stages of breast cancer and with risk factors for locoregional recurrence (LRR) and worse overall survival (OS), including involved axillary lymph nodes, large tumor size, young age, or more aggressive molecular subtypes. Available evidence also suggests that PMRT reduces the risks of locoregional failure (LRF), any recurrence, and breast cancer mortality for patients with T1–2 breast cancer with one to three positive axillary nodes as well as large tumors (> 5 cm) without lymph node involvement at diagnoses (T3N0) [1–7, 8•, 9•].

Current multimodal approach for breast cancer includes the combination of systemic treatment, surgery, and radiation therapy. In recent years, it became increasingly common to administer primary or preoperative systemic treatment (PST) prior to surgery and radiation therapy. The purpose of this review is to identify criteria that can be used to identify patients for whom we can avoid PMRT in the setting of PST.

Primary Systemic Treatment: Implications for Radiation Therapy

Primary systemic treatment for breast cancer was originally conceived to allow more conservative surgeries for initially unresectable tumors. An analysis based on 5500 women

This article is part of the Topical Collection on *Breast Cancer*

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Published online: 29 October 2019

included in different randomized studies comparing primary versus adjuvant systemic treatment showed equivalent results in terms of survival. However, PST could prevent mastectomy in 25% of patients unsuitable for conservative surgery upfront, although < 5% of patients initially eligible for conservative surgery required a mastectomy due to disease progression under PST [10].

Although PST has not shown survival improvement compared to the same scheme delivered postoperatively, there are some advantages next to an increased breast conservation rate that justifies its use in selected groups of patients: monitoring of clinical and pathological response in response to chemotherapy in clinical trials, switching to other systemic therapy in case of lack of response, allowing patients to think about locoregional treatments, buying time for performing genetic tests, and avoiding axillary surgery in clinically node-positive (cN+) patients who have a pathological complete response (pCR) and can progress with nodal irradiation without surgery. Therefore, currently, PST is progressively used for breast cancer patients with unfavorable prognostic factors to achieve high rates of pCR, which has been recognized as a predictive prognostic factor for survival in both HER2-positive (HER2+)/hormone receptor-negative (HR–) and triple-negative (TN) breast cancer patients [11, 12, 13•]. However, this association between pCR and survival outcomes is not seen in slowly proliferating, hormone receptor-positive, mainly luminal A-type cancers [14]. Results from large randomized clinical trials (NeoSphere, TRYPHAENA, and BERENICE trials) demonstrated that dual HER2-targetedblockade with trastuzumab/lapatinib and trastuzumab/pertuzumab together with standard chemotherapy works synergistically in HER2+ patients, reaching pCR in more than 50% of women and favorably impacting OS [15–17]. Similarly, in women with TN disease, PST is being increasingly used, with the addition of platinum-derived compounds to a classical taxane–anthracycline schedule improving pCR rates to over 50% [18, 19].

After PST, there exists an absolute consensus in favor of postoperative radiation therapy after breast-conserving surgery, regardless of the pathological response. In contrast, the role of radiation therapy after PST and mastectomy is subject to a continued debate due to the absence of high-level evidence. Initially, PMRT guidelines after PST recommended PMRT according to the initial stage of disease pre-PST, which required pre-PST staging of the axilla, a practice that has been largely abandoned over the years [20•]. Following the high rates of pCR following contemporary PST, one of the most controversial issues is how to identify patients having a low enough risk of LRR to avoid PMRT after PST. Since data from randomized trials answering this question are lacking, guidelines are based on available evidence coming from retrospective studies, several using data from prospective studies evaluating chemotherapy questions, with heterogeneity in the sample sizes, different stages at diagnosis, older chemotherapy schedules, and nonuniform criteria for PMRT administration.

The first evidence for PMRT after PST [21] comes from a retrospective analysis of data from prospective PST studies of the MD Anderson Cancer Center (MDACC) that analyzed 542 women with stage II–III breast cancer who received PST followed by mastectomy and PMRT versus 134 patients with similar PST who did not receive PMRT. PMRT administration was based on investigator's choice. Overall, the 10-year LRR rates were lower with PMRT (11 vs. 22%, $p = 0.0001$). Patients with clinical stage III disease who obtained a pCR after PST had a 10-year LRR rate of 33% without PMRT, compared to 3% after PMRT ($p = 0.006$) [22, 23]. Subsequently, the same researchers retrospectively identified 226 patients who achieved a pCR at surgery after receiving PST. They subsequently analyzed 106 patients with stage I–III without inflammatory breast cancer treated with PST and mastectomy that had achieved pCR. Patients who received PMRT were compared with those who did not. With a median follow-up of 62 months, results showed no benefit of PMRT in patients with stage I–II breast cancer in reducing LRR (0% at 10 years in both groups), but in patients with stage III tumors, the LRR rate at 10 years decreased from 33% without PMRT to 7.3% following PMRT. Distant metastasis-free survival (DMFS), cause-specific survival (CSS), and overall survival (OS) rates differed significantly between irradiated and nonirradiated patients with stage III disease. In this cohort, the 10-year DMFS rate was 87.9%for the irradiated patients and 40.7% for the nonirradiated patients ($p = 0.0006$). The 10-year CSS rate was 87% for the irradiated patients and 40% for the nonirradiated patients ($p = 0.0014$). Lastly, the 10-year OS rate was 77.3% for the irradiated and 33.3% for the nonirradiated patients ($p = 0.0016$) [24].

The results of these studies clearly confirmed the value of PMRT irrespective of the pathologic response to PST, at least in certain subgroups of patients. Therefore, PMRT should be part of the treatment discussion in all women who received PST.

Pathological Complete Response After PST: What Is the Definition of Complete Pathological Response in the Breast and Lymph Nodes?

Achieving a complete response is a clear objective of the administration of PST. However, the first challenge lies in defining the concept of "complete pathological response" with notable differences among different studies [25]. The evaluation of the tumor response in breast and lymph nodes is variable. The possibility of performing sentinel lymph node biopsy (SLNB) after PST has aroused an attractive option to avoid complete axillary lymph node dissection (ALND) in

clinically node negative (cN0) patients. Studies examining node-positive patients diagnosed by needle biopsy who undergo PST report rates of nodal pCR ranging from 35 to 68% [26]. However, the use of SLNB after PST is not devoid of risks, mainly due to the high rate of false negative results (FNR), which may lead to undertreatment. The SENTinel NeoAdjuvant study (SENTINA) [27] evaluated axillary surgery strategies among four subgroups of patients. A subgroup included cN0 patients who underwent SLNB before PST, and those with confirmation of a positive SLN underwent a repeated SLNB and axillary lymph node dissection after PST. In this latter cohort, the rate of identification of SLN in the second SLNB ($n = 64$) was 61% and 52% were false negative. In the arm of cN+ patients who achieved a complete lymph node response (ypN0), the FNR rate was 14% overall, but it varied if one, two, or three sentinel lymph nodes were identified up to 24, 18, and 5%, respectively.

The Z1071 trial of the American College of Surgeons Group (ACOSOG) [28] also evaluated the viability of SLNB after PST in patients with confirmed cN+ disease by biopsy. The main objective of the study was to reach 10% or less FNR. Patients were required to have at least two SLN identified. The FNR among these women was 13%, failing to meet the predefined rate of 10% to consider the procedure as satisfactory. However, when at least three SLN were identified, the FN rate was significantly lower (FNR 9% with ≥ 3 SLN vs. 21% with two or less SLN, $p = 0.007$). In an unplanned exploratory analysis, a significant reduction in the FNR was observed with the use of a dual tracer instead of a single tracer to identify the SLN. FNR using a dual tracer technique was 11 versus 20% with a single agent, $p = 0.05$.

Finally, the SLNB study after primary chemotherapy (SN FNAC) [29] included cN+ patients by biopsy and examined the reliability of the SLNB after PST with a predefined optimal identification rate of 90% and a FNR of ≤ 10%. Although the study was closed early after the results of SENTINA and ACOSOGZ1071 were published, 51% of the initially planned recruitment was achieved and the authors observed an identification rate of the sentinel lymph node in 87.6% and a FNR of 8.4%. The FNR increased to 18.2% when only one sentinel lymph node was identified and 14.2% in cT3 tumors.

Numerous studies have analyzed axillary status before PST through the use of focused ultrasound and FNA of suspicious lymph nodes then marking the nodes using clips or radioiodine seeds [30, 31]. Clip placement at diagnosis of node-positive disease with removal of the clipped node during SLN surgery can reduce the FNR of SLNB surgery after PST. However, the involved clipped lymph node can be different from the identified SLN in 9 to 24% of cases. Moreover, a negative resected clipped LN does not reflect the pathological response in the rest of the ALNs; therefore, several studies suggested that a combination of SLNB and excision of clipped node(s) is required to reduce the FNR [30, 32, 33].

The pooled "Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC)" analysis including 11,955 patients from 12 international PST trials for which long-term data were available concluded that both a pCR defined as ypT0 ypN0 or as ypT0/Tis ypN0 positively impacts on survival rates. This association was strongest in patients with aggressive breast cancer subtypes [18]. Thus, it seems reasonable to consider pCR as the total absence of invasive carcinoma in the breast and lymph nodes (ypT0/Tis and ypN0) after mastectomy with axillary lymph node evaluation, for which a SLNB using a dual tracer technique and removing at least three sentinel lymph nodes is recommended.

Are There Patients Who Do Not Need PMRT After PST?

Identifying a subgroup of breast cancer patients with a risk of LRR after PST and mastectomy low enough to avoid PMRT remains a challenge. Table 1 summarizes the clinical and pathological risk factors for LRR in various studies of PST followed by mastectomy with or without PMRT.

Beriwal et al. [51] proposed five hypothetical scenarios for clinical T2–4, N0–1 tumors, with the aim of reaching a broad consensus for PMRT among experts, defined as > 80% agreement in pooled answers. Researchers reached a consensus to recommend PMRT in patients with clinical stage III tumors. However, there was variation in responses for postmenopausal patients with clinical stage II and ypN+ after PST and in women stage II–IIIA who achieved a pCR following PST.

Fowble et al. [52] reviewed the role of PMRT after PST in women with stage II–III breast cancer at diagnosis. The authors identified 24 studies, 23 of which were single institutional retrospective studies and only 1 was a multi-institutional prospective clinical trial. In the majority of studies, PMRT reduced the risk of LRR. High-risk factors for LRR were young age (< 35 years), clinical stage III at diagnosis (cT3, cN2–3), tumor persistence after PST (ypN1–3), TN subtype, and the presence of LVI or extracapsular extension (ECE) in axillary lymph nodes. The authors identified a low-risk group (≤ 10% LRR) suitable for PMRT omission: patients older than 35–40 years with clinically T1–2 tumors (cT1–2) achieving a pCR in the tumor after PST (ypN0 or ypN1). A particular group that requires an individualized discussion includes cT3N0 tumors with a pCR in the breast and axilla (ypN0) after PST. Although the authors state that the objective of the analysis was to identify a group of patients treated by PST followed by mastectomy with a sufficiently low risk of LRR to avoid PMRT, a statistically significant survival benefit with PMRT was seen for patients with clinical stage III disease, those with at least four positive lymph nodes or LVI, and in women < 35 years.

Table 1 Summary of reported risk factors for LRR (locoregional relapse) after PST (primary systemic treatment) and mastectomy

	N	MFU (years)	Patients receiving PMRT (%)	Clinical stage II	Clinical stage III	cT3	cN+	No pCR	ypN0	ypN+	LVI/ ECE	Molecular subtype	PMRT omission*
Huang 2004 [22]	676	5.8	80		+					+	+	+ (HR−)	+
Huang 2005 [23]	542	5.8	100		+		+			+	+	+ (HR)	
McGuire 2007 [24]	106	5.2	67.9		+								+
Le Scodan 2010 [34]	134	7.8	58.2										
Nagar 2011 [35]	162	6.3	73.45			+							+
Mamounas 2012 [36]	1947	11.75	0			+	+	+		+			
Wright 2013 [37]	464	4.2	100			+	+	+		+		+ (HR−, TN)	
Diaz 2014 [38]	116	5.3	87				+						
Shim 2014 [39]	151	4.9	69.5										
Meattini 2014 [40]	170	7.7	57.6			+	+ (N2)			+	+		+
Arsenault 2015 [41]	157	3.7	79.9							+		+ (HR−)	+
Yang 2015 [42]	233	5.2	100					+		+		+ (TN)	
Liu 2016 [43]	1560	4.8	57.9		+	+		+					+
Rusthoven 2016 [44]	10,283	3.3	71.82			+			+	+		+ (ER−)	+
Huang 2017 [45]	510	5.1	100							+ (ypN2–3)		+ (luminal B)	
Gillon 2017 [46•]	76	4.4	NE					+		+ (ypN2–3)		+ (luminal B, HER2+/ trastuzumab−, TN)	
Rong 2017 [47]	185	5.8	48.10	+	+								+
Ohri 2017 [48•]	29,270	5	62.5							+ (ypN3)			+
Cao 2018 [49]	88	5.7	85.22				+		+	+			+
Chen 2018 [50]	104	5.4	76								+		+

MFU, median follow-up; *PMRT*, postmastectomy radiation therapy; *pCR*, pathologic complete response; *LVI*, lymphovascular invasion; *ECE*, extracapsular ganglionar extension; *HR*, hormone receptors; *TN*, triple negative

*Clinical studies that specifically mentioned PMRT omission as a factor related to the increased risk of LRR

Pathologic Complete Response in Lymph Nodes After PST (ypN0)

The presence of axillary lymph node involvement is directly related to the risk of LRR, regardless of a complete response in the lymph nodes (ypN0) occurring after PST.

Table 2 and Fig. 1 summarize the importance of the axillary lymph node response after PST on LRR observed in various studies, which analyzed local relapse rates in relation to the lymph node response.

Kantor et al. [53] analyzed the role of PMRT in 8321 women diagnosed with cN1–2 breast cancer treated with PST and mastectomy, of which 73.1% received PMRT. With a median follow-up of 69 months, a significant benefit was observed in actuarial OS at 5 years with the use of PMRT in patients with both cN1 (75.8 vs. 71.9%, $p < 0.001$) and cN2 (69.2 vs. 58.6%, $p < 0.001$) disease, as compared to those who did not received PMRT, respectively. A benefit in survival was not observed in patients achieving ypN0 after PST, except for the subgroup of patients with negative hormone receptors (HR−).

Rong et al. [47] retrospectively analyzed 185 patients with breast cancer, stage II (84 patients) and stage III (101 patients) with ypN0 after PST and mastectomy. Eighty-nine patients received additional PMRT and 96 patients did not. For patients who received PMRT versus those who did not, the 5-year LRR rates were 1.1 and 7.5% ($p = 0.071$), the 5-year distant metastasis (DM) rates were 5.1 and 15.0% ($p = 0.023$), the disease-free survival (DFS) rates were 95.0 and 79.0% ($p = 0.008$), and the OS rates were 100.0 and 94.5% ($p = 0.089$), respectively. In patients with stage II tumors at diagnosis, PMRT significantly improved DFS compared with those who did not receive PMRT (100 vs. 84.9%, $p = 0.023$), while for stage III patients at diagnosis, PMRT significantly reduced the risk of LRR (1.9 vs. 14.4%, $p = 0.041$) and increased DFS compared with those who did not receive PMRT, respectively (91.9 vs. 67.4%, $p = 0.022$).

Shim et al. [39] retrospectively studied 417 women with stage II–III breast cancer who achieved ypN0 after PST. Of these, 151 underwent mastectomy, and 105 (69.5%) received PMRT. With a median follow-up of 59 months, 5 patients (3.3%) developed LRR and 14 patients (9.3%) developed DM. The 5-year DFS, locoregional relapse-free survival (LRRFS), and OS rates were 91.2, 98.1, and 93.3% with PMRT and 83.0, 92.3, and 89.9% without PMRT, respectively, but the difference did not reach statistical significance. In this trial, young age (≤ 40 vs. > 40 years) was associated with higher risks of LRR and breast cancer mortality.

Liu et al. [43] used data from the National Cancer Database (NCDB) to analyze the effect of PMRT in 1560 women, cN+, who achieved ypN0 after PST and mastectomy. PMRT was administered to 57.9% of patients. With a median follow-up of 56 months, no statistically significant differences were observed between the groups. However, the authors observed that PMRT significantly increased survival in patients with stage IIIB/IIIC or T3/T4 tumors at diagnosis and among those with residual breast cancer after PST ($p < 0.05$).

Pathologic Residual Disease in Lymph Nodes After PST (ypN+)

There is no uniform conclusion of the impact of PMRT in patients who do not achieve a nodal disease response (ypN+) following PST. Rusthoven et al. [44] analyzed 10,283 women with breast cancer, cT1–3, and cN1 M0 disease, treated with PST and mastectomy. Analysis showed that PMRT improved OS in both ypN0 ($p = 0.019$) and ypN+ ($p < 0.001$) patients, and maintained this benefit as an independent factor in both ypN0 (HR = 0.729, $p = 0.015$) and ypN+ (HR = 0.772, $p > 0.001$) scenarios. Ohri et al. analyzed 29,270 women with breast cancer treated with PST followed by mastectomy [48•], of which 62.5% received PMRT. Remarkably, one third of the ypN2–ypN3 patients did not receive PMRT. PMRT only improved survival in patients with ypN3 disease (66 vs. 63%, $p = 0.042$).

Le Scodan et al. [34] performed a retrospective study analyzing the efficacy of PMRT in 1054 women with stage II–III breast cancer treated with PST. A total of 134 patients had ypN0 disease after PST and mastectomy. Seventy-eight (58.2%) received PMRT and 56 (41.8%) did not. With a median follow-up of 91.4 months, the 5- and 10-year rates of LRRFS were 96.2 and 96.2% with PMRT and 92.5 and 86.8% without PMRT, respectively (p = NS), and OS was 88.3 and 77.2% with PMRT and 94.3 and 87.7% without PMRT (p = NS), respectively. The authors conclude that the omission of PMRT did not worsen the prognosis in this setting of patients.

The need for PMRT in 88 patients with cT1–2N1 treated with PST and mastectomy, of which 75 (85.2%) received PMRT, has also been studied by Cao et al. [49]. After mastectomy, 53 patients (60%) achieved ypN0. With a median

Table 2 Median rates of reported locoregional relapses according to lymph node response following PST and PMRT use

	PMRT+	PMRT−	References
ypN0	3.15% (0–7.69%)	24.4% (7.7-41.67%)	[24, 34, 36, 39, 47, 49, 50]
ypN+	10.8% (0–46%)	56.25% (11.2–100%)	[36, 49, 50]
References	[23, 37, 42, 45, 49, 50]	[23, 49, 50]	

PMRT, postmastectomy radiation therapy; *PST*, primary systemic treatment

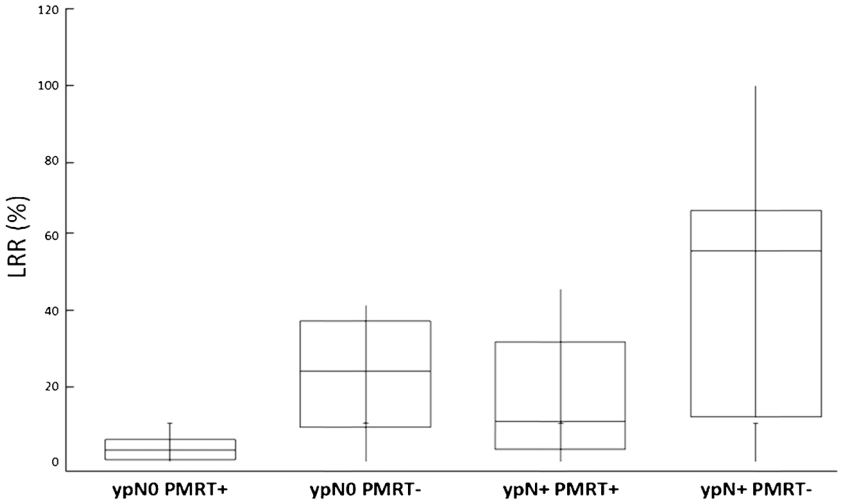

Fig. 1 Box plot figures of locoregional relapse (LRR) according to pathologic lymph node response after primary systemic treatment and the use of post-mastectomy radiation therapy (PMRT)

follow-up of 67 months, PMRT significantly improved 5-year LRRFS in all ypN0 patients (94.7% with PMRT vs. 72.9% without PMRT, $p = 0.02$). Five-year DMFS was 92.9 versus 81.5%, respectively, with and without PMRT, and 5-year DFS was 92.9 versus 72.9%. Similarly, in the ypN0 subgroup of patients, PMRT increased the rates of 5-year LRRFS, DMFS, and DFS.

Diaz et al. [38] retrospectively analyzed 116 women with clinical stage IIB tumors treated with PST and mastectomy, of which 87% of the patients received PMRT. With a median follow-up of 63 months, the authors found significant differences in LRR rates when comparing stage cT2N1 versus cT3N0 (HR = 6.03, $p = 0.015$) in favor of cT3N0, suggesting that lymph node involvement confers a worse prognosis.

Furthermore, the efficacy of PMRT in cT3cN0 patients was assessed by Nagar et al., who analyzed 162 patients treated with PST and mastectomy [35]. A total of 73.45% received PMRT. With a median follow-up of 75 months, 15 patients (9.25%) developed LRR. The 5-year LRR rates were 4% (PMRT) versus 24% (no PMRT) ($p < 0.001$). The group of patients who received PMRT included significantly more patients with affected axillary lymph nodes (ypN+) and more frequently were ≤ 40 years of age.

Meattini et al. reported their retrospective experience for 170 patients with locally advanced breast cancer treated with PST and mastectomy, of which 57.6% underwent PMRT [40]. With a median follow-up of 7.7 years (range 2–16), the actuarial rate of LRR at 5 and 10 years was 14.5% (PMRT) and 15.9% (no PMRT). The factors that were significantly correlated with increased risk of LRR were clinical stages cN2 or cT4 and the presence of LVI and ECE. Those correlated with a higher risk of DM were cN2 at diagnosis, ypN2–3 lymph node involvement after PST and mastectomy, and the existence of LVI and ECE. Finally, ypN+ after mastectomy (HR = 5.0, $p = 0.035$) and ECE (HR = 2.18, $p = 0.009$) were unfavorable risk factors for overall survival, while the presence of positive estrogen receptors conferred relative protection (HR = 0.57, $p = 0.003$). The administration of PMRT reduced the risk of LRR in patients with T3 clinical stage tumors ($p = 0.015$). The authors performed an analysis of LRR according to the accumulation of these risk factors, and LRR was 10.9% with one risk factor, 24.5% with two risk factors, and 54.3% with three risk factors.

Molecular Subtype

Breast cancer is not a molecularly homogeneous entity and can be classified according to gene expression in intrinsic subtypes (luminal A and B, HER2-enriched, basal-like, and normal-like), which primarily correspond to hormone receptor and HER2 status. Different intrinsic subtypes carry specific clinical, histopathologic, and molecular properties that entail a distinct prognosis, which can help to tailor treatments adjusted to each patient.

Different molecular subtypes have been studied in the context of primary treatment of breast cancer. Wright et al. [37] published the results of a prospective analysis conducted on 464 patients with stage II–III breast cancer treated with PST and mastectomy followed by PMRT, of which 19.6% achieved a pCR in the breast and axilla. With a median follow-up of 50.5 months, the accumulated rate of LRR at 5 years was 6%. Clinical stage III ($p = 0.038$), presence of lymph node involvement (cN+) at diagnosis ($p = 0.025$), ypN+ after mastectomy ($p = 0.003$), negative ER status ($p = 0.006$), negative PR state ($p = 0.015$), TN status ($p < 0.001$), and pathological tumor size > 2 cm ($p = 0.045$) were identified as predictors of LRR.

In addition, Yang et al. [42] studied the impact of the biological subtype on the risk of LRR in women with breast cancer treated by PST followed by mastectomy and PMRT. The study included 233 patients with clinical stages II–III, 14% of whom

achieved a pCR. With a median follow-up of 62 months, the 5-year actuarial rate of LRR was 8%. The risk factors significantly associated with an increased risk of LRR were the absence of pCR after PST ($p = 0.05$), TN status ($p = 0.005$), and presence of positive lymph nodes alone (ypN+) after PST and mastectomy ($p = 0.03$). Similarly, Chen et al. [50] studied 104 patients with stage II–III TN breast cancer treated with PST and mastectomy. PMRT was used in 76% of the patients. With a median follow-up of 64 months, the rates of LRR and any disease recurrence (DR) were 26.5 and 49.6%, respectively. Patients who received PMRT had lower rates of LRR and DR compared with those who did not (LRR 18.3 vs. 52.2%, respectively, $p = 0.0005$; DR 45 vs. 69.1%, $p = 0.0334$, respectively). Results showed that PMRT and absence of LVI were prognostic factors for lower LRR and DR (HR = 3.97, $p = 0.001$ and HR = 3.70, $p = 0.003$, respectively).

HER2 overexpression has also been linked to a worse prognosis in breast cancer. Arsenault et al. [50] retrospectively reviewed 157 patients with stages II–III and HER2+ disease treated by PST and PMRT. One third of the patients were cN+. All patients received PST, including 94% who received trastuzumab. Mastectomy was the surgical treatment in 90.4% of patients and 79.9% received PMRT. With a median follow-up of 43 months, the accumulated rate of LRR at 3 years was 8.2%. The risk of LRR was directly related to the absence of PMRT (HR = 4.70, $p = 0.006$), the nodal status of ypN1 (HR = 10.8, $p = 0.031$), pN2–3 (HR = 19.00, $p = 0.008$), and negative hormone receptors (HR = 6.02, $p = 0.006$).

Huang et al. [45] investigated prognostic factors associated with an increase in LRR risk among women with locally advanced breast cancer who did not achieve a pCR after PST. A total of 510 patients treated with PST and mastectomy with axillary lymph node dissection followed by PMRT were retrospectively analyzed. With a median follow-up of 61 months, the 5-year cumulative LRRFS rate was 88.0%, OS of 79.0%, and DFS of 63.1%. LRR rates were 6.44% (luminal A) and 22.86% (luminal B), respectively. In the multivariate analysis, the authors identified that ypN2–3 and Ki-67 index ≥ 14% were independent factors for predicting LRR. The authors constructed a model assigning 1 point to each of these factors, thus identifying three risk groups (0, 1, and 2 points) with significant differences favoring the low-risk group in both locoregional-free survival (LRFS) ($p < 0.0001$) and OS ($p < 0.0001$).

With the same intention, the EORTC study 10994/BIG 1-00 [46•] sought to identify clinical and pathological risk factors for LRR after PST and mastectomy in women with operable and locally advanced large breast cancer. The authors identified 76 cases of LRR in the 1553 patients analyzed, with an actuarial rate at 5 years of LRR of 4.9%. With a median follow-up of 4.4 years, the authors identified molecular subtype and pathological response after PST as risk factors for LRR ($p < 0.0001$ in both cases). The LRR rates were significantly lower for patients with luminal A tumors compared with those having luminal B tumors (HR = 2.29), those with HER2+ disease who did not receive trastuzumab (HR = 6.26), those with HER2+ disease who did receive trastuzumab (HR = 3.37), and those with TN disease (HR = 6.44), respectively. Lymph node pathological response was also associated with a significantly higher risk of LRR in the subgroup of women having ypN positive disease with > 4 affected nodes after PST (HR = 2.43, $p < 0.0001$).

Young Age

Young age is an independent factor directly associated with a worse prognosis in breast cancer. Different retrospective analyses, including a meta-analysis of five NSABP trials, have shown that young patients have a worse local regional control (LRC) with comparable treatment compared with older patients [54–56]. The benefit of PMRT after PST is greater in younger patients. Garg et al. [54] retrospectively analyzed 107 young women under 35 years of age with clinical stage IIA–IIIC breast cancer treated with PST followed by mastectomy. Eighty patients (74.76%) received PMRT, while 27 (25.23%) did not. With a median follow-up of 72 months, patients allocated to receive PMRT had an actuarial LRC rate at 5 years which was higher than that among patients who did not receive PMRT (88 vs. 63%, respectively, $p = 0.001$) as well as a higher actuarial OS rate at 5 years (67 vs. 48%, respectively, $p = 0.03$).

Ongoing Changing Practice Trials

The results of the studies summarized in Table 1 are mostly derived from retrospective single institutional analyses. Prospective, randomized, multicenter, and well-designed studies are needed to confirm these results and to clarify the gray areas that still exist in the use of PST, mastectomy, and PMRT for the treatment of women with breast cancer.

Current ongoing trials hope to more accurately define the role of PMRT after PST. The NSABP B-51/Radiation Therapy Oncology Group (RTOG) 1304 study initiated in 2013 aims to evaluate the benefit of radiation therapy after surgery in patients with a pCR after PST [57]. This study includes women with T1–3, N1 clinical stage breast carcinoma with histological confirmation of axillary involvement prior to systemic treatment with anthracycline and/or taxane-based regimens which allow anti-HER2 therapies (trastuzumab, pertuzumab) in HER2+ patients. The staging of the axilla after PST will be performed by ALND, SLNB, or SLNB followed by ALND. After surgery with negative margins, patients with a pCR in the breast and ypN0 will be included. In addition, patients with minimally persistent tumor in the lymph nodes (ypN0 (i+)/ypN0 (mol+)) are included. Patients treated by

mastectomy will be randomized to non-PMRT or PMRT to chest wall and regional lymph nodes. Similarly, the ALLIANCE 011202 study [58] will include patients with ypN+ by SLNB after PST. Those patients are randomly allocated to ALND and locoregional radiation therapy or locoregional radiation therapy alone. In addition, the ongoing RAPCHEM trial is a prospective nonrandomized study including breast cancer patients with clinical stage cT1–2, N0–1, and histologically proven nodal disease undergoing PST and risk-adapted PMRT. Patients with ypN0 are considered low risk and will not receive PMRT. The results of these studies are expected to clarify the definitive role of PMRT after PST in breast cancer.

Conclusion

In view of the heterogeneity among different studies, and while waiting for the results of the current ongoing studies, PMRT has proven to be an important treatment to reduce the risk of LRR and increase OS in patients with locally advanced breast cancer treated with PST and mastectomy. As such, it should be recommended regardless of the disease response to PST. In the case of patients with earlier stage disease treated with PST and mastectomy, the omission of PMRT could be considered in patients over the age of 40 years, with clinical stage II tumors (except for cT3, N0 tumors), luminal A subtype, and those who achieve a pCR in the breast and lymph nodes (ypN0), without LVI or ECE.

Overall, the decision to omit PMRT is part of a complex set of predictive and prognostic factors. It should always be discussed with the patient and her radiation oncologist, evaluating pros and cons of each alternative according to the specific case and their particular circumstances.

Compliance with Ethical Standards

Conflict of Interest The authors declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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