Management of Axilla in 2015 in Indian Scenario

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Abstract Sentinel lymph node biopsy is now increasingly being considered the favored method to treat low volume axilla. Most often this is followed by adjuvant radiation directed at axilla. In India however, sentinel node itself is still not widely practiced. The radiotherapy facilities are also not uniform, with cobalt units still being used in many centers. The long-term complications related to radiation are not assessed well. In fact there are also questions whether the evidence from early screen detected cancers in western population can be blindly followed in our population with a possibly different tumor biology and presentation as locally advanced being the norm. However, it is possible that we will see lesser axillary surgery in the minimal axillary disease group, in the not so distant future. We will look at the emerging evidence with an open mind and try to look at how this is applicable to our scenario.

Keywords Breast cancer · Axillary dissection · Sentinel node · axillary radiation · Regional nodal irradiation

Introduction

Historically axillary dissection has always been considered an integral part in the management of breast cancer. It had its

importance in staging, prognostication and selection of adjuvant treatment. But in the current era where predictive genomic assays are being increasingly used for deciding adjuvant treatment of breast cancer and lack of survival advantage with dissection in low volume axilla being increasingly evident, there is a trend to move away from routine axillary dissection. But as the surgical pendulum is slowly swinging away from aggressive management of regional nodes the radiation oncology community is hearing more and more about comprehensive regional radiation in breast cancer.

At the heart of the debate lie crucial conceptual questions regarding the delineation of clinical target volumes (CTV). Whether CTV should be guided by surgical histopathological data showing pattern of involvement or should it be guided by pattern of relapse? More importantly whether treating microscopic nodal burden will decrease the distant relapse and lead to improved overall survival or simply improve the regional control. Similar questions also used to arise when one discussed elective nodal irradiation in lung, prostate and esophageal malignancies.

Comparison of Surgery Versus Observation in the Pre Sentinel Node Era

In the NSABP 04 [1] Fisher et al. reported the long-term results of a randomized trial comparing Radical Mastectomy, Mastectomy with RT and Mastectomy alone. It was found that even with a mean follow up of 25 years only 18.6 % of the mastectomy patients relapsed in axilla where the Radical Mastectomy arm had 38.6 % pathological nodal positivity.

From the Istituto Nazionale Tumori, Milan, Martelli et al. [2] reported on a randomized trial of axillary dissection versus no axillary dissection in 219 patients aged 65–80 with early breast cancer. All patients received adjuvant radiation using

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tangents to the breast but there was no effort to cover the regional nodes. At a median follow up of 5 years only 2 patients had recurrence in the axilla (1.8 %) versus the 23 % pathological nodal positivity observed in the dissection arm. There was no difference in local recurrence, metastasis or survival.

In IBSCG 10–93 [3] Rudenstam et al. randomized 473 postmenopausal women aged more than 60 with clinically negative axilla to axillary dissection versus no axillary dissection. With a median follow up of 6.6 years only 6 patients (3 %) had axillary recurrence in the observation arm whereas the pathological nodal positivity was 28 % in the other arm. Interestingly only 33 % of patients in the whole cohort had adjuvant radiation.

This difference between pathological nodal positivity and axillary nodal recurrence has been called the ‘Recurrence Gap’ by Liyi Xie [4]. The article goes on to hypothesize four reasons for this phenomenon - the effect of systemic therapy, incidental radiation of nodes, under reporting of nodal recurrence and competing risk of metastatic disease.

Can Sentinel Node Biopsy Replace Axillary Lymph Node Dissection?

The Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC Trial) [5] was one of the earliest randomized trials discussing the use of Sentinel Lymph node biopsy. One thousand thirty one patients were randomly assigned to undergo sentinel lymph node biopsy ($n=515$) or standard axillary surgery ($n=516$). It was clear that rates of lymph edema, sensory deficit and shoulder dysfunction as well as post-operative hospital stay were significantly favoring sentinel lymph node biopsy arm. Similar observations along with the accuracy of sentinel lymph node biopsy and its negative predictive value were made by a single institution randomized study by Veronesi et al. from Italy [6] and Sentinel node Biopsy versus Axillary clearance (SNAC) trial [7] from Australia. But important questions regarding survival and loco regional control still remained.

NSABP B-32 [8] published in 2010 investigated whether further axillary dissection can be avoided in sentinel Node negative axilla. Five thousand six hundred eleven women with invasive breast cancer were randomly assigned to sentinel node resection plus axillary dissection (Group 1) or to sentinel node resection alone with axillary dissection only if sentinel nodes were positive (Group 2). With an 8-year follow-up, the study reported a survival of 91.8 % in the axillary dissection group and 90.3 % in the no dissection group. There were 8 regional node recurrences as first events in Group 1 and 14 in Group 2 ($P=0.22$). They concluded that further axillary dissection could be safely avoided in the sentinel node negative group without any impact on survival.

The remaining question was whether axillary dissection can be avoided even in the sentinel lymph node positive group and whether radiation directed at axilla will give favorable results.

In the ACOSOG Z011 trial [9] 891 early breast cancer patients with 1–2 positive sentinel lymph nodes were randomized after to further axillary dissection versus observation. 21.0 % of patients undergoing ALND had 3 or more involved nodes compared with 3.7 % undergoing SLND alone. Four or more involved nodes were seen in 13.7 % of patients receiving ALND and 1.0 % of those receiving SLND alone. Despite this with a median follow up of 6.3 years there was no survival difference between the two arms [10]. The 5 year local recurrence [1.6 % vs 3.1 % $P=.11$] and the loco regional recurrence-free survival [96.7 % vs 95.7 %] did not differ between the SLND group and ALND group. Adverse surgical effects were reported in 70 % (278 of 399) of patients after SLND+ALND and 25 % (103 of 411) after SLND alone ($p<or=.001$) [11].

In the IBCSG 23–01 trial [12] 931 patients were randomized (464 in the AD group and 467 in the no AD group). After a median follow-up of 5 years, the survival or loco-regional recurrence rate did not differ in between the two arms.

The AATRM048/13/2000 trial [13] randomized 247 newly diagnosed early-stage breast cancer ($T<3.5$ cm, clinical N0, M0) with micro metastatic sentinel nodes. Patients were randomly assigned to one of the two study arms: complete ALND (control arm) or clinical follow-up (experimental arm). The study reported an OS of 95 % versus 93 % at 10-year follow-up in the axillary dissection versus no-dissection groups. Four patients experienced disease recurrence: 1 (1 %) of 108 control subjects and 3 (2.5 %) of 119 experimental patients.

In the OTASOR trial from Budapest [14], 474 early breast cancer patients (T size <3 cm) with sentinel lymph node positive were randomized to further axillary surgery versus observation. There was no significant difference between the two arms in terms of survival with a mean follow up of around 70 months

Axillary recurrence (primary endpoint) was 1.6 % vs. 1.7 % ($p=NS$). The 5.8 years overall survival was 84.9 % vs. 91.2 %; 5-year disease-free survival was 79.9 % with cALND and 85.6 % with SLND plus ANI.

In the AMAROS Trial, [15] of the 1425 patients with a positive sentinel node, 744 had been randomly assigned to axillary lymph node dissection and 681 to axillary radiotherapy. With a median follow up of 6.1 years, axillary recurrence occurred in four of 744 patients in the axillary lymph node dissection group (.43 %) and seven of 681 in the axillary radiotherapy group (1.19 %). 5-year overall survival was 93.3 % in the axillary lymph node dissection group and 92.5 % in the axillary radiotherapy group ($p=0.34$). In this trial, signs of lymphedema were noted at 5 years in 23 % of the patients after axillary lymph node dissection and 11 % of those after axillary radiotherapy.

Thus these trials establish the role of sentinel lymph node biopsy with no further axillary dissection in clinically node negative axilla.

Who are the Patients Suitable for Receiving Sentinel Node Biopsy Without Further ALND?

It must however be noted that most of this data supporting no axillary dissection comes from patients with low risk of disease recurrence (<T3 tumors, micro metastatic nodes) to begin with and those who have also received axillary radiation. While the overall false negativity of the sentinel node procedure is around 8 %, the risk is much lower for T1 and T2 tumors, than for T3 tumors, where it can be as high as 18 %. In the ACOSOG 11, [9] the median tumor size was 1.6 cm and 84 % of patients were Hormone positive. The mean tumor size in OTASOR [14] was 2.1 cm with 84 % ER positive. The AMAROS [15] trial when it started in 2001 included only unifocal tumors <3 cm. Later the protocol was amended to include tumors up to 5 cm in size and multifocal tumors. The IBCSG [12] trial allowed tumors <5 cm with only microscopic nodal positivity. 90 % of the tumors were hormone positive. Thus it will be prudent to remember these inclusion criteria while adopting sentinel lymph node biopsy only as the standard, especially in India.

What Should be the Radiation Fields in Sentinel Era?

The trial design in ACSZ011 specified only tangent fields and not a 3rd field to cover the Axilla or Supraclavicular fossa [16, 17]. To understand whether the low loco regional recurrence in SLND arm can be explained by the regional nodal coverage in ACSZ011, a review of the fields used were done by Jagsi et al. [18]. Of the 856 patients randomized, completed case reports were available for 605. 89 % received whole-breast RT. Of these, 89 (15 %) were recorded as also receiving treatment to the supraclavicular region. Detailed RT records were obtained for 228 patients, of whom 185 (81.1 %) received tangent-only treatment. Using the definition used by Schlembach et al. [19] to define high tangent as upper field border within 2 cm from the humeral head, high-tangent RT fields were used in 50 % of patients (33 of 66) in the ALND arm and 52.6 % of patients (40 of 76) randomly assigned to the SLND arm. Reznik et al. [20] had suggested that Level I axillary dose increases from 66 % of prescribed dose with standard tangents to 86 % with high tangents, and level II from 44 to 71 %. The proportion of level I receiving 95 % of prescribed dose increases from 51 % with standard tangents to 79 % with high tangents, and the proportion of level II receiving 95 % of prescribed dose increases from 26 to 51 %. 43

(18.9 %) patients received directed regional nodal RT using three fields: 22 in the ALND arm and 21 in the SLND arm. Eighteen patients also received a posterior axillary boost.

In OTOSAR [21] trial all the patients in the No ALND arm received radiation to cover all levels of axilla and supraclavicular fossa. It is interesting that as per institutional protocol postoperative RNI in patients undergoing ALND was given to all patients with 4 or more positive nodes (pN2a-3a) and to patients with 1 to 3 positive nodes (pN1a) having other high-risk patient and tumor characteristics (e.g., premenopausal status, lymphovascular invasion, histologic grade III tumor) Thus up to 30 % (76 patients out of 244) in the ALND arm also received RNI. In the AMAROS Trial, [15] radiation in the SLND only arm included all three levels of Axilla and Supraclavicular fossa. In the IBCSG 23, [12] 19 % of the patients received only partial breast radiation where as others received radiation to the whole breast. Interestingly, in 9 % of the patient's mastectomy was done instead of BCS.

In conclusion in patients who are Sentinel Lymph node negative and no further ALND has been done, no further axillary directed treatments including high tangents are required. For patients who undergo MRM and have no indication of radiation otherwise and are p N0, radiation can be safely omitted with the caveat that most of the sentinel lymph node data comes from breast conservation surgery. In patients who do not undergo further axillary dissection after a positive axillary node, radiation directed at all levels of axilla and supraclavicular fossa is recommended.

Supraclavicular and Internal Mammary Radiation

One of the other remaining considerations is the management of supraclavicular nodes and internal mammary nodes in patients with positive nodes. The landmark Radiation Oncology trials Danish 82 a [22] and 82 b [23] and the British Columbia trial [24], all had regional nodal radiation as a part of its treatment protocol. But since the recurrence pattern did not favor radiating these nodes most of the institutional guidelines till recently omitted internal mammary radiation and limited supraclavicular fossa radiation to high axillary burden patients. Two recent trials have been published questioning this conventional wisdom. The EORCTC trial [25] by Poortmans et al. randomized 4004 women who had a centrally or medially located primary tumor, irrespective of axillary involvement, or an externally located tumor with axillary involvement to undergo either whole-breast or thoracic-wall irradiation in addition to regional nodal irradiation versus no regional nodal radiation. At 10 years, overall survival was 82.3 % in the nodal-irradiation group and 80.7 % in the control group ($ds=0.06$). The rate of disease-free survival, distant disease-free survival for breast-cancer was better with regional radiation. The MA 20 trial [26] also showed a 10-year DFS benefit

for regional nodal radiation. It is not yet clear whether these trials will make any impact on the routine management of nodes in Breast cancer

The Indian Scenario

Sentinel node biopsy is an accepted standard of care for a N0 disease in most developed countries. In India however, it is practiced at very few centers across the country. There are many reasons for this. Breast cancer has become the number one cancer in all the urban registries. However organized population screening is non-existent and most patients still present with a palpable lump. The proportion of LABC's ranges from 40 to 60 % in most HCR statistics. Screen detected cancers and non-palpable cancers form a minuscule of the total breast ca patients. Palpable nodes are also not uncommon. Secondly the expertise for sentinel node biopsy is limited to a few major hospitals. Nuclear medicine facilities are not that common and availability of blue dye is an issue. Also most general surgeons, many of whom are not trained in the finer aspects of breast conservation and sentinel node biopsy, manage breast cancer. Some centers practice alternative methods like axillary sampling or limited axillary dissection. In such a scenario, it is unlikely that sentinel node will become the standard of care for N0 breast ca across the country in the near future. Secondly, the percentage of early breast ca undergoing breast conservation treatment is possibly less than 20 % even in major centers in India. Even where sentinel node is routinely practiced, more patients undergo mastectomy with sentinel node biopsy than BCS with sentinel node biopsy. Another concern is the limited follow up of these trials. Radiation to larger fields can have impact on the non-cancer related mortality on a long-term follow up. Although there is some data to suggest that using modern radiotherapy and careful attention to dose received by normal tissues can mitigate these toxicities, it is unclear how much of the Indian population has access to these facilities.

Conclusion

It is clear that in future we will be moving more and more towards less aggressive management of regional lymph nodes. Avoiding axillary dissection may be safe in early breast cancers that are sentinel node negative and low burden sentinel node positive cancers that are scheduled to receive radiation. As genomic profiling and adjuvant management based on such risk stratification becomes increasingly common it is clear that we will have to move away from conventional risk factors for decision-making. The tumor biology, natural history and clinical presentation of disease of our population must be kept in mind before rejecting time-tested approaches.

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