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Post-mastectomy radiation therapy in breast cancer patients with 1–3 positive lymph nodes: No one size fits all

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ABSTRACT

Post-mastectomy radiation therapy (PMRT) is standard therapy for advanced breast cancer. However, given the lower risk of recurrence, PMRT administration remains controversial in select patients with limited nodal disease. We performed a review of the literature that focuses on the effect of PMRT in breast cancer patients with 1–3 positive lymph nodes, mainly examining loco-regional recurrence (LRR) and overall survival (OS). Most studies, including a large meta-analysis by the EBCTCG, showed a significant improvement in LRR rates among patients receiving PMRT. While most studies demonstrated a trend towards OS improvement, only few studies showed a statistically significant OS or breast cancer-specific survival benefit for PMRT. As such, individualized treatment decisions are recommended, taking into consideration clinicopathological findings. Future studies with large sample sizes and long follow-up times are still needed to better assess the role of PMRT in patients with limited nodal involvement.

1. Introduction

Post-mastectomy radiation therapy (PMRT) is an integral part in the management of breast cancer. It has been shown to decrease the incidence of loco-regional recurrence and improve breast cancer survival (Senkus et al., 2015). In patients with node positive disease or high risk node negative disease, chest wall and nodal irradiation is commonly performed. The extent of axillary lymph node spread plays a major role in radiation therapy decisions (Senkus et al., 2015). Despite the fact that past trials showed survival improvement in all node positive patients, the applicability of these findings to patients with N1 disease is still debatable. In this context, data from recent randomized controlled trials is scarce. As a result, there are notable differences in international guidelines regarding radiotherapy administration for 1–3 positive LN patients.

The National Comprehensive Cancer Network (NCCN) recommends strongly considering PMRT, even with limited nodal involvement (1–3 + LNs) (Network NCC, 2019). However, during the most recent St. Gallen consensus discussions, only 29 % of the panel members felt that radiation therapy should be offered for 1–3 positive LNs disease, while the majority (56 %) agreed that regional nodal irradiation should only be administrated in these patients when they present with poor prognostic features (eg: triple negative cancer or residual disease after primary systemic therapy) (Balic et al., 2019). The ASCO/ASTRO/SSO joint panel recently agreed that available evidence is in favor of PMRT administration in order to reduce loco-regional recurrence (LRR) and breast cancer mortality. However, in some subsets of breast cancer, the risk of LRR is low, and the absolute benefit of radiation therapy might be outweighed by its associated toxicities (Recht et al., 2016).

In this context, PMRT administration is still controversial in breast cancer patients with 1–3 positive lymph nodes. We aim to perform a review of the literature, focusing on studies that assess PMRT in this subset.

2. Methods

2.1. Search strategy and selection/exclusion criteria

In this review, we searched PubMed, Medline and Google Scholar for material in English from the inception of the database until July 8,

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Table 1
Literature Review for Clinical Outcomes of PMRT in N1 Patients.

Author, Year	Number of Patients	Median Follow-up (years)	Inclusion Criteria	Recruitment period	Sx Type	Systemic Therapy	Study Type	PMRT vs no PMRT	LRR (%)	HR	p-value	OS (%)	HR	p-value
Abdel-Rahman (2019)	1053	9.7	T1-2, 1–3 + LNs	BCIRG 001 (1997–1999) BIG 02/98 (1998–2001) BCIRG 005 (2000–2003) BIG 02/98 (1998–2001)	M	Institutional preference	Retrospective Study	PMRT: 568 no PMRT: 485	5.60 % 6.60 %	1.750*	0.034	– –	0.953*	0.740
Zeidan et al. (2018)	684	9	T1-2, 1–3 + LNs		M	CT	Retrospective Study	PMRT: 337 no PMRT: 347	2.50 % 6.50 %	0.290	0.005	81.70 % 78.30 %	0.790*	0.240
Muhsen et al. (2018)	1087	10.8	T1-2, 1–3 + LNs	1995-2006	M	CT and/or HT	RCT	PMRT: 163	4.00 % 7.00 %	–	0.320	81.00 % 80.00 %	–	0.440
Tam et al. (2017)	523	10	1–3 + LNs	2000-2003	M	CT and/or HT	RCT	no PMRT: 924 PMRT: 206	2.00 % 9.00 %	0.150*	0.002	86.00 % 84.00 %	–	0.900
Miyashita et al. (2017)	658	7.3	1–3 + LNs	1999-2012	M	Guideline based	Retrisoective Study	no PMRT: 317 PMRT: 100 no PMRT: 558	3.20 % 11.20 %	3.760	0.009	– –	–	–
Kim et al. (2017)	714	5.8	T1-2, 1–3 + LNs	2006-2010	M	CT	Retrospective Study	PMRT: 130 no PMRT: 584	3.00 % 4.00 %	0.830*	0.734	98.00 % 96.00 %	1.140*	0.793
Huo et al. (2015)	130092 (NCDB + SEER)	5.7 (NCDB), 6.3 (SEER)	T1-2, 1–3 + LNs	SEER (1998–2008)	M	Institutional preferences	Retrospective Study	PMRT: 28175 no PMRT: 101917	– –	–	–	– –	0.94* (NCDB), 0.89* (SEER)	0.007 (NCDB), < 0.001 (SEER)
He et al. (2015)	697	5.4	T1-2, 1–3 + LNs	1998-2007	M + AND	CT	Retrospective Study	PMRT:79 no PMRT: 618	11.10 % 1.30 %	–	0.005	93.10 % 87.30 %	–	0.646
McBride et al. (2014)	1027	17.1 (early era), 7 (late era)	T1-2, 1–3 + LNs	Early era (1978–1997) Late Era (2000–2007)	M (+ SNB in late era)	CT and/or HT (late era), No CT/HT (early era)	Retrospective Study	**Early era:** PMRT: 98 no PMRT: 407 **Late era:**	PMRT: 5.10 %, no PMRT: 13.80 %	0.370*	0.035	– –	–	–

(*continued on next page*)

Table 1 (*continued*)

Author, Year	Number of Patients	Median Follow-up (years)	Inclusion Criteria	Recruitment period	Sx Type	Systemic Therapy	Study Type	PMRT vs no PMRT	LRR (%)	HR	p-value	OS (%)	HR	p-value
								PMRT: 137	PMRT: 4.40 %, no PMRT: 3.90 %	1.410*	0.480		–	–
								no PMRT: 385				–	–	–
EBCTCG et al. (2014)	1314 (1–3 + LN)	10	Any breast cancer	1964-1986	M + AND	CT	Meta-analysis	PMRT: 539	4.30 %	–	< 0.001	–	–	–
								no PMRT: 594	21.00 %			–		
Moo et al. (2013)	1087	7	T1-2, 1–3+ LNs	1995-2006	M	Unknown	Retrospective Study	PMRT: 163	3.20 %	–	0.570	94.00 %	–	0.280
								no PMRT:924	4.30 %			91.00 %		
Tendulkar et al. (2012)	369	5.5	1–3 + LNs	2000-2007	M	Institutional preferences	Retrospective Study	PMRT:271	0.00 %	–	0.004	–	–	–
								no PMRT: 98	8.90 %			–		
Cosar et al. (2011)	90	6	T1-2, 1–3 + LNs	1999-2006	MRM	CT	Retrospective Study	PMRT: 66	3.00 %	–	0.038	90.20 %	2.143	0.087
								no PMRT: 24	17.00 %			61.90 %		
Overgaard et al. (2007)	522	18	1–3 + LNs	1982-1990	M	CT	Retrospective Study	PMRT: 276	4.00 %	–	< 0.001	57.00 %	–	0.030
								no PMRT: 276				48.00 %		
Ragaz et al. (2005)	183 (1–3 + LN)	20.75	Any + LNs	1979-1986	MRM	CT	RCT	PMRT:91	9.00 %	–	> 0.05	57.00 %	–	> 0.05
								no PMRT:92	21.00 %			50.00 %		

Abbreviations: LN lymph nodes; Sx surgery; M mastectomy; BCS breast-conserving surgery; MRM modified radical mastectomy; AND axillary lymph node dissection; SNB sentinel lymph node biopsy; CT chemotherapy; HT hormone therapy; PMRT post-mastectomy radiation therapy; HR hazard ratio; OS overall survival; RCT randomized controlled trial.
- Adjusted HR and propensity-matched models were included when available. *: Adjusted HR.

2019. We chose studies that analyzed the effect of radiation therapy versus no radiation therapy in breast cancer patients. All studies that recruited patients with 1–3 positive lymph nodes were included in our review. Randomized and non-randomized trials, systematic reviews of randomized trials, and retrospective studies that reported either loco-regional recurrence or overall survival are presented in this review.

Unpublished material, abstracts and ongoing trials were excluded from this review. Any study that did not stratify patients into a "1–3 positive lymph node" group was omitted. Additionally, studies that reported neither loco-regional recurrence nor overall survival were excluded.

2.2. Data analysis

Data was manually extracted from studies and inserted into spreadsheets. Table 1 summarizes our literature review regarding clinical outcomes of breast cancer patients with 1–3 positive lymph nodes. Number of patients, median follow-up, study inclusion criteria, surgery, and systematic therapy use were all recorded in tables. The main outcomes of interest were loco-regional recurrence rates and overall survival. For these outcomes, percentages and hazard ratios (HRs) with corresponding *p-values* were presented when available. Also, adjusted models or propensity-matched models were used when possible. Each study was analyzed in the context of its population characteristics, considering T staging, hormone receptor status, HER-2 receptor status, type of surgery and the use of systemic therapy.

3. Results

Results from the majority of studies demonstrate a positive effect of radiation therapy in decreasing LRR, with ten studies showing statistically significant LRR improvement (Ebctcg et al., 2014; Zeidan et al., 2018; Tam et al., 2017; He et al., 2015; Abdel-Rahman, 2019; Miyashita et al., 2017; McBride et al., 2014; Tendulkar et al., 2012; Cosar et al., 2011; Overgaard et al., 2007) (Table 1). Most notably, the EBCTCG meta-analysis was performed on studies recruiting more than 8000 women between 1964 and 1986. The study had a long follow-up for breast cancer recurrence at around 10 years, and a 20-year follow-up for breast cancer mortality. The study included trials with patients that completed mastectomy and axillary surgery, and that were then randomized to receiving PMRT or no PMRT. The meta-analysis showed that within the pN1 subgroup (1314 patients) treated with systemic therapy, PMRT decreased the 10 year rate of LRR by 16.5 % ($p < 0.001$) and reduced the 20-year breast cancer mortality by 7.9 % (RR = 0.78, 95 % CI = [0.64–0.94], p = 0.01) (Ebctcg et al., 2014). Additionally, the study showed a lower rate of any recurrences in patients receiving PMRT as compared to those who did not (RR = 0.67, 95 % CI = [0.55–0.82], $p < 0.001$). Overgaard et al. performed a retrospective subgroup analysis on the Danish Breast Cancer Co-operative Group 82 b& c trials. 3083 patients underwent total mastectomy and partial axillary dissection. Pre and postmenopausal women were included, and subsequently randomized to receiving PMRT and chemotherapy versus chemotherapy alone. All patients received CMF chemotherapy, and post-menopausal patients received additional Tamoxifen to their regimen. With a median follow-up of 18 years, the study showed that PMRT in patients with 1–3 positive lymph nodes (552 patients) decreased LRR risk from 27 % to 4 % ($p < 0.001$) and increased overall survival from 48 % to 57 % (p = 0.03) (Overgaard et al., 2007). N1 patients in this study had either T1 (47 %) or T2 (48 %) disease, with only 5 % of patients having T3 disease. Hormone receptor and HER-2 receptor status were not reported. Furthermore, this study showed that the benefit of PMRT in N1 patients was similar to that seen in patients with 4 or more positive lymph nodes.

Results from the 20-year follow-up of the British Columbia study by Ragaz et al. showed that the magnitude of the impact of radiotherapy in N1 subgroup was similar to those with greater nodal involvement in terms of survival rates after treatment with CMF chemotherapy and modified radical mastectomy (Ragaz et al., 2005). However, in the 1–3 positive lymph nodes subgroup, PMRT only showed statistically significant improvement in breast cancer specific survival ([Relative Risk (RR) = 0.64, 95 % CI = [0.42–0.97]). In this same subgroup, LRR (RR = 0.46, 95 % CI = [0.18–1.13]), OS (RR = 0.76, 95 % CI = [0.50–1.15]) and systemic breast cancer-free survival (RR = 0.68, 95 % CI = [0.45–1.04])showed a non-significant improvement with PMRT (Ragaz et al., 2005). These studies represent data that involved the use of less effective chemotherapeutic agents and lacked targeted and hormonal therapies (Ragaz et al., 2005).

In more recent studies that involve the use of effective systemic therapies, the effect of PMRT on OS and LRR was less pronounced. Zeidan et al. performed a retrospective analysis of the Breast International Group 02-98 trial where patients were randomized to receive adjuvant anthracycline with or without taxane therapy. The study included 684 N1 breast cancer patients. Approximately 2/3 of the patients had T2 disease and positive ER status. Results from this study only showed a significant decrease in LRR when patients were not on taxane based chemotherapy (No Taxane-group: LRR decrease from 9.1%–3.4 % p = 0.02 vs Taxane-group: LRR decrease from 5.3 % to 2.0 %, p = 0.08) (Zeidan et al., 2018). In this same study, PMRT showed a non-significant improvement in OS (HR = 0.79, p = 0.24) (Zeidan et al., 2018). Additionally, in 2017, Tam et al. analyzed the BCIRG-005 trial for the effect of PMRT on LRR and OS (Tam et al., 2017). The trial was originally designed as a randomized controlled trial that recruited patients between 2000 and 2003 to compare concomitant vs sequential docetaxel. The study identified 523 N1 breast cancer patients, with the majority having positive ER or PR status. Tam et al. showed that LRR significantly decreased with PMRT (HR = 0.15, p = 0.002) while there was no significant effect on OS (p = 0.9) (Tam et al., 2017). This trend is common among recent studies where improvements only show statistical significance in LRR, and PMRT tends to show only milder, non-significant OS benefit (He et al., 2015; Abdel-Rahman, 2019).

4. Discussion

Radiation therapy often improves survival by preventing recurrences not prevented by the sole use of chemotherapy (Whelan and Levine, 2005). In this article, we examined the effect of PMRT on breast cancer patients with 1–3 positive lymph nodes, through analyzing 15 studies published since 2005.

Breast/chest wall with nodal radiation therapy is commonly performed on patients with node positive disease or high-risk node negative disease. The extent of nodal irradiation is typically medial to the coracoid process unless in bulky disease or extensive nodal involvement (N2-3) where axillary nodes lateral to the coracoid process are included in the irradiation field.

Generally, PMRT is well tolerated with patients being able to continue their normal routines, notwithstanding specific acute and late side effects. Toxicities of PMRT are divided into acute (occurring within 3 months of radiotherapy) and chronic. Most common acute adverse events include fatigue, sore throat, cutaneous fibrosis, and dermatitis. Chronic side effects associated with PMRT include radiation pneumonitis, secondary malignancies, radiation induced cardio-toxicity, hypothyroidism, and arm lymphedema (Christante et al., 2010). In particular, late cardio-toxicity associated with PMRT might play a role in counterbalancing the OS benefit of PMRT. A recent study by Warren et al. reported that the 2-year cumulative incidence of lymphedema significantly increased with radiotherapy reaching as high as 21.9 % in patients with regional nodal irradiation (supraclavicular nodes) compared to 3.0 % in patients not receiving radiotherapy (Warren et al., 2014). PMRT also poses a significant risk on patients planned to undergo immediate prosthetic breast reconstruction. A meta-analysis of 15 RCTs demonstrated an increased risk of overall complications (OR:3.45, $p < 0.00001$) and capsular contracture (OR:5.26,

$p < 0.00001$) (Pu et al., 2018).

Overall, in the published studies analyzed, the effect of PMRT on OS was not as significant as its effect on LRR. Despite many studies showing trends towards improved OS in patients receiving PMRT, only two of the studies showed statistically significant results (Huo et al., 2015; Overgaard et al., 2007). The following portrays a discrepancy between LRR and OS benefit in patients with limited nodal involvement breast cancer. While it is possible that LRR improvement does not translate in survival benefit, this inconsistency can be attributed to the fact that many of the studies had a short follow-up time. Additionally, it is possible that most studies did not have large enough samples to detect benefits in OS. This is particularly evident in the EBCTCG meta-analysis, in which the large number of patients with long follow-up time did lead to a statistically significant breast cancer mortality benefit in patients receiving PMRT (Ebctcg et al., 2014). For N1 patients, the meta-analysis shows that the OS benefit of PMRT start at 10 years out. As such, future prospective trials with longer follow-up times are required to better assess the role of PMRT on OS.

Most of the studies included in this article involved the use of complete axillary node dissection. Multiple studies have shown the safety of omission of axillary lymph node dissection (ALND) in sentinel node (SN) negative disease (Giuliano et al., 2000; Bergkvist et al., 2008; Veronesi et al., 2003). Furthermore, results of the randomized controlled trial, AMAROS, show that in T1-2 breast cancer patients with positive sentinel lymph nodes, axillary radiation therapy provides comparable disease control to axillary lymph node dissection, with even less morbidity (Donker et al., 2014). Galimberti et al., in the IBCSG 23-01 trial, supported omission of lymph node dissection in minimal to moderate sentinel lymph node involvement (Galimberti et al., 2018). Thus, current surgical practices tend to shift away from ALND towards a more conservative approach in the management of micrometastatic lymph node disease. Further de-escalation of ALND is being evaluated in the SOUND (Gentilini and Veronesi, 2012) and SENOMAC (de Boniface et al., 2017) trials that aim to investigate disease control and prognosis in selected group of patients who omitted sentinel biopsy. All in all, these changes impose a further limitation on the applicability of the studies we are reviewing in the modern era.

Another shift in current practice is the increased use of neoadjuvant systemic therapy in breast cancer (Santa-Maria et al., 2015). Many patients presenting initially with limited positive nodal breast cancer respond to neoadjuvant chemotherapy. In this population, the question remains on whether PMRT would derive further recurrence and survival benefit. The NSABP B51 trial evaluates whether there is added benefit of chest wall and regional irradiation after surgery for patients with complete pathological response in the previously positive LNs following neoadjuvant chemotherapy (Clinical Trials.gov [Internet]: National Library of Medicine (US), 2013).

Finally, SUPREMO is an open-label, international randomized controlled trial that compares the use of radiation therapy versus no radiation therapy (Velikova et al., 2018). The trial focuses on patients with intermediate-risk breast cancer, including N1 patients, and aims at studying overall survival as a primary endpoint. Another ongoing RCT, TAILOR RT, focuses on regional radiotherapy for biomarker low risk (ER positive, HER-2 negative) patients of limited nodal involvement (Clinical Trials.gov [Internet]: National Library of Medicine (US), 2018). With large sample size and long follow-up times, these trials might give better insight in the treatment of intermediate and low risk breast cancers, respectively.

This article is a narrative review which presents qualitative research where systematic data analysis is not presented. Therefore, the findings presented should be considered in the light of some limitations. Risk of bias was not assessed in this study, and as such, a systematic review is still needed to better clarify the debate regarding N1 breast cancer patients. However, our study presents the largest review of the literature to date in regard to that topic.

In the absence of high-level evidence and in the light of the stated limitations of this article, we recommend that treatment decisions be based on individual clinicopathologic factors associated with significant risks of locoregional recurrence. These include age, positive surgical margins, advanced stage, molecular subtype (especially HER-2 positive and triple negative disease), and high lymphatic involvement (Merino et al., 2018; Li et al., 2014). Those patients are most likely to derive benefit from PMRT. It is also prudent to consider the overall treatment benefit in context of the patient's performance status and existing co-morbidities. While the PMRT benefit might seem smaller in recent studies due to the advances of chemotherapy, it is worth noting that the adverse events of PMRT are also significantly less, especially with modern radiation therapy techniques (Shaitelman1 TAB et al., 2014). This was demonstrated in a 2-year follow-up of an RCT that compared IMRT to the standard two-field technique that showed a decrease in late toxicity, especially telangiectasia (Barnett et al., 2012).

Recent advances in molecular profiling of breast cancer allow clinicians to individually tailor radiation therapy decisions based on locoregional risk stratification and radio-sensitivity of each cancer subtype. Kyndi et al. investigated the role of PMRT based on biological subtypes (Kyndi et al., 2008). In this analysis, hormone receptor negativity and positive HER-2 expression were significantly associated with increased risk of LRR. Moreover, no survival benefit was seen in those patients. However, improved OS after PMRT was noted in patients with positive hormone receptor status (Kyndi et al., 2008). Additionally, a recent analysis of HER-2 positive breast cancer patients showed a loco-regional control benefit for the addition of PMRT in patients with either ER or PR expression HR = 0.26, CI = [0.08-0.79], p = 0.02). However, no PMRT benefit was shown in patients that did not express neither ER nor PR (p = 0.07) (Abi Jaoude et al., 2019). Others have proposed the 21-gene recurrence score assay to predict benefit of PMRT in N1 patients (Goodman et al., 2018). Moving forward, molecular profiling seems to be a promising approach to identify the subset of N1 patients who benefit from addition of PMRT.

In conclusion, data from previous studies have shown improvement in LRR rates in breast cancer patients with 1–3 positive lymph nodes receiving PMRT. However, in this population, PMRT might play a smaller role in improving overall survival. Also, the magnitude of the LRR and OS benefit is smaller in more recent studies compared to historical ones, showing a shift to decreasing benefit of PMRT over time. Our review shows that N1 breast cancer patients with bad prognostic factors might still derive benefit from the addition of PMRT to their treatment. Future studies, including analysis of real-life data and possibly randomized trials, are needed to better assess the role of PMRT in 1–3 positive lymph nodes breast cancer patients and to identify those who can benefit the most from PMRT, based on specific risk factors.

Contributors

YZ, MK and JAJ led on study design and concept. MK and JAJ led on data extraction. YZ, MK, AT, NES, JAJ and PP all contributed substantially to the writing of this manuscript, through performing literature review, data interpretation, manuscript drafting and providing comments and edits to the final manuscript.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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