Post mastectomy radiotherapy in one to three lymph node positive breast cancer

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Surgery and radiotherapy predominantly aim at loco-regional control in breast cancer, whereas systemic therapy is believed to control distant organ disease [1,2]. Recent evidence, however, has established the importance of controlling loco-regional disease with respect to overall survival of breast cancer patients. The DBCG 82b and 82c trials and a smaller Canadian trial have demonstrated the ability of post mastectomy radiotherapy (PMRT) in reducing the risk of loco-regional failure by approximately two thirds and increasing survival by 7–10% [3–6]. The EBCTCG (Oxford Early Breast Cancer Trialists Group) meta-analysis has shown that for every four local recurrences avoided, one breast cancer death would be prevented [7].

This establishment of role of radiotherapy after mastectomy has led researchers and clinicians to ask if patients having T1/T2 lesions with one to three positive lymph nodes could benefit from radiation as well. Various guidelines have acknowledged the lesser clarity of PMRT in one to three lymph node positive patients [8–12]. The possible reasons for this are: 1) There is a lack of separate group of one to three positive nodes before start of study in randomized trials; 2) Ongoing randomized trials for one to three node patients are still in the early accrual phase; 3) Possible benefit of radiotherapy in one to three nodal group needs to be balanced against the possible side effects [13].

Critical available evidence for PMRT in one to three lymph node positive patients

A number of studies have quantified the risk of loco-regional recurrence in the absence of PMRT in one to three lymph node positive patients. Recht et al. reported 10 year loco-regional failure rates as a function of clinic pathological features in more than 2000 patients treated with mastectomy and anthracycline-based chemotherapy in four ECOG trials [14]. Thirteen percent of patients with one to three positive nodes had loco-regional failure at 10 years as compared to 29% of patients with at least four positive nodes. In another study of 5000 patients treated on NSABP trials, loco-regional recurrences occurred in 13%, 24% and 32% for patients with one to three, four to nine and >10 positive lymph nodes [15]. A similar study from MD Anderson Cancer Center reported loco-regional failure rates among more than 1000 patients treated in five trials [16]. Loco-regional recurrences occurred in 4%, 10%, 21% and 22% for patients with none, one to three, four to nine and >10 positive nodes. Table I outlines the major studies addressing this issue [3,4,17].

Do any risk factors predict benefit from local radiotherapy in patients with one to three nodes?

There is some evidence that PMRT should be offered to all patients with involved axillary nodes [4,18,19]. It is imperative, however, to be cognizant of the complications of PMRT [20,21]. Patt et al. reported a significant excess incidence of contra lateral breast cancer and a significant increase in non-breast cancer mortality in irradiated women and this issue has been corroborated in the EBCTCG findings as well [2,20]. The mortality was mainly from heart disease and lung cancer. Hence, it is essential to identify additional risk factors in one to three lymph node positive patients associated with high risk of LRR who have a higher benefit risk ratio with PMRT.

The British Columbia Cancer Agency performed a large retrospective study of 847 patients who underwent mastectomy, with T1, T2 tumors and one to three positive nodes (mean follow-up 7.7 years), none of them having received PMRT [18]. They identified that the overall baseline risk was 13–16% at 10 years and age <45 years, $>25\%$ positive lymph

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Table I. Studies analysing outcome of post mastectomy patients with 1–3 positive nodes.

Study	Nodal Status	Year	No. of pts	Median f/u (mths)	LRR% - No PMRT	LRR% - PMRT	OS% - No PMRT	OS% - PMRT
DBCG 82b[3]	All		1708	114	32	9	45	54
	1–3 +ve	1997	1061	114	30	7	54	62
	≥4 +ve		510	114	42	14	20	32
DBCG 82c[4]	All		1375	123	35	8	36	45
	1–3 +ve	1999	794	123	31	6	44	55
	≥4 +ve		448	123	46	11	17	24
BCG [17]	All		318	150	33	13	46	54
	1–3 +ve	1997	183	150	33	13	NR	NR
	≥4 +ve		112	150	46	21	NR	NR

BCG, British Columbia group; DBCG, Danish Breast Cancer Group; f/u, follow-up; LRR, loco-regional recurrence; OS, overall survival; PMRT, Post Mastectomy Radiotherapy.

nodes, medial tumor location and estrogen receptor negative tumor status were all independently significant factors increasing the risk of loco-regional recurrence from baseline.

Another retrospective study reported high nuclear grade ($p = 0.04$), negative estrogen receptor (ER) status ($p = 0.001$), presence of lymph vascular invasion (LVI) ($p = 0.003$), and no radiotherapy ($p = 0.0015$) as risk factors associated with a significantly higher rate of LRR on univariate analysis [22]. With ER negative and positive LVI status, radiotherapy reduced LRR from 40% to 12.5% and increase the 5-year overall survival from 43.7% to 87.1%. The authors concluded that radiotherapy can reduce LRR and increase survival in T1–2 N1 breast cancer patients with negative ER status and presence of LVI.

Nodal ratios (NR) have also been studied as a possible prognostic factor for patients with one to three positive nodes. Lee et al. reported that nodal ratio > 0.20 was associated with LRR $> 20\%$, warranting PMRT consideration in patients with one to three positive nodes [23]. Another relevant study was reported from the M.D. Anderson Cancer Center (MDACC) and British Columbia (BC) [24]. In patients with NR < 0.20, the 10-year LRR rate was 17.7% BC vs. 10.9% MDACC (p - 0.27). In patients with NR > 0.20, the 10-year LRR rate was 28.7% BC vs. 22.7% MDACC (p - 0.32). Using Cox regression analysis, the authors found that NR was a stronger prognostic factor compared with number of positive nodes.

An interesting subgroup analysis of DBCG 82b & c was done of previously randomized patients of PMRT [25,26]. Three prognostic subgroups of LR risk were defined based on number of nodes, tumor size, grade and receptor positivity. The best prognostic subgroup had the smallest absolute reduction in 5-year LR probability (11%). However, it also had a similar absolute reduction in 15-year breast cancer mortality after radiotherapy (11%) for the good prognosis group (i.e. one local recurrence prevented = one life saved). The largest absolute reduction in 5-year LR probability after radiotherapy was seen for the poor prognosis group (36%). However, this large LR reduction did not translate into any reduction in 15-year breast cancer mortality (0%), i.e. 1 local recurrence prevented = 0 life saved.

These results bring forth a cardinal question: do patients with lower risk of recurrence benefitted even more as compared to high risk subgroup? Is it that the high risk subgroup would fail systemically from already spread micro metastatic disease anyway and hence local radiotherapy would not affect overall survival? This hypothesis would have to be tested in prospective trials.

In addition, biological factors may also play an important role in the outcome of patients after PMRT and systemic therapy. These findings will be need to be prospectively validated. Such data is being collected in the BIG 2-04 MRC/EORTC SUPREMO trial in the biological sub study, TRANS SUPREMO [27].

Target area for radiotherapy in patients with one to three nodes

The target volume that should be irradiated in patients with one to three nodes is another important issue. Should the treatment area include chest wall, supraclavicular fossa, axilla and internal mammary area? The Danish studies which reported an equivalent survival benefit in one to three nodes versus > 3 node patients indeed irradiated a large volume including chest wall, suprclavicular fossa/axilla and internal mammary nodes. This would be the cardinal argument for continuing to treat patients with one to three nodes with these volumes. However, most radiation oncologists in contemporary practice use only chest wall fields along with a small supraclavicular portal for most patients after mastectomy (and > 3 positive nodes). The EORTC trial powered to answer the possible benefit of internal mammary radiation is yet to report its findings [28].

Of interest is a retrospective study which analyzed 238 patients with stage II breast cancer (one to three positive lymph nodes) treated with mastectomy at the Massachusetts General Hospital between 1990 and 2004 [29]. This trial reported a similar benefit for patients treated with RT to the chest wall alone as compared to more comprehensive loco-regional radiotherapy (axilla, internal mammary). The LRR, DFS, and overall survival rate for patients treated to the chest wall alone was 0%, 96%, and 95% at 10 years, respectively. Other authors have reported similar trends [30].

Current trials and future direction

The US Intergroup trial S9927 was designed specifically to answer the question of PMRT with one to three positive nodes. But this phase 3 trial was terminated early due to poor accrual. As of now the SUPREMO trial is randomizing patients with one to three positive nodes to radiotherapy versus no radiotherapy [31]. The trial has an ambitious target of 1600 patients and has accrued nearly 1000 patients to date. Hopefully the results of this trial would give us a clear answer to the question of radiotherapy with such patients.

Conclusion

Patients with one to three nodes may be paradoxically poised to gain proportionately more as compared to patients with a stronger evidence base for adjuvant radiotherapy. This optimism however has to be tempered with cognizance of the late sequelae produced by radiotherapy. The ongoing BIG 2-04 MRC SUPREMO trial randomized trial is best poised to answer this important question and its results are eagerly awaited.

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