Review Article

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Postmastectomy Radiation Therapy in Patients With Minimally Involved Lymph Nodes: A Review of the Current Data and Future Directions

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ABSTRACT

Radiation therapy for patients with pN1mi or pN1 disease breast cancer undergoing mastectomy has been debated for a long time. Even in low metastatic burden in sentinel node biopsy, occult non-sentinel axillary nodal involvement can exist. Radiotherapy can sterilize axillary metastatic burden and seems to contribute a very low local recurrence rate in mastectomy patients with minimally involved lymph nodes. However, it should be considered that systemic therapy is evolving and the local recurrence difference between radiotherapy and no radiotherapy is relatively small. Regarding postmastectomy radiotherapy in patients pN1mi or pN1 cancer, published prospective clinical trial results should be considered; however, there are no such relevant results of clinical trials yet. Consideration of postmastectomy radiation therapy in pN1mi or pN1 patients should be based on identifying the high-risk group in terms of recurrence, stage, or tumor biology. When radiotherapy is determined, radiation oncologists should attempt individualized treatment approaches, such as irradiation field, and consider specific settings, such as neoadjuvant therapy. In this review, the role of radiotherapy in mastectomy patients with minimally involved lymph nodes and the relevant considerations are discussed.

Keywords: Breast Neoplasms; Lymph Nodes; Mastectomy; Radiotherapy

INTRODUCTION

Mastectomy is considered for cases detected with multicentric tumors or when breast-conserving surgery is not indicated. Postmastectomy radiation therapy (PMRT) is conditionally recommended in postmastectomy settings, particularly when four or more pathologically positive nodes are involved [1]. However, there is no clinical trial-based guideline for radiation therapy in patients with pN1 disease undergoing mastectomy. Indeed, the role of PMRT in pN1 disease has been a subject for a long-running debate. Moreover, whether PMRT might benefit patients with minimal axillary disease detected on sentinel node biopsy or axillary node dissection remains unknown.

The Early Breast Cancer Trialists Collaborative Group (EBCTCG) meta-analysis [1] pooled 22 available trials from 1964 to 1986 and compared the survival outcomes between those

who received PMRT, including chest wall and regional nodes, and those who did not receive PMRT. This evidence confirmed the survival benefits of PMRT in patients with 1–3 positive nodes, including reducing locoregional recurrence, any recurrence, and breast cancer-related mortality. Even when the use of adjuvant chemotherapy or the number of involved nodes is considered, the beneficial effects of PMRT on recurrence and breast cancer mortality remained significant. However, there is an apparent gap between the current practice and historical landmark trials. The EBCTCG meta-analysis addressing the efficacy of PMRT in patients with 1–3 positive nodes was mostly based on Danish trials [2,3]. In these trials, anthracyclines, taxanes, or anti-HER2 agents were not used. Thus, the benefits of PMRT may be smaller in the contemporary era.

Such uncertainty is reflected in clinical practice patterns. A nationwide cohort, case-based survey study for surgeons and radiation oncologists [4] was conducted in 2020 to review national practice patterns regarding axillary management in patients undergoing upfront mastectomy. In the case of a 57-year-old patient having two involved gross sentinel lymph nodes with micrometastases in one node, most radiation oncologists (204/265, 77.0%) favored PMRT, whereas only eight radiation oncologists recommended no further treatment. Since the impact of pN1 or pN1mi on axillary nodal involvement is uncertain, radiation oncologists tend to use a differential PMRT approach according to the number of axillary lymph nodes involved or their ratios. Thus, the role of PMRT in patients with minimally involved nodes remains to elucidated.

In this review, we aimed to investigate the impact of PMRT in breast cancer patients who have minimally involved lymph nodes. For the current review, we defined the minimally involved nodes as pN1 or pN1mi.

MINIMALLY INVOLVED WHEN RADIOTHERAPY IS INVOLVED

Based on the 6th American Joint Committee on Cancer (AJCC) staging system, histopathologic sentinel lymph node metastasis was classified into three categories: macrometastasis (pN1), diameter > 2 mm; micrometastases, diameter > 0.2 and ≤ 2 mm; and isolated tumor cells, diameter ≤ 0.2 mm. pN1mi can be considered as pN1 in the context of T2–T4, based on the AJCC 8th edition staging [5], which incorporates biomarkers and known prognostic factors to develop clinical and pathological prognostic stage groups. Regarding the pathologic prognostic stage group, pN1mi has the same prognostic status as pN0 as long as the T stage is T0 or T1. However, in a systematic review analyzing the clinical relevance of isolated tumor cells and micrometastases, Boer et al. [6] reported that the presence of metastases of ≤ 2 mm detected with one section of axillary lymph node was associated with decreased overall survival.

Minimally involved nodes identified by the sentinel node biopsy indicate the potential presence of additional involved nodes in the axilla. AATRM trials [7] randomized 247 patients with sentinel micrometastases into axillary lymph node dissection vs. axillary lymph node observation. Out of 112 patients in the axillary node dissection group, 13% (n = 15) demonstrated further axillary node macrometastases. In the interim result of the AMROS trial [8], further nodal involvement was observed in 18% of patients with pN1mi and pN0(i+) examined by sentinel lymph node biopsy. The IBCSG 23-01 trial [9], comparing axillary

dissection with no dissection in patients with sentinel-node micrometastases, revealed that 13% of the axillary dissection group patients showed metastatic non-sentinel axillary nodes. Meanwhile, a low rate (< 1%) of axillary recurrence was observed in the no axillary dissection group, supporting the role of radiotherapy that can eradicate a low volume of axillary metastasis in patients undergoing breast conserving surgery. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 trial, a randomized study comparing sentinel node biopsy with axillary dissection versus sentinel node biopsy alone, Weaver et al. [10] reviewed paraffin-embedded tissue blocks of sentinel lymph nodes collected from patients designated as pN0. For mastectomy patients (n = 488), occult metastases were detected in 21.9%: 13.9% with pN0(i+) and 8% with pN1mi or pN1. Patients showing occult metastases demonstrated significantly inferior clinical outcomes compared with those without occult metastases, although the difference was relatively small. Regarding the size of occult metastases, the impact of pN1mi or pN1 on the risk of death and recurrence was larger than that of pN0(i+). Of note, both adjuvant hormone therapy and radiation therapy were likely to reduce the hazard ratio of death among patients showing occult metastases.

Several studies have reported a low rate of locoregional recurrences in patients who did not receive PMRT. The effect of PMRT in patients with pN1mi disease was investigated using the National Cancer Institute's Surveillance, Epidemiology, and End Results database [11]. In the propensity score-matched cohort, no significant difference in the overall survival and cancer-specific survival was found between PMRT and no PMRT arms (both n = 1,142). In the secondary analysis of the NASBP B-28 [12], pN1 patients with estrogen receptor (ER) positivity showed low locoregional relapse without PMRT. However, these patients received anthracycline-based chemotherapy and anti-hormone therapy. When considering the OncotypeDx (Genomic Health, Redwood City, USA) Recurrence Score (RS), the 10-year LRR risk was 6% in high-risk patients (RS > 30).

The PMRT-NNBC trial (NCT02992574) is an ongoing trial with the aim to evaluate the role of PMRT in node-negative early breast cancer. Radiotherapy covers the chest wall and ipsilateral supraclavicular fossa. Since patients showing micro-metastasis can be enrolled, we can expect to identify the role of PMRT in patients with pN1mi cancer. Although the TAILOR RT trial is a similar study, there is a difference in terms of eligibility and radiation field. The TAILOR RT excludes patients with disease limited to nodal micrometastases and includes Oncotype DX RS ≤ 25. Apart from the PMRT-NNBC trial, the TAILOR RT allows a large PMRT target volume to irradiate the internal mammary nodes.

Studies investigating the role of PMRT in patients with minimally involved nodes are presented in **Table 1**.

IRRADIATION FIELD CONUNDRUM: MORE OR LESS?

In the EORTC 22922/10925 trial [16], patients with pN1 cancer were 43.3% and 42.9% in the no regional and regional irradiation groups, respectively. In mastectomy patients (n = 955, 23.9%), chest wall irradiation was administered to most patients in both groups (n = 701, 73.4%). For the overall study population, the benefit of regional nodal irradiation, including elective internal mammary and medial supraclavicular area, significantly reduced recurrence of any breast cancer and breast cancer mortality. However, there was no significant difference in overall survival in the subgroup of patients with pN1 cancer, as well as in the total study

Table 1. Studies on the role of postmastectomy radiation therapy after upfront surgery or neoadjuvant treatment

Study	Year	Total No.	Mastectomy	Variables			Median F/U (yr)	LRR	OS
				pN1 or pN1mi	PMRT	No PMRT			
Patel et al. [11]	2020	5,878	5,878 (100)	5,620 (95.6)	1,142 (matched)	1,142 (matched)	≥4 (estimated)	NA	HR = 1.10, p = 0.436
EBCTCG [1]	2014	8,135	8,135 (100)	1,314 (16.2)	632	682	10	10-year: 3.8% vs. 20.3% (p < 0.001)	Breast cancer-specific 20-year relative risk: 0.80 (p = 0.01)
Zeidan et al. [13]	2018	684	684 (100)	684 (100)	337	347	9	10-year: 2.5% vs. 6.5%, p = 0.005	10-year: 81.7% vs. 78.3%, p = 0.47
Killander et al. [14]	2007	668	668 (100)	264 (39.5)	91	94	22.9	20-year: 8.1% vs. 25.9% (significant)	NA
Moo et al. [15]	2013	1,087	1,087 (100)	93 (1.1)	163	924	7	5-year: 4.3% vs. 3.2%, p = 0.57	5-year: 91% vs. 94%, p = 0.28
				pN1 or pN1mi	PMRT to CW	PMRT to CW+SCL/IMN			
EORTC 22922/10925 trial [16]	2020	4,004	955 (23.9)	1,725 (43.2)	866	859	15.7	HR = 0.87, p = 0.055 for all population	HR = 0.94, p = NS for pN1
				pN1 or pN1mi	PMRT to CW/SCL	PMRT to CW/SCL+IMN			
DBCG-IMN [17]	2016	3,089	2016 (65.3)	1,818 (58.9), dissected LN ≥ 10	950	868	8.9	N/A	HR = 0.97, p = NS for pN1
				ypN1 or ypN1mi	PMRT	No PMRT			
Ohri et al. [18]	2017	29,270	29,270 (100)	15,876 (54.2)	9,184 for ypN1	6,692 for ypN1	≥5	N/A	HR = 1.06, p = NS
Rusthoven et al [19]	2016	15,315	10,283 (67.1)	6,764 (44.2)	3,186 for mastectomy/ypN1	1,318 for mastectomy/ypN1	3.3	N/A	HR = 0.835, p = 0.026 for mastectomy/ypN1
Krug et al. [20]	2019	817	817 (100)	207 (25.3)	421 for ypN+	43 for ypN+	4.3	HR = 0.81, p = 0.64 for ypN+	N/A

Values are presented as number (%).
PMRT = postmastectomy radiation therapy; LRR = locoregional recurrence; OS = overall survival; HR = hazard ratio; F/U = follow-up; CW = chest wall; SCL = supraclavicular lymph node; IMN = internal mammary node; NS = not significant; NA = not available.

population. Although the recurrence data for pN1 cancer patients was not separately presented, PMRT including regional nodes can be considered in patients with pN1 cancer, based on the main trial findings. Meanwhile, it is also possible to deliver PMRT to regional nodes only, excluding the chest wall. In the EBCTCG meta-analysis [1], eight review trials noted that patients were treated with locoregional radiation therapy, excluding the chest wall. They demonstrated that, unlike the benefit of including both regional nodes and chest wall, the benefit of PMRT was shown only for locoregional control, not for any recurrence or breast cancer mortality. Given that the most common recurrent site is the chest wall, these trials suggested the importance of PMRT to the chest wall, even in patients with minimally involved nodes.

In the proceedings of the 2018 San Antonio Breast Cancer Symposium [21], the result of EBCTCG meta-analysis investigating the role of regional RT in early breast cancer was presented. A relatively modern series of six trials (1989–2003) showed that patients who received nodal irradiation demonstrated reduced breast cancer recurrence, breast cancer mortality, and overall mortality compared with those without nodal irradiation.

Two practice-changing trials [22,23] provided an insight into the benefit of the regional node irradiation in patients with minimally involved nodes. The ACOSOG Z0011 trial [22] randomized cN0 patients receiving lumpectomy for 1 or 2 sentinel lymph node metastases into further axillary lymph node dissection versus sentinel node biopsy alone. Standard tangential field irradiation but not the direct regional nodal irradiation was allowed. With a median follow-up of 9.3 years, the overall survival in the sentinel lymph node dissection alone group was not inferior to that in the axillary lymph node dissection group. However,

there seems to be a heterogeneity in terms of radiation delivery according to the extent of axillary surgery. Jagsi et al. [24] retrospectively reviewed the radiation field design of the ACOSOG Z0011 participants. Although the tangent height was not significantly different between the two study arms, the superior border of the tangential field was within 2 cm from the humeral head in approximately half of the patients. This indicates that substantial axillary levels were likely to be irradiated, and this partial regional irradiation can potentially contribute to the low regional failure rates observed in the ACOSOG Z0011 trial—single regional recurrence in the sentinel lymph node biopsy alone group. Indeed, this so-called high-tangential field, in which the superior border was within 2 cm of the humeral head, is known to increase volumes receiving 95% of the prescribed dose from 26% to 51% and 15% to 49% in axillary levels II and III, respectively [25]. Similarly, the AMOROS trial [23] compared initial cN0 in 2,402 patients who underwent axillary lymph node dissection and 2,404 patients who received axillary radiotherapy. Most patients in both arms demonstrated pN1 disease: 737 (99%) and 673 (99%) in the axillary lymph node dissection and radiation therapy arm, respectively. Of note, approximately 75% of patients had one positive sentinel node. In this study population, an extensive field of irradiation was used, irradiating all three levels of the axilla and the medial part of the supraclavicular fossa. Although axillary radiotherapy could be performed instead of axillary lymph node dissection due to the main result of the AMOROS trial, there are still concerns about the overtreatment in irradiating the peri-supraclavicular area.

The DBCG-IMN [17], a prospective population-based cohort study, assigned 1,492 patients with right-sided disease and 1,597 patients with left-sided disease to PMRT with and without internal mammary node irradiation, respectively. PMRT covered the breast/chest wall, scar, axillary levels II and III, and supra/infraclavicular nodes. In addition, ≥ 10 lymph nodes were dissected in more than 95% of the patients in both groups. The proportion of pN1 patients receiving internal mammary node irradiation and not receiving irradiation was 60% (n = 950) and 58% (n = 868), respectively. Overall, PMRT, including the internal mammary nodes, increased overall survival. However, in subgroup analysis, 1–3 positive nodes were not associated with the benefit of PMRT, irrespective of tumor location. This result suggests that internal mammary node irradiation is disregarded in pN1 cancer, especially when the number of examined nodes was ≥ 10. The ongoing ALLIANCE A011202 (NCT01901094) trial aims to compare axillary lymph node dissection with axillary irradiation in ypN+ patients having 1–8 positive nodes, in which radiation therapy covers supraclavicular nodes and internal mammary nodes in both arms.

Collectively, the high-tangential field of radiation therapy may be a feasible option for patients with minimally involved lymph nodes.

RISK STRATIFICATION MATTERS

Although the EORTC 22922/10925 trial [16] showed the benefit of PMRT in pN0-1 patients, the heterogeneity in the beneficial effect of PMRT was observed according to the number of examined lymph nodes. When pN0–1 stage was determined based on < 10 examined nodes, the significance of PMRT benefit was pronounced in terms of overall survival. Although minimally involved lymph nodes can be currently identified with sentinel lymph node biopsy, the ratio of involved/non-involved lymph nodes is suggested as an important predictive factor for PMRT. In this trial, even in pN0, patients with medial or central tumors demonstrated a

disease-free survival benefit from PMRT, including regional nodal irradiation, suggesting the importance of risk stratification.

Multi-institutional retrospective studies were performed to identify PMRT prognosis and beneficial subgroups in pN1 patients. In the Korean Radiation Oncology Group (KROG) 14-23 [26], 1,382 pT1-2N1M0 mastectomy patients with no PMRT between 2005 and 2010 were collected. In this population, the cumulative locoregional recurrence rates at 5, 7, and 10 years were 6.1%, 7.7%, and 10.5%, respectively. The authors identified six risk factors to be eligible for PMRT: age (≤ 35 vs. > 35 years), tumor size (T1 vs. T2), resection margin status (negative vs. close), number of metastatic LNs (1 vs. 2–3), tumor grade (low-intermediate vs. high), and biological subtype (triple-negative vs. others). The 10-year cumulative LRR rates of 9.1%, 11.6%, and 17.5% were observed in patients with 0–1 risk factor, 2–3 risk factors, and 4–6 risk factors, respectively. Pooled analysis from KROG 14-22 and KROG 14-23 [27] analyzed the chest wall recurrence in pT1-2N0-1 breast cancer patients (n = 2,409) after mastectomy alone without PMRT. In pN1 patients, chest wall recurrence rate of 2.82% was observed. However, patients aged ≤ 35 years ($p < 0.001$), T2 stage ($p = 0.006$), or lymphovascular invasion ($p = 0.011$) was associated with poor chest wall recurrence-free survival rate in the propensity score-matched cohort (n = 1,588). Pooled analysis from KROG 14-18 and KROG 14-23 [28] reviewed 320 patients with pT1-2N1 triple-negative breast cancer who received taxane-based adjuvant chemotherapy to compare treatment outcomes between breast-conserving surgery and radiotherapy (n = 212) and mastectomy alone without PMRT (n = 108). A worse 5-year regional recurrence-free survival rate was observed in the mastectomy without PMRT group (89.6% vs. 96.6%, $p = 0.011$), compared with the breast-conserving therapy group. Five-year locoregional recurrence rate in the mastectomy alone group was 12.3%. This result may support the beneficial role of PMRT in triple-negative patients having minimally involved nodal disease.

Wang et al. [29] retrospectively reviewed 1,986 postmastectomy patients with pT1–2N1 breast cancer according to the AJCC 8th edition and concluded that PMRT was significantly associated with reduced locoregional recurrences, improved disease-free survival, and overall survival in the high-risk group. High risk was defined as an RS of ≥ 3. Points are summed to calculate the RS: age ≤ 40 years, inner quadrant tumor location, 2–3 positive nodes, presence of LVI, or stage IB–IIA was assigned 1 point, whereas stage IIB–IIIA was assigned 2 points. This RS system assigned 0 points to one positive node, indicating no impact on prognosis after PMRT. A significant risk in pN0 may also be significant in pN1 as well. Kim et al. [30] retrospectively analyzed 3,800 patients with pT1-3N0 breast cancer and reported an overall regional recurrence rate of 2.0%. The authors stratified pN0 patients into high- and low-risk groups based on the following factors: high histologic grade, positive lymphovascular invasion, or pT2-3 stage. The high-risk group, defined as those with ≥ 2 risk factors, demonstrated a lower 10-year cumulative recurrence rate than the low-risk group (1.2% vs. 5.5%, $p < 0.001$). It should be noted that 5.5% of the 10-year cumulative recurrence rate is still low; however, if these factors are extrapolated to patients with pN1 cancer, the recurrence rate would be higher. Collectively, these results can guide radiation oncologists to stratify patients with minimally involved lymph nodes.

Genomically guided radiotherapy has evolved in recent years [31]. The Oncotype DX RS [32] was used to determine the benefit of chemotherapy in patients with hormone-positive and HER2-negative breast cancer in postmenopausal women. This rationale was based on the first result of the randomized RxPONDER trial in the proceeding of the 2020 San Antonio Breast Cancer Symposium [33], which reported that postmenopausal women with RS of ≤ 25

had no benefit from adjuvant chemotherapy, whereas premenopausal women had a longer invasive disease-free survival with chemotherapy. The RS-guided PMRT can be possible. The TAILOR RT (Regional Radiation Therapy in Biomarker Low Risk Node Positive Breast Cancer, NCT03488693) trial aims to compare patients receiving PMRT, including chest wall/regional lymph nodes, versus those not receiving PMRT or patients with whole breast irradiation versus those with whole breast irradiation including regional nodes. Eligible patients should have positive hormone, pN1, and a low risk of RS cancer and must receive endocrine therapy. Adjuvant chemotherapy can be administered but is not mandated. Regional nodes include supraclavicular, non-dissected axillary, and internal mammary nodes that can be irradiated. This trial is expected to identify the predictive value of RS in terms of radiation therapy in the postmastectomy setting, particularly for patients having minimally involved nodal disease. Apart from the results of the RxPONDER study, the TAILOR RT trial will be expected to show how the genomic profile impacts PMRT prognosis in premenopausal women as well.

Studies that revealed risk factors in patients without PMRT are summarized in **Table 2**. Based on these data, PMRT should be considered in pN1mi or pN1 patients having known risk factors.

Table 2. Risk factors in patients who did not receive postmastectomy radiation therapy

Study	Year	Total No.	Mastectomy	Stage	Risk factors	No PMRT	Median F/U (yr)	LRR	OS
				pN1 or pN1mi					
Park et al. [26]	2017	1,382	1,382 (100)	1,382 (100)	Age < 35 years, T2 stage, high tumor grade, close resection margin, triple-negative biological subtype	1,382	5.9	10-year: 9.1% (0–1 risk factor), 11.6% (2–3 risk factors), 17.5% (4–6 risk factors)	NA
Wang et al. [29]	2020	1,986	1,986 (100)	1,023 (51.5)	0 point = Age > 40 years, other quadrant tumor location, 1 positive node, absence of LVI, stage IA; 1 point = Age ≤ 40 years, inner quadrant tumor location, 2–3 positive nodes, LVI, stage IB–IIA; 2 points = Stage IIB–IIIA ‣ low-risk = 0–1 point, intermediate-risk = 2 points, and high-risk ≥ 3 points	1,512	5.7	5-year: 2.5% (low-risk), 5.4% (intermediate-risk), 16.2% (high-risk)	NA
Chang et al. [27]	2018	2,409	1,588 (matched)	795 (matched)	Age < 35 years, LVI, T2 stage, hormone receptor negative	1,588 (matched)	6.0	2.82% for total pN1 patients	10-year: 88.4% for total pN1 patients
Mamounas et al. [12]	2017	1,065	604 (56.7)	722 (62.8)	RS-low (< 18), RS-intermediate (18–30), and RS-high (> 31)	722	11.2	10-year: 7.9% (RS-high), 5.1% (RS-intermediate), 3.2% (RS-low)	NA
Moo et al. [15]	2013	1,087	1,087 (100)	93 (1.1)	Age ≤ 50 years and LVI	924	7	5-year: 1.1% for Age 50 > years and no LVI, 11.1% for Age ≤ 50 years and LVI	NA
				ypN1 or ypN1mi					
Mamounas et al. [34]	2012	2,961	1,071 (36.2)	N/A	Clinical tumor size > 5 cm, cN+, ypN+, and no pCR with ypN0	1,947	11.75	10-year: 11.2% for cN0/ypN1/mastectomy ≤ 5 cm 14.4% for cN+/ypN1/mastectomy ≤ 5 cm, 10.6% for cN0/ypN1/mastectomy > 5 cm, 14.7% for cN+/ypN1/mastectomy > 5 cm	N/A
Ma et al. [35]	2021	1,118	1,118 (100)	319 (28.5)	Nomogram-based: Histology (other than IDC), LVI, higher ypT and ypN stage, negative ER status, Ki-67 expression > 20%.	418	7.5	5-year: 1.9% for low-risk vs 15.5% for high-risk	5-year Breast cancer-specific: 6.5% vs. 20.4%

Values are presented as number (%).
PMRT = postmastectomy radiation therapy; LRR = locoregional recurrence; OS = overall survival; F/U = follow-up; LVI = lymphovascular invasion; RS = recurrence score; pCR = pathologically complete response; IDC = invasive ductal carcinoma; ER = estrogen receptor; NA = not available.

MINIMALLY INVOLVED AFTER NEOADJUVANT CHEMOTHERAPY

According to the AJCC breast cancer staging system [5], the designation of ypN is the same as that used for pN. Any treatment-associated fibrosis is not included, but only the largest contiguous focus of the residual tumor is evaluated for classification. Additional information, such as the distance over the extent of tumor foci and the number of tumor foci, can be reported.

For women treated with neoadjuvant chemotherapy, randomized trials investigating the role of PMRT according to post-neoadjuvant status are lacking. Most data are obtained from retrospective studies or retrospective analyses of prospective studies. Rusthoven et al. [19] analyzed the impact of PMRT according to ypN stage using the National Cancer Database cohort. Of the 4,504 mastectomy ypN1 patients, 1,318 patients received no PMRT, and 3,186 patients received PMRT. Improved overall survival with PMRT is consistently observed in the ypN1 stage as well as in the ypN2-3 stage. Krug et al. [20] retrospectively analyzed pooled data from three prospective randomized trials. In the subgroup analysis, RT was associated with a lower risk of locoregional recurrence in ypN0 patients with cT3/4 or cN+ disease. PMRT showed a better trend of locoregional control in all patients with ypN+ (n = 464) (5-year locoregional recurrence rate, 13.6% with PMRT versus 17.0% with no PMRT, $p = 0.64$), although no statistical significance was found. The detailed impact of PMRT by ypN stages such as ypN1mi or ypN1 was not available. Montero et al. [36] reviewed 19 retrospective studies and summarized the clinical results according to the receipt of PMRT and lymph node response status. Even in patients with ypN0, median rates of locoregional relapses were 3.15% (range, 0%–7.69%) with PMRT and 24.4% (range, 7.7%–41.67%) without PMRT. This difference widens for patients with ypN+: 10.8% (0%–46%) with PMRT versus 56.25% (11.2%–100%) without PMRT. Thus, PMRT in patients with residual minimally involved lymph nodes may be a reasonable approach.

Prediction of locoregional recurrence after neoadjuvant chemotherapy may further guide the decision to perform PMRT in patients with minimally involved nodal disease. From NSABP-18 and B-27 combined results with a 10-year follow-up period, Mamounas et al. [34] found that clinical tumor size, clinical nodal status, and pathologic nodal/primary tumor response after neoadjuvant chemotherapy were predictors of locoregional recurrence in patients who did not receive PMRT. Based on these factors, a nomogram was developed; however, we could not discern ypN1mi/ypN1 from ypN+ disease in prediction. Instead, the authors found that the 10-year cumulative locoregional recurrence rate was above 10% in patients with 1–3 positive nodes, regardless of tumor size and clinical nodal status. Similarly, Ma et al. [35] retrospectively analyzed 1,118 patients who underwent neoadjuvant chemotherapy and mastectomy and developed a nomogram based on 418 patients who did not receive PMRT. Risk factors included histologic classification, lymphovascular invasion, ypT stage, ypN stage, ER status, and Ki-67 expression. Of note, the molecular subtype was incorporated into the nomogram to predict a 5-year locoregional recurrence. According to the nomogram, we may recommend PMRT for patients with ypN1, since ypN1 without any risk factors is enough to indicate approximately 10% of 5-year locoregional recurrence. PMRT was administered to 700 patients in which the radiotherapy field included the chest wall and peri-clavicular area. When a central tumor was found, the internal mammary nodes were also irradiated.

The National Comprehensive Cancer Network Guidelines for breast cancer (version 5, 2021) recommends PMRT to the chest wall, ipsilateral supraclavicular area, and internal mammary node for patients with any ypN+ disease and strongly recommends PMRT for patients with cN+ and ypN0. However, the indications for PMRT in patients with ypN1mi are uncertain. The Ontario Health (Cancer Care Ontario) and ASCO Guideline [37] recommend PMRT for the postmastectomy node-positive cohort after neoadjuvant chemotherapy, particularly in cases of extensive nodal involvement. Meanwhile, the indications for radiation therapy in postmastectomy patients with minimally involved lymph nodes vary. In the 2021 St. Gallen International Consensus Guidelines [38], many panelists addressed that axillary radiation could be performed as an alternative to axillary dissection in lower sentinel nodal tumor burden after neoadjuvant chemotherapy, such as ypN1mi or ypN0(i+). However, other panelists adhered to axillary node dissection while awaiting the results of the ALLIANCE A011202 (NCT01901094) trial because of the risk of further axillary involvement. Indeed, Moo et al. [39] examined the association between the size of sentinel lymph node metastasis and residual disease after neoadjuvant chemotherapy and after axillary lymph node dissection. In patients having residual micrometastases in sentinel node biopsy (n = 44), 64% of patients were reported to have further nodal involvement in axillary node dissection. Consistently, Almahariq et al. [40] analyzed NCDB patients showing ypN1 after neoadjuvant chemotherapy. Subgroup analysis showed that patients having residual 2–3 metastatic lymph nodes could benefit from further axillary node dissection rather than sentinel node biopsy alone in terms of overall survival. Leonardi et al. [41] reviewed 256 patients who received neoadjuvant chemotherapy to identify positive non-sentinel lymph nodes after positive sentinel node biopsy. Overall, both ypN1mi and ypN1 were 60.3% (n =160) in the study population. Additional positive non-sentinel nodes were found in 62.3% (156/256) patients after neoadjuvant chemotherapy and positive sentinel node biopsy. Predictors of non-sentinel lymph node involvement were extra-capsular extension and a higher nodal ratio in sentinel nodes. Collectively, PMRT can be considered when additional axillary nodal involvement is expected.

The Radiotherapy After Primary Chemotherapy (RAPCHEM, NCT01279304) is a prospective cohort study conducted in 2011–2015, which enrolled patients with cT1-2N1 breast cancer who were treated with neoadjuvant chemotherapy followed by surgery and radiation therapy. Risk groups were predefined based only on ypN status. For ypN1 mastectomy patients, only the chest wall was irradiated if axillary lymph node dissection was performed, and chest wall plus axillary levels I–II were irradiated if only sentinel biopsy was performed. Although substantial PMRT deviation from the study protocol existed [42], preliminary results presented in ESTRO 2021 demonstrated that a 5-year locoregional recurrence was 1.1% in both cN+ and ypN1 patients even without regional nodal irradiation. This indicates that omission of regional radiotherapy may be considered in patients with both cN+ and ypN1; however, data on the proportion of mastectomy patients in this group are not currently available.

CONCLUSION

Although randomized clinical trials are not available, PMRT can be considered as a treatment option for mastectomy patients with minimally involved lymph nodes. Radiation oncologists should stratify patients, identify risk groups, and attempt individualized PMRT approaches. This involves consideration of tumor factors such as clinical/pathologic stage, tumor biology, or genomic profile, and treatment factors such as receipt of neoadjuvant treatment. Since there is no well-designed randomized clinical trial result yet, PMRT should be considered in pN1mi or pN1 patients with high risk factors.

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