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RESEARCH ARTICLE

De-escalation of Radiation in Positive Axilla for Breast Cancer

Dr Gargi Sharma, DNB[1], Dr Tejinder Kataria, MD, DNB*[1], Dr Deepak Gupta, MD[1], Mr Venkatesan Kaliyapervmal, PHD[1], Dr Shyam Singh Bisht, MD[1], Dr Sorun Sishak MD[1]

[1] Division of Radiation Oncology, Medanta, Sector 38, Gurgaon, Haryana 122001, India.

Corresponding Author: tejinder.kataria@medanta.org or Teji1960@gmail.com

ABSTRACT

Introduction: There has been a trend towards de-escalation in the management of axilla over the last two decades in the form of shift from axillary lymph node dissection to sentinel lymph node dissection in early stage breast cancer. This de-escalation has main advantage in terms of reducing the incidence of lymphedema without compromising the local control. However, when it comes to axillary radiation, there is lack of consensus regarding its use . In this context we reviewed our prospectively maintained data base for axillary recurrences, without radiation to axilla in axillary node positive patient cohort.

Materials and methods: The data of breast cancer patients treated at Medanta, Cancer Institute from 2010 till 2020 was analyzed by querying the electronic health records. Minimum follow up was 2 years after completion of radiation treatment. During follow up, patients were assessed clinically and underwent yearly mammogram, bi-annual ultrasound abdomen and annual chest X-Ray. In case of clinically palpable or suspicious lymph nodes in axilla, a histopathological confirmation was required. The axilla was not irradiated intentionally except in very few cases where the decision was individualized as per surgical and pathological findings after discussion in the tumour board meeting.

Results: Of the 2400 breast cancer patients treated from 2010-2020, final analysis included 1422 patients as per the inclusion criteria. Pathological node positive cases were 827(58.15%). Of which 446/827(53.9%) had N1, 283/827(34.2%) were N2 and 98/827(11.8%) were with N3 disease status. 69.19% patients had undergone axillary dissection. A total of 35 patients received axillary radiation, 7 of them had early stage disease, underwent sentinel lymph node biopsy and were treated before 2013, and rest of them had advanced local disease, post axillary dissection with high axillary burden and presence of high risk features. None (0%) of the patients developed ipsilateral axillary relapse.

Conclusion: The results of this study are a step further in de-escalation of axillary management in terms of radiation, and provide robust data in support of omitting the axillary radiation for breast cancer patients even when sentinel node biopsy shows (1-2) positive nodes for early stage breast disease and in locally advanced breast disease when adequate axillary dissection (even with heavy axillary node burden) has been performed.

Introduction:

The 5yr disease specific survival rate for breast cancer were in the range of 92-95% for early stage disease, whilst for the loco-regional disease the control rates were 80-85%, at the start of present century.[1,2,3] The standard management of axilla recommended was axillary lymph node dissection(ALND), that was defined as adequate, if the surgeons removed at least 10 lymph nodes, as per National Cancer Comprehensive Network (NCCN) guidelines.[4] After ALND, axillary radiation was indicated in presence of 4 or more positive lymph nodes. However, many of the studies started reporting axillary recurrence rates of 1-2% after ALND [5,6] around the same era.

Given the excellent survival outcomes and low rates of axillary recurrence, clinicians focussed their attention to reducing the toxicity of multimodality treatment to the axilla.

From 2000-2010, many studies reported the axillary recurrence rates (less than 3%) after sentinel lymph node biopsy (SLNB) without ALND. A few studies compared the axillary recurrence rates between SLNB having 1-2positive lymph nodes without axillary dissection and adequate axillary dissection and it was found that axillary recurrence rates were still low and did not differ significantly between both the arms. Most of these were small single institution studies.[7,8,9,10] The landmark ACOSOG Z0011 was the first randomised study which proved non-inferiority of SLNB over ALND in early stage breast cancer with 1-2 positive lymph nodes replacing the ALND by SLNB in early stage breast cancer.[11] However, regarding axillary radiation this study did not give any recommendation.

AMAROS trial, published in 2014, showed that axillary radiation therapy (ART) can serve as an alternative to ALND, reducing the incidence of lymphedema without affecting the oncological outcomes. However, in this study, patients in ALND arm also received axillary radiation in presence of 4 or more positive lymph nodes after ALND.[12] Later on, few other studies, aimed to prove safety and efficacy of SLNB over ALND, could not provide clear and consistent indications regarding use of axillary radiation.

In this context a study by Kataria et al, reported, for early stage breast cancer patients, treated with breast conservation surgery with sentinel node biopsy alone followed by whole breast irradiation, axillary levels I and II (lower axilla) receive substantial amount of incidental radiation doses with both the techniques -Intensity modulated radiation therapy(IMRT) and 3D Conformal radiation therapy (3D CRT) that could be one of the reasons for good axillary control even in absence of axillary radiation.[13]

Last decade has seen an improvement in the prognostic molecular markers and newer systemic therapies which have further complicated the contribution of axillary radiation in breast cancer management. There is a discrepancy regarding indications of axillary radiation at many institutes treating breast cancer patients in the available literature.

The current study reports the outcomes of ipsilateral axillary recurrence in breast cancer patients with positive nodes from an institute where we do not practice axillary radiation routinely.

Materials and Methods:

This is a retrospective cohort analysis of breast cancer patients captured prospectively in electronic health information system (eHIS) receiving primary treatment with a curative intent. All women with breast cancer who underwent surgical treatment followed by radiation at Medanta Cancer Institute from 2010 to 2020 were included in the study. Patients with upfront metastatic disease were excluded from the study.

Patient's clinicopathological details and follow-up were collected from the hospital-based electronic medical record system. Hospital-based cancer registry helped complete the details of last follow-up and survival status by telephonic communication.

Patients who did not come back for follow-up after the primary treatment or patients who did not complete all treatment were excluded. Patients who were treated earlier for breast cancer on one side and developed a second primary in the opposite breast were included.

The data was analyzed by dividing the study cohort in to AJCC stages I, II and III. Surgery was either modified radical mastectomy or breast-conserving surgery. Most common chemotherapy protocol was four cycles of Adriamycin and Cyclophosphamide (AC) with four cycles of Paclitaxel/Docetaxel; anti-HER2 therapy was administered to HER 2 positive cases. Radiotherapy schedule followed was either 50 Gy/25# or 40 Gy/15# followed by boost to the cavity in breast conserved cases, either electron boost 12.5Gy in 5 fractions or simultaneous integrated boost to a dose of 62.5Gy in 50Gy/25 fraction cohort. Hormone therapy was either Tamoxifen or Letrozole based on menopausal status for a minimum period of 5 years; extended adjuvant hormone therapy was given to patients with positive nodes.

Results:

There were 2400 breast cancer patients, treated at Medanta Cancer Institute since December 2010-December 2020. Of these, 59%(1422/2400) patients' data sets were evaluable for the current study. The clinicopathological characteristics of these patients are reported in Table 1.

Table 1. Clinicopathological characters of patients

	Number	%
Menopausal status		
Pre menopausal	331	23
Perimenopausal	157	11
Post Menopausal	936	65
Stage		
Stage 0	4	0.28
Stage I	308	21.6
Stage II	560	39.38
Stage III	546	38.39
Types of Surgery		
MRM*	899	63.2
BCS#	520	36.5
ALND*#	984	69.19
SLNB**	436	30.6
Molecular Classification		
Luminal A	754	53
Luminal B	215	15.11
Her 2 rich	165	11.6
TNBC***	284	19.9
Pathological Nodal status		
p N1	446	31.36
p N2	283	19.9
p N3	98	6.8
Radiation site wise		
Chest wall	899	63.2
Whole Breast	520	36.5
SCF@	610	42.8
IMN##	36	2.5
Axilla	30	2.1

*MRM-Modified radical mastectomy
#BCS-Breast conserving surgery
*# ALND-Axillary lymph node dissection
**SLNB-Sentinel lymph node dissection
***TNBC- Triple negative breast cancer
@SCF-Supraclavicular fossa
IMN-Internal mammary nodes

Majority of the patients (n=936, 65%) were in post-menopausal group. On stratifying the patients as per AJCC staging, 4/1422(0.28 %), 308/1422(21.6 %), 560/1422(39.38 %) and 546/1422(38.39 %) were in stage 0, I, II and III respectively. Most common surgical management was mastectomy (in 63.2%, 899/1422) and 36.5% (520/1422) underwent BCS. Most common surgical magement of axilla was ALND (in 69%) and 30% underwent SLNB. On stratifying the patients with molecular subtypes, 53% were luminal A, 15% luminal B, 11% patients HER 2 rich and 20% were triple negative breast cancer. Of 1422 patients, 43% received radiation to SCF and 2.5% received radiation to IMN. Patients who had more than 10 lymph nodes positive on ALND were 110 (7.7 %) and 145 (10.19 %) patients had extra nodal extension (ENE).

In view of a good axillary clearance (at least 10 or more nodes dissected) axillary radiation was omitted since 2010 and only 2.4% (35/1422) of the patients received axillary radiation, 7 of them had early stage breast cancer with 1-2 LNs positive on SLNB and these patients were treated before 2013. Remaining 28 patients had residual axillary nodes even after neoadjuvant chemotherapy (NAC) and after ALND, had more than 10 LNs positive for malignancy with extra nodal extension, presence of other high risk features (TNBC, younger age) and were discussed in the Tumour-Board.

After treatment, patients were followed up clinically every 3 months for 2 years, every 6 months for 1year and yearly thereafter for a total of 10 yrs. Follow up investigations included USG abdomen & transvaginal ultrasound 6 monthly for women on Tamoxifen and yearly chest X-Ray &mammogram for all women. In case of clinical suspicion of recurrence in axilla, a histopathological confirmation was asked. Minimum follow up duration was 2 yrs as this is the peak period of axillary recurrence as shown in previous studies[19, 20] however, 60% of patients were available for 5yrs follow.

Ipsilateral axillary recurrence was reported in none of the patients (0/1422). During follow up 2 patients had suspicious axillary lymph node enlargement, however on histopathological confirmation it was reported as reactive axillary lymphadenitis.

Discussion:

In this study, none of the patients were found to have ipsilateral axillary recurrence, in a setting, where axilla was not treated with external beam radiation intentionally. Those were who received ART, few of them were treated before 2013, when the landmark trials for non-inferiority of SLNB alone over ALND in 1-2 positive nodes were published and we were still incorporating the results in practice. In others, the reason for treating axilla was high axillary burden in addition to presence of high risk features.

It is important to note here, that, in the present study, not all patients with high axillary burden disease received axillary radiation. There were 117 patients with more than 10 lymph node positive and 145 patients had ENE, and only 28 of these patients received axillary radiation. This is to reflect that, in our institute, radiation is not routinely practiced in early stage breast cancer if SLNB shows 1-2 positive lymph nodes and have received adjuvant chemotherapy and also in locally advanced breast cancer when adequate axillary dissection has been performed (i.e if more than 10 lymph nodes have been removed).

It has been reported in several studies, that after an adequate axillary lymph node dissection, isolated axillary node failure is relatively rare(14-17) occurring in 1% to 3% of patients between 19 and 27 months after initial treatment.[14,15] Researchers then attempted towards de-escalating the management in axilla, starting from surgery and found that axillary recurrence rates were still lower after SLNB in clinically and pathologically node negative cases.[16] Again attempts were made to reduce the surgical management in axilla and studies analysed the recurrence rates after SLNB alone in 1-2 postive lymph nodes on SLNB.[17] In the last decade, introduction of newer systemic therapies have further improved the local control.[18] In such a scenario, there is a need to properly define the indication of axillary radiation in order to minimize the overtreatment of axilla and the morbidity associated with it.

Study by Igor at al in 2005, reported the axillary recurrence rate in patients with early stage breast cancers. Patients were randomized in 2 arms, those who received SLNB alone (n=150) and those who had macrometastasis on SLNB, underwent ALND(n=74). None of the patients received radiation to axilla. Median follow up was 42 months. Axillary recurrences were observed in 2 patients. In 1 patient after formal ALND and in 1 patient with a negative SLNB. Both patients developed axillary recurrence at 12 and 14 months respectively and histologically both were invasive lobular carcinoma. The axillary recurrence rate in the subset with negative SLN was 0.8% (1/122), in patients with SLN micrometastases 0% (0/27), and in patients with SLN macrometastases 1.4% (1/73).[19]

ACOSOG study was published in 2011, and included patients with early stage breast cancer with 1-2 positive lymph nodes on SLNB and randomized them into SLNB alone vs ALND arms. Details regarding axillary radiation was provided for 228 of 605 patints, of which, 18% had received axillary radiation, exact indication was not reported for these patients.[20]

In the AMAROS trial, of the 1425 patients with a positive sentinel node, 744 had been randomly assigned to axillary lymph node dissection and 681 to axillary radiotherapy. Axillary recurrence occurred in four of 744 patients in the axillary lymph node dissection group and seven of 681 in the axillary radiotherapy group. The 5-year axillary recurrence was 0·43% (95% CI 0·00–0·92) after axillary lymph node dissection versus 1·19%

(0·31–2·08) after axillary radiotherapy. In this study, patients who had more than 4 lymph nodes positive after ALND had also received axillary radiation.[21]

The OTOASOR trial, where they evaluated the optimum treatment of axilla, randomized early stage breast cancer patients into ALND arm versus axillary radiation arm. Results of this single centre study were published in 2016, showing that axillary recurrence rate was 2% in the ALND arm and 1.7% in the axillary radiation arm, concluding that axillary RT is equivalent to ALND. However, the important thing to note is that in this study too, patients having 4 or more positive lymph nodes after ALND were prescribed axillary radiation. They also prescribed axillary radiation to patients with 1-3 positive nodes on SLNB with presence of additional risk factors (premenopausal status, LVSI, histological grade III).[22]

Study by Diane et al analysed the regional recurrence rates with or without ALND in patients with positive node on SLNB after neo-adjuvant chemotherapy. A total of 161 patients were evaluated, 53 in SLNB alone arm and 108 in SLNB+ALND arm. In the SLNB arm, 40 patients and in SLNB+ALND arm, 90 patients received axillary radiation. Regional nodal recurrence occurred in 9 patients (5.6%) and axillary level 1-2 recurrence noted in 5(3%) patients.[23]

All these studies, who have reported the axillary recurrence rates, do not have consistency regarding indication of axillary radiation, as shown in the table 2.

Table 2. Studies aimed towards de-escalation in the management of Axilla

Study	SLND Involvement	Arms	Axillary RT Details	Axillary recurrence rate
ACOSOG Z001	1-2 Macrometastases	SLNB alone Vs ALND	228/605 patients had RT details 18% received axillary RT combined	1 patient in SLNB 0 in ALND arm
AMAROS	>85% with 1-2 macrometastases	SLNB→ALND SLNB→ART	Patients with >4LN+ in ALND arm received axillary RT	0.4% in ALND 1.19% IN ART arm
SINODAR ONE	1-2 Macrometastases	SLNB alone Vs ALND	No RT details available	<1% in both arms
OTOASAR	1-2 Macrometastases	SLNB→ALND SLNB→ART	Patients with >4LN+ in ALND arm received ART	2% in ALND arm 1.75 in SLNB arm

Furthermore, majority of these studies are the analysis of early stage breast cancer, very few of them mentioned the role of axillary radiation in locally advanced setting after ALND.

Study published by Kataria et al recorded the incidental radiation in axilla in breast cancer patients and found that there is substantial amount of radiation received in axilla in spite of no intentional axillary radiation with conventional as well with advanced radiotherapy techniques like Intensity modulated radiotherapy(IMRT) and Volumetric arc radiotherapy(VMAT).[13] This could also be a factor for good axillary control rate reported in this study as well as in others where axillary radiation was not practiced.

In our review of literature, very few studies have evaluated recurrence rates after omitting axillary radiation, one of them is a recently published study by Jagsi et al, where they evaluated the role of omitting regional nodal irradiation (RNI) in favourable risk, node positive breast cancer patients, and the rates of loco-regional recurrence were low for patients who did not receive axillary radiation.[24]

Similarly, Taylor et al have published a meta-analysis of 16 trials recently where no benefit of regional radiation was seen in trials before 1980s for all-cause mortality however a benefit was reported after the 1980, which is attributed by authors to improvement in radiation therapy techniques.[25]

There is a discrepancy in some of the guidelines regarding indication of axillary radiation at present. Recently published ASCO guidelines recommend axillary radiation in early stage breast cancer with 1-2 positive lymph nodes and in locally advanced breast cancer even after adequate ALND if there are more than or equal to 4 lymph nodes positive.[26] Similarly, the recently published NCCN guidelines for breast cancer recommend axillary radiation in 1-2 positive nodes on SLNB in early stage breast cancer if ALND has not been performed and after adequate ALND in presence of hight risk features for example extracapsular extension, lymphovascular space invasion.[27] While the Central-Eastern European Academy of Oncology (CEEAO) consensus guideline published in june, 2022, recommend to give axillary radiation in

p N1a(SN) early stage breast cancer patients and no axillary radiation is required if sufficient axillary dissection has been performed in advanced breast cancer.[28]

Many centres still practice axillary radiation after adequate ALND if there are more than 4 positive lymph nodes. In this context results of this study provides strong data in support of de-escalation of radiation and omitting the overtreatment of axilla.

Conclusion:

This single centre study with large sample size (over 1400 patients) and a minimum 2year follow up showing zero percent ipsilateral axillary recurrence provides robust evidence in support of de-escalation of radiation in axilla in breast cancer patients. To conclude, since axillary recurrence rates are lower in present era even in node positive cases and substantial amount of incidental radiation is received in axillary level 1 and 2, it can be recommended that use of radiation in axilla may be omitted for 1)Early stage breast cancer where SLNB shows 1-2 positive lymph nodes and 2)Locally advanced breast cancer if >10 lymph nodes have been removed during axillary dissection, irrespective of presence of other high risk features, to decrease the co-morbidity associated with lymphedema.

Conflicts of interest: The authors have no conflicts of interest to declare.

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