Review Article

Post-mastectomy radiotherapy for one to three axillary node positive early breast cancer: To radiate or not to radiate?

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ABSTRACT

Post-mastectomy radiotherapy (PMRT) in early breast cancer has long been a matter of debate among oncologists. The American Society of Clinical Oncology (ASCO) and the American Society for Therapeutic Radiology and Oncology (ASTRO) recommend the use of PMRT for patients, whose primary tumor is larger than 5 cm and/or patients who have four or more involved axillary lymph nodes (ALNs). Recently, few trials have been published showing the positive impact of PMRT on overall survival (OS) even in patients having 1-3 positive ALNs with T1-T2 primary disease or early breast cancer (EBC). So, it has become a matter of controversy whether to radiate or not to radiate? We have made an extensive search in the internet in Pubmed and other sites of medical publication mentioning our topic of discussion and reviewed the relevant articles. We nearly got 3,220 articles. After reviewing the available publications in the internet, we blended the elixir with our experience and tried to find an answer of our question. In conclusion, PMRT significantly and substantially improved loco-regional control and overall survival in patients with 1-3 positive nodes as in patients with 4 or more positive nodes, and nearly the same number of patients is needed to treat to avoid a loco-regional recurrence and/or death in both groups. We should reconsider the current guidelines for the indication for PMRT.

Key words: Breast cancer, disease-free survival, loco-regional recurrence, overall survival, post mastectomy radiation therapy, positive 1-3 axillary lymph nodes

INTRODUCTION

Radiation treatment has been used after mastectomy in the management of breast cancer for many decades; however, post mastectomy radiotherapy (PMRT) in early breast cancer (EBC) has long been a matter of debate amongst oncologists. The American Society of Clinical Oncology (ASCO) and the American Society for Therapeutic Radiology and Oncology (ASTRO) recommend the use of PMRT for patients whose primary tumor is larger than 5 cm (T3 disease) and/or patients who have ≥4 involved axillary lymph nodes (ALNs).[1,2]

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Recently, few trials have been published showing the positive impact of PMRT on overall survival (OS) even in patients having 1-3 positive ALNs with T1-T2 primary disease or EBC.[3-6] Since then, the issue has become a matter of controversy amongst oncologists and patients are being subjected to PMRT without knowing the exact benefit. There is mounting evidence of favourable impact of PMRT in patients in this sub group, provided advanced radiotherapy technology is used. It is important for everyone involved in breast cancer treatment to identify the patient population with EBC who will be benefited by adjuvant radiotherapy. The present review discusses the current indications for post-mastectomy radiotherapy in EBC.

MATERIALS AND METHODS

We have made an extensive search in the internet in pubmed and other sites of medical publication mentioning our topic of discussion. We have given importance to the articles published in high impact factor journals and the recent ones. We have gone through the relevant articles. In some

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cases, we have contacted the author for full text and or their comment on this topic also.

RESULTS

We found approximately 3,220 articles. We have eliminated the articles that included more than three node positive breast disease and included only those that address the topic of our interest. Around 47 articles addressed this issue in some part of their article. After reviewing the available publications in the internet, we blended the elixir with our experience and tried to find an answer of our question.

DISCUSSION

Many questions still need to be answered in the purview of: 1) increased cardiotoxicity with systemic therapy, 2) improving surgical skills, 3) limited resources, 4) concerns about second primaries especially with improving survival, and 5) advancing diagnostics to better identify patients having bad prognosis. We have tried here to emphasize that nodal positivity is not the only factor to categorize patients for receiving PMRT. EBC could be a very heterogeneous disease with regard to the tumor size and grade, nodal positivity, estrogen receptor (ER) and progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER-2/neu) status, genetic profiles and other markers. Ratio of involved lymph nodes, extracapsular extension (ECE) and lymphovascular space invasion (LVSI) are the other important factors. Some trials have shown benefit of PMRT even in node negative patients having high-risk factors.[7] It is critical that the factors predicting local failure be identified so that the appropriate local treatment is planned to achieve maximum local control and survival benefit with minimum morbidity in this subset of EBC patients.

It is, therefore, time to abandon the "one size fits all" approach and thoughtfully individualize treatment recommendations. This issue is more important in developing countries where a large number of women who are good candidates for breast conserving surgery prefer to undergo mastectomy due to resource constraints and unavailability of advanced radiotherapy techniques at most of the centres.

The two Danish trials and one British Columbia trial have established the survival benefit of PMRT in node positive disease (Level I evidence) and a subgroup analysis of these trials has shown survival benefit even in 1-3 positive ALN group.[3-6] These trials, however, have been amply criticized for their short comings in terms of higher loco-regional recurrence (LRR), inadequate axillary dissection and improper usage of systemic therapy. The most recent update of the Danish studies reported 43% LRRs in the axilla.[8]

The earlier meta-analysis by Cuzic *et al*., clearly showed that there is improvement in loco-regional control (LRC), but no survival advantage of adding radiotherapy in EBC, and later, a cause-specific mortality identified cardiac mortality as the primary reason.[9] There are a number of reasons why a survival advantage may not have been apparent initially. Original studies were conducted in the era prior to adjuvant systemic therapy. Reduction of distant failure with systemic therapy may allow the survival effect of PMRT to be more evident. Analysis of cause-specific mortality in the older PMRT studies revealed that the reduction in breast cancer deaths was cancelled out by an increase in late cardiac mortality secondary to radiotherapy. With modern radiotherapy techniques, delivery of dose to the chest wall is more uniform and cardiac dose is minimized. Older studies were also not stratified according to risk and being of small sample size not powered sufficiently to detect a small survival advantage. In the Danish Breast Cancer Cooperative Group trials, major effort was made to optimize the treatment with regard to dose, fractionation, timing and treatment technique, so no radiation-related excess non-breast cancer death or unacceptable toxicity was found. The controversy is more significant in a developing country where long term follow-up of patients, waiting list on machines, surgical skills, and pathological reporting in community based practice all contribute to the dilemma of giving PMRT in this subgroup.

LRC is an important goal in oncologic management as only 50% of failures could be treated effectively. Radiotherapy should be delivered in a manner so that it completely sterilizes the loco-regional disease which, if left untreated, would lead to distant spread and the treatment should also have minimum toxicity. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview of more than 30 randomized trials clearly demonstrated that adjuvant radiotherapy confers a consistent relative reduction in LRR of approximately two-thirds, independent of tumor or nodal characteristics. The overview also suggested that absolute reductions in LRR of 20% corresponded to absolute reductions in breast cancer-specific mortality of approximately 5% that demonstrated a survival benefit with avoidance of one breast cancer death for every four LRRs avoided.[10]

We believe that comprehensive PMRT is appropriate for the great majority of node-positive patients undergoing mastectomy. However, number of positive ALNs may not be the only criteria and some selection based on other clinical and biologic factors may be important and appropriate. For example, Cheng *et al*., developed a model to predict LRR and the impact of PMRT on survival. In addition to ALN status, ER status, LVSI, and age at diagnosis were all found to be significant.[11] To determine the effectiveness of PMRT in women with node-negative breast cancer with particular reference to those patient and tumour factors, which contribute to an increased risk of LRR, a systematic literature review was reported by Rowell NP *et al*. In this

report, baseline risk of LRR was increased in the presence of LVSI, a grade 3 tumor, tumors greater than 2 cm or a close resection margin, and in patients who were pre-menopausal or aged less than 50 years. Those with no risk factors had a baseline risk of LRR of approximately 5% or less rising to a risk of 15% or more for those with two or more risk factors.[12]

The extent of surgery performed and the surgical skills may vary amongst different institutions and therefore to compare the results some other parameter was searched for and nodal ratio was utilised by some for this purpose. When LRR was examined using nodal ratios, differences between institutions were no longer significant. These observations support the hypothesis that using the nodal ratio rather than the absolute number of positive nodes reduced inter-institutional differences in LRR risk estimates that may exist because of variations in the number of nodes excised. Nodal ratio > 0.20 identified patient subsets with baseline LRR risks in excess of 20%, a risk magnitude that warrants consideration of PMRT.[13]

The commonest site of LRR following mastectomy and axillary nodal dissection is the chest wall (50-75%) followed by the supraclavicular fossa and infraclavicular region (20-40%).[14] The rate of axillary recurrence following a level I/II axillary dissection is <5% at 10 years, and as such the axilla is not routinely irradiated as part of PMRT. Furthermore, irradiating the entire axilla following axillary dissection would significantly increase the rate of chronic arm morbidity and lymphedema.

There is a lot of heterogeneity with regard to radiotherapy techniques, e.g., dosage, fractionation, volume/fields, sequencing, application of bolus, reporting of cardiac doses, treated with photons, electrons or a combination of both; all need to be elaborated upon to achieve maximum benefit.[15] Various efforts are being made now-a-days to minimize the cardiac dose such as delineating important cardiac structures: For example, left anterior descending coronary artery, respiratory gating or alternatively positioning patients in prone position.

All the trials which have shown survival benefit with adjuvant radiation in EBC, have utilized advanced radiotherapy techniques to minimize cardiac dose and the volume irradiated including locoregional nodes and chest wall (CW).[16] However, the controversy regarding the target volume has not been put to rest as recent studies have advocated radiotherapy to CW only.[17] Mc Donald *et al*., retrospectively analyzed 238 patients with Stage II breast cancer (1-3 positive ALNs) treated with mastectomy. The five and 10-year DFS rate without PMRT was 85% and 75%, respectively, and, with PMRT, was 93% at both five and 10 years (P = 0.03). A similar benefit was found for patients treated with RT to the CW alone. The LRR, DFS, and OS rate for patients treated to the CW only were 0%, 96%, and 95% at 10 years, respectively.[17] Some information about the target may come from the Selective Use of Post-operative Radiotherapy aftEr MastectOmy study, which only included the CW in the target irrespective of tumor location and presence of positive nodes, and from the EORTC 22922/10925 study, which on the contrary only included the supraclavicular and internal mammary (IM) nodes, in an almost similar patient group.[18] Guidelines are awaited for several technique related issues such as structures to be delineated as OAR (heart, pericardium, some or all coronary vessels, and cardiac valves) and how to delineate them? What to report, point dose maximum or volume based dosimetric parameters, e.g., V5, V10, V20?[19,20] Moderate hypofractionation in the adjuvant setting using 2.6-2.7 Gy per fraction to total doses of 40-42.5 Gy is gaining more use, but there may be an increased risk of fatal myocardial infarcts by using hypofractionation.[21]

A clear cut cardiac toxicity of 1.3 % has been established on long term follow up by the EBCTCG Meta analysis.[10] Therefore, patient selection should be such that a higher benefit risk ratio with PMRT is achieved. The benefit should also be analyzed in the purview of enhanced cardiotoxicity of the present day systemic therapy, which usually includes anthracyclines, taxanes, and trastuzumab. The heart mortality has decreased in more recent trials as demonstrated by the data from the US Surveillance Epidemiology and End Results (SEER) cancer registries. They have documented in a cohort of more than 115,000 irradiated breast cancer patients with known tumour laterality that for patients treated during 1973-82. The cardiac mortality ratio (left versus right tumour) was 1.20 (95% CI, 1.04-1.38) less than 10 years after irradiation, 1.42 (1.11-1.82) 10-14 years after irradiation, and 1.58 (1.29-1.95) after 15 years or more.[22]

Researchers have also found that women treated for cancer of the left breast had higher rates of chest pain, coronary artery disease, and myocardial infarction. Correa *et al*., reported a statistically significant higher prevalence of stress test abnormalities among left-sided than right-sided irradiated patients, and 70% of left-sided abnormalities were in the region of the left anterior descending artery (LAD).[23] There are no guidelines or recommendations regarding the cardiac volume that can be irradiated safely or how to best minimize cardiac dose. Certain specific remedial measures for left sided PMRT have been proposed by MacIntosh *et al*.,[24] in the form of voluntary deep inhalation breath holding, thereby, reducing the total dose delivered to heart and LAD.

Papers based on a large, well conduced clinical epidemiological study called the RACE study give a good estimate on the frequency of different heart diseases in the context of estimated mean doses to the heart and LAD with

a follow up period up to 30 years. Estimated cardiac doses from common breast cancer radiotherapy regimens used to irradiate the breast, CW, and IM nodes in Denmark from 1977-2001, was reported in a study conducted by Taylor *et al*. Twenty two different radiotherapy regimens commonly used in this period were compared and these resulted in radiation doses of between 1.7 to 14 Gy to the heart and 0.5 and 43Gy to the coronary arteries. Women irradiated for left-sided breast cancer generally received higher doses than those irradiated for right-sided cancer.[20]

In the NSABP B-14 trial conducted from 1982 to 1988 for ER/PR positive patients with negative margins and with a median follow up of 19.9 years, the respective 10 year actuarial local failure rate after RT alone and RT plus tamoxifen were 11% and 4%, respectively; the crude rates were 17% and 8%, respectively. Similarly in NSABP B-13 trial chemotherapy has reduced the incidence of local failure in node negative patients.[25] The EBCTCG meta-analysis of systemic therapy trials demonstrated that chemotherapy reduced LRR rate by approximately one-third and five years of tamoxifen reduced the LRR rate by about one-half in women with ER-positive breast cancer.[26]

Systemic therapy of EBC has evolved considerably since many of the PMRT studies were conducted. Women are more likely to receive more cardiotoxic adjuvant systemic therapy. There is a significant survival advantage with anthracyline-based regimens compared to CMF, and as a result anthracyclines are now routinely incorporated into most adjuvant chemotherapy schedules. High-risk patients may also receive taxanes following evidence of a further survival advantage when added to anthracyclines. Furthermore, recent studies have demonstrated a survival benefit from the addition of trastuzumab in patients with HER2-positive tumours. The potential cardiotoxicity of trastuzumab is now well-established. Whether PMRT offers a further advantage in patients receiving optimal systemic adjuvant therapy is unclear. However, the MD Anderson Cancer Center and the NSABP series assessing LRR in patients receiving anthracycline based chemotherapy suggest that locoregional failure remains an important concern.[27]

The current recommended duration of adjuvant hormonal therapy is five years, compared to one as in the Danish 82c study, which may also have an impact on LRR. Furthermore, in postmenopausal women, the aromatase inhibitors (AIs) are increasingly being used instead of tamoxifen. AIs have been shown to reduce both local and distal relapse compared to tamoxifen. It is well documented that the risk of both LRR and distant recurrence increases with the number of nodes involved as well as increasing tumor size and other adverse prognostic factors. This implies that in patients who have many nodes involved, the likelihood of developing distant metastases is very large; and therefore, only a limited proportion of these patients can obtain survival benefit, despite their possibility of obtaining a large reduction in locoregional failures. On the contrary, in patients with fewer nodes involved and a consequential lower risk of distant metastases, a larger proportion can obtain survival benefit although they have a smaller risk of local failures. Thus, the improvement in survival may not be directly linked and proportionate to the improvement in LRC. Another argument states that patients with less nodal burden are more likely to express the benefit of PMRT because the micrometastatic disease, which if exits, is more likely to be controlled by adjuvant systemic therapy and similarly the locoregional disease would have less tumor burden as compared to patients with higher nodal disease and PMRT would be effective in eradicating it. This was also observed in the meta-analysis published by Van de Steene *et al*., and similar observations have been made by other authors also.[28,29]

Information regarding the benefits of regional RT in EBC, applicable to both breast conserving surgery (BCS) and mastectomy patients, will be obtained from the EORTC 22922 and the NCIC-CTG MA.20 trials. MA.20 included patients with high-risk node-negative or node-positive breast cancer treated with BCS and adjuvant chemotherapy and/or endocrine therapy. The patients were stratified by positive nodes, ALNs removed, chemo-and endocrine therapy and randomized to standard whole breast irradiation (WBI) (50Gy in 25 fractions +/- boost irradiation) or WBI plus regional nodal irradiation (RNI) (45Gy in 25 fractions) to the IM, supraclavicular, and high ALNs. At median follow-up of 62 months, WBI + RNI in comparison to WBI alone was associated with an improvement in isolated loco-regional disease free survival (DFS; $P = 0.02$), distant DFS ($P = 0.002$), DFS ($P = 0.003$) and OS ($P = 0.07$). But at the same time, WBI + RNI in comparison to WBI was associated with an increase in grade 2 or greater pneumonitis (1.3% and 0.2%, respectively, $P = 0.01$), and lymphedema (7.3% and 4.1%, respectively, $P = 0.004$).[30] The EORTC 22922/10925 trial investigated the potential survival benefit and toxicity of elective irradiation of the IM and medial supraclavicular (IM-MS) nodes in stage I-III breast cancer. Accrual was completed in January 2004 with 4,004 patients and first results were expected in 2012. Toxicity at three years in this trial was reported by Matzinger O *et al*. In that report, only lung (fibrosis, dyspnoea, pneumonitis, any lung toxicities) (4.3% vs. 1.3%; $P < 0.0001$) but not cardiactoxicity (0.3% vs. 0.4%; $P = 0.55$) was significantly increased with IM-MS treatment, and no significant worsening of the performance status was observed ($P = 0.79$). Finally, the authors concluded that IM-MS irradiation seemed well tolerated and did not significantly impair WHO performance status at three years, but a follow-up of at least 10 years was needed to determine whether cardiotoxicity was increased after radiotherapy.[31] A phase III randomized

trial of PMRT in stage II breast cancer in women with 1-3positive ALNs, previously open in the US (US intergroup trial S9927), was closed secondary to inadequate accrual. Another trial, closed due to poor inclusion, was the MA25 trial, testing the effect of adding PMRT in patients with N1 disease. To resolve whether patients with 1-3positive ALNs should undergo PMRT a phase III randomized trial-Selective Use of Post-operative Radiotherapy aftEr MastectOmy (SUPREMO), is currently being conducted in Europe randomizing patients with tumours less than 5 cm in size and 1-3 positive ALNs.

In their retrospective study, Chih-Jen Huang *et al*., compared the clinical outcome of breast cancer patients with T1-2 tumor and 1-3 positive ALNs with or without PMRT. At a median follow-up of 102 months, the clinical outcomes in PMRT versus no-PMRT groups were as follows: LRR rate (3.1 versus 11.0%, P = 0.006); distant metastasis rate (20.9 versus 27.7%, P = 0.152); 10-year DFS (73.8 versus 61.3%, P = 0.001); and 10-year OS (82.1 versus 76.1%, P = 0.239). The reduction in LRR (P = 0.004) by PMRT was found to be significant. Based on this result, the authors recommended PMRT for breast cancer patients with T1-2 and 1-3 positive ALNs, especially for high-risk subgroups with a positive nodal ratio of ≥ 25% and positive LVSI, not only for reducing LRR but also for improving DFS.[32]

In their retrospective review, Offersen *et al*., had recommended PMRT in breast cancer patients with small tumors and 1-3 positive ALNs.[33] Hamamoto *et al*., had tried to define the factors associated with increased risk of isolated locoregional failure that may justify the use of PMRT in patients with T1/2 breast cancer and 1-3 positive ALNs. In their report, the authors concluded that, with regard to the patients who had pT1/2 breast cancer and 1-3 positive lymph nodes, isolated locoregional failure was not common in general; however, patients who had both negative hormone receptor status and vascular invasion were comparatively high-risk patients for isolated locoregional failure.[34] Tendulkar *et al*., reported a retrospective review of 369 breast cancer patients with 1-3 positive ALNs who underwent mastectomy without neoadjuvant systemic therapy between 2000 and 2007 at Cleveland Clinic. In this study, the 5-year rate of LRR was 8.9% without PMRT vs. 0% with PMRT (P = 0.004). For patients who did not receive PMRT, univariate analysis showed six risk factors significantly (P < 0.05) correlated with LRR: ER/PR negative, lymphovascular invasion, 2-3 LN+, nodal ratio >25%, ECE and Bloom-Richardson grade III. Finally, the authors concluded that, PMRT offered excellent control for patients with 1-3 LN+. Patients with 1-3 LN+, who had grade III disease and/or ECE, should be strongly considered for PMRT.[35]

CONCLUSION

PMRT significantly and substantially improved LRC and OS in all node-positive patients. This improvement was as pronounced in patients with 1-3 positive nodes as in patients with 4 or more positive nodes, and nearly the same number of patients is needed to treat to avoid a LRR and/or death in both groups. This does add to the need for reconsideration and modification of the current guidelines for the indication for PMRT. There are always some inherent risks associated with any treatment, and one needs to carefully consider the overall clinical situation and co-morbidities to assure a favourable therapeutic ratio. The potential benefits of PMRT in patients with < 4 positive ALNs remain controversial and recruitment to ongoing clinical trials should be encouraged. Role of PMRT would be better highlighted in patients where distant metastasis is expected to be efficiently controlled by the effective systemic therapy. The impact of PMRT in eradicating the locoregional disease and, thereby, decreasing the generation of ultimately lethal distant metastasis would reflect upon the improvement in OS. In the strict sense of the word, this does not preclude that breast cancer is a systemic disease, but it further supports the importance of LRC. We suggest that the decision to use PMRT should be tailored according to all the risk factors, laterality and not only the nodal status. In all patients, advanced radiotherapy technology along with the skills and experience should be used. The results of SUPREMO trial will perhaps answer this question.

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