Clinics in Oncology

Commentary
Published: 19 Oct, 2016

Internal Mammary Nodal Irradiation: The Jury is Still Out!

*Tabassum Wadasadawala[1] and Jyoti Bajpai[2]**

[1]Department of Radiation Oncology, Advanced Centre for Treatment, Research and Education, Navi Mumbai, India

[2]Department of Medical Oncology, Tata Memorial Hospital, Mumbai, India

Abstract

In the current era of "minimal treatment" and "personalized" multi-disciplinary management for breast cancer, the data from thousands of women participating in the Regional Nodal Irradiation (RNI) trials has raised several concerns and opened up debate surrounding internal mammary chain (IMC) irradiation. These issues include the relative contribution of irradiation of the IMC, the target volume and dose to be delivered, the lack of overall survival benefit with RNI, and whether to treat IMC when overall regional recurrences are rare especially in the current era of effective systemic therapy. We recommend that caution should be exercised while adopting this into clinical practice as the data is not mature enough to prove its safety especially with respect to cardiac morbidity as well as second malignancy.

Introduction

The current of "personalized medicine" has made its place to some extent in prevention as well as therapy for breast cancer. The genetic and genomic tests employed in treatment of breast cancer usually help oncologists in systemic therapy decision making. The "personalized" approach has yet to evolve as far as loco-regional treatment for breast cancer is concerned. The role of Internal Mammary Nodal Irradiation (IMNI) for early breast cancer is one such example which is currently a heavily debated topic and needs "personalized" approach to get optimal balance between treatment efficacy and toxicity. This commentary discusses the issues surrounding the IMNI in detail and its impact if adopted as a standard of care in the developing world.

The Evidence for Internal Mammary Nodal Irradiation

Mature data from 10,260 women on early breast cancer from the three large randomized trials and the Danish Internal Mammary Chain (IMC) population based study has been published recently [1-4]. The three randomized trials studied the role of Regional Nodal Irradiation (RNI) in patient population having varied clinical and pathological risk factors (especially with respect to axillary node positivity) and target volumes of radiotherapy. French trial was done in women who underwent mastectomy and had predominantly node positive disease. It was the only trial which specifically evaluated the benefit of additional IMC irradiation versus only supra-clavicular fossa (SCF) irradiation [1]. The other two trials (EORTC 22922 and MA 20) were done in women with breast conservation and evaluated the role of comprehensive RNI (axilla, IMC and SCF) versus no RNI [2,3]. The Danish IMC study was a population based study wherein patients with left side disease did not undergo Internal Mammary Nodal Irradiation (IMNI) whereas those with right side underwent IMNI [4]. The primary endpoint of the three randomized trials was Overall Survival (OS). The French study was overoptimistic in design and hence underpowered to answer the question. At median follow up of 8.6 years, no difference in OS was observed. The 10-year overall survival was 59.3% in the IMN nonirradiated group versus 62.6% in the IMN-irradiated group (P=0.8). The EORTC trial reported that at a median follow up of 10.9 years, the overall survival was 82.3% in the RNI group and 80.7% in the control group (hazard ratio (HR) for death with nodal irradiation, 0.87; 95% confidence interval [CI], 0.76 to 1.00; P = 0.06). However, the rate of Disease Free Survival (DFS), Distant Disease Free Survival (DDFS) and breast cancer mortality (BCM) favored RNI group and the difference was statistically significant. Similarly, in the MA 20 trial, at a median follow up of 9.5 years, there was no significant difference in OS, with a rate of 82.8% in the nodal-irradiation group and 81.8% in the control group (HR, 0.91; 95% CI, 0.72 to 1.13; P=0.38). The DFS was significantly better in the RNI group. The Danish IMC study reported that the 8-year overall survival rates were 75.9% with IMNI versus 72.2% without IMNI (HR for death was 0.82,

OPEN ACCESS

Correspondence:
Jyoti Bajpai, Department of Medical Oncology, Tata Memorial Hospital, Mumbai, India,
E-mail: dr_jyotibajpai@yahoo.co.in

Received Date: *23 Aug 2016*
Accepted Date: *20 Sep 2016*
Published Date: *19 Oct 2016*

Citation:
Wadasadawala T, Bajpai J. Internal Mammary Nodal Irradiation: The Jury is Still Out!. Clin Oncol. 2016; 1: 1119.

95% CI, 0.72 to 0.94; P=0.005) at a median follow up of 8.9 years. Breast cancer mortality was 20.9% with IMNI versus 23.4% without IMNI (adjusted HR, 0.85; 95% CI, 0.73 to 0.98; P=0.03). However, there was no difference in the risk of distant recurrence at 8 years, 27.4% with IMNI versus 29.7% without IMNI (adjusted HR, 0.89; 95% CI, 0.78 to 1.01; P=0.07).

More questions than answers?

The rationale behind treating IMC in breast cancer is to sterilize the dormant and potential nidus of distant dissemination. It is however, notable that despite the benefit seen in DFS and DDFS in the randomized trials, there was no significant improvement in the overall survival at 10 years. The Danish study on the contrary reported significant improvement in overall survival without significant difference in the DDFS. It is known from the recent Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of post mastectomy radiotherapy in node-positive patients that the impact of reducing any recurrence (either loco regional or distant) up to 10 years is seen on breast cancer mortality only at 20 years. Hence all the trials are not mature enough to answer what impact RNI will have on breast cancer as well as overall mortality. Moreover, there is no robust data on cardiac safety data from women adequately treated in the modern era with optimal systemic therapy and advanced radiotherapy techniques [5]. It is also important to note that the Danish IMC study was discontinued after the introduction of taxanes.

Target volume and dose

All the three trials differed with respect to the target volume, treatment techniques, dose fractionation and planning methodology which are known to have profound impact on cardiac and lung doses. The French trial was based on two dimensional planning employing photon-electron technique and treating upper 5 inter-costal spaces to a dose fractionation of 45 Gy in 18 fractions, 4 fractions a week. The EORTC trail irradiated IMC using partially wide tangents by going 3 cm across midline in all patients irrespective of patient anatomy which is known to affect coverage of IMC. The target volume of IMC varied according to tumor location (first five inter-costal spaces in patients with lower inner-quadrant tumors, otherwise first three inter-costal) and conventionally fractionation (50Gy in 25 fractions over 5 weeks) was employed. Imaging (lateral radiograph, CT scan or ultrasound) was used for treatment planning to know chest wall thickness but did not mandate contouring of the IMC. The MA20 trial on the hand, allowed both photon-electron as well as partially wide tangent techniques for IMNI using conventional fractionation. CT planning was recommended, with the IMC volume defined as 1 cm around internal mammary vessels in the first three inter-costal spaces. Both the trials accepted IMN coverage between 80% -85% of prescription isodose which is less than the conventionally accepted criteria of 95% while treating any site. Radiotherapy Quality Assurance (QA) program was reported for EORTC and MA 20 trials but not for the French trial.

Variability in IMC localization and delineation guidelines

Patient anatomy leads to a considerable variation in the location of IMC with respect to its depth and lateral distance from the sternum. This has been shown in earlier reports and thus makes 2D planning an ineffective method of treating IMC. This has a direct implication on the amount of coverage of IMC as well as irradiation of the ipsi-lateral lung, heart and contra-lateral lung raising concerns of radiation pneumonitis, cardiac morbidity as well as second cancers [6]. As none of the trials involved 3-dimensional conformal radiotherapy, it becomes very difficult to extrapolate the results from these studies in the era of modern radiotherapy. Moreover, the delineation guidelines for contouring IMC are also being refined by various professional bodies [7-8].

Incidental irradiation of IMC

Report of quality assurance of the EORTC trial as well as a sub-study of the Danish IMC study have shown that the IMC receives incidental radiation ranging from 21- 35% from the standard tangents [9-10]. The incidental coverage of the IMC was dependent upon patient anatomy and the treatment technique used. Similarly, a New York series of lympho-scintigraphy also studied the inclusion of IMC in the standard tangents and found direct correlation of the pre-sternal fat thickness with IMC coverage. If the fat thickness is ≤10 mm then IMC was covered all the times at least partially whereas otherwise it was covered partially in 60% of the times [11]. Collectively, these findings suggest that it is difficult to avoid IMC irradiation completely from the standard tangents or electron fields in case of mastectomy i.e. IMC is any how partially treated unintentionally. This could have confounded the trial results which failed to show survival benefit.

Incidence of isolated IMC recurrence

Isolated IMC recurrence is very rare. It is usually involved in conjunction with other regional nodes. One possible explanation for the low rate of IMN recurrence is that IMN chain environment is somehow less conducive to the growth of metastatic tumor cells than other nodal sites. As a result, IMN metastases are likely to remain indolent even without specific local-regional treatment. Moreover, it is difficult to pick up IMC recurrence clinically without imaging. As a result, randomized trials have not reported the incidence of IMC recurrence separately.

Should IMC irradiation become standard of care?

Adopting IMC irradiation as a standard of care has huge resource implications especially for developing countries where majority of women do not have access to RT facilities with 3D planning capability. Moreover, a recent report by Taylor et al highlights the regional differences with respect to the mean heart dose across different countries of the same continent [12]. Hence adopting IMC irradiation as a standard of care would be very challenging at least for developing countries. In fact Professor Poortmans recommends that "Further research is needed to more precisely define the *subgroup* of patients that benefit most [from] this treatment, [however] these data should be discussed with current node-positive patients, especially as late toxicity is limited in recent studies". Given these data, it seems prudent, that a sub group should be indentified on the basis of nodal status, tumor location, and other clinical, pathology-derived, and imaging-based information, to assess the risk of internal mammary nodal involvement. It is equally important to accomplish this with acceptable cardiac and pulmonary radiation dose constraints respecting patient anatomy.

Conclusion

As discussed, the chance of routine adoption of IMNI in clinical practice seems murkier. Probably future studies incorporating genomic information may be able to precisely identify the subgroup most likely to benefit from IMNI. Till then clinicians should "personalize" the decision for IMNI based on conventional risk factors, respecting patient anatomy.

References

1. Hennequin C, Bossard N, Servagi-Vernat S, Maingon P, Dubois JB, Datchary J, et al. Ten-year survival results of a randomized trial of irradiation of internal mammary nodes after mastectomy. Int J Radiat Oncol Biol Phys. 2013; 86: 860-866.

2. Poortmans PS, Collette S, Kirkove C, Van Limbergen E, Budach V, Struikmans H, et al. Internal mammary and medial supraclavicular irradiation in breast cancer. N Engl J Med. 2015; 373: 317-327.

3. Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, et al. Regional nodal irradiation in early- stage breast cancer. N Engl J Med 2015; 373: 307-316.

4. Thorsen LB, Offersen BV, Danø H, Berg M, Jensen I, Pedersen AN, et al. DBCG-IMN: A population-based cohort study on the effect of internal mammary node irradiation in early node-positive breast cancer. J Clin Oncol. 2016; 34: 314-320.

5. Henson KE, McGale P, Taylor C, Darby SC. Radiation-related mortality from heart disease and lung cancer more than 20 years after radiotherapy for breast cancer. Br J Cancer. 2013; 108: 179-182.

6. Courdi A, Chamorey E, Ferrero JM, Hannoun-Lévi JM. Influence of internal mammary node irradiation on long-term outcome and contralateral breast cancer incidence in node-negative breast cancer patients. Radiother Oncol. 2013; 108: 259-265.

7. https://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspxhttps://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx

8. Verhoeven K, Weltens C, Remouchamps V, Mahjoubi K, Veldeman L, Lengele B, et al. Vessel based delineation guidelines for the elective lymph node regions in breast cancer radiation therapy - PROCAB guidelines. Radiother Oncol. 2015; 114: 11-16.

9. Poortmans P, Kouloulias VE, Venselaar JL, Struikmans H, Davis JB, Huyskens D, et al. Quality assurance of EORTC trial 22922/10925 investigating the role of internal mammary--medial supraclavicular irradiation in stage I-III breast cancer: the individual case review. Eur J Cancer. 2003; 39: 2035-2042.

10. Thorsen LB, Thomsen MS, Berg M, Jensen I, Josipovic M, Overgaard M, et al. Danish Breast Cancer Cooperative Group Radiotherapy committee. CT-planned internal mammary node radiotherapy in the DBCG-IMN study: benefit versus potentially harmful effects. Acta Oncol. 2014; 53: 1027-1034.

11. Hare GB, Proulx GM, Lamonica DM, Stomper PC. Internal mammary lymph node (IMN) coverage by standard radiation tangent fields in patients showing IMN drainage on lymphoscintigraphy: therapeutic implications. Am J Clin Oncol. 2004; 27: 274-278.

12. Taylor CW, Wang Z, Macaulay E, Jagsi R, Duane F, Darby SC. Exposure of the Heart in Breast Cancer Radiation Therapy: A Systematic Review of Heart Doses Published During 2003 to 2013. Int J Radiat Oncol Biol Phys. 2015; 93: 845-853.