

Practical consensus recommendations regarding role of postmastectomy radiation therapy

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Abstract

The use of radiation therapy after mastectomy (PMRT) has been limited to those patients who are at significant risk of cancer recurring in the chest wall or in the nodal basins. The use of PMRT has been widely accepted for patients with four or more positive lymph nodes,^[1,2] but there is still controversy regarding the value of PMRT for those with one to three positive nodes. This expert group used data from published literature, practical experience and opinion of a large group of academic oncologists to arrive at these practical consensus recommendations for the benefit of community oncologists.

Key words: Boost, early breast cancer, hypofractionation, node positive

Introduction

Radiation therapy has been used over the years as a supplemental treatment after surgery to resect tumors from the body. The main purpose of this use of radiation therapy is to kill any residual cancer cells at the site of the tumor and to improve a patient's long-term chances of survival. Radiation therapy after lumpectomy has been the trend for all invasive breast cancer in patients younger than 70 years of age. In case of mastectomy, Radiation Therapy is currently the standard of care for all patients with stage III breast cancers,^[3-5] but whether or not PMRT is beneficial for stage II breast cancers is a matter of debate.

Expert oncologists from all over India met to discuss and reach a consensus statement to provide community oncologists practical guidelines on when to go for Post Mastectomy Radiation Therapy. The discussion was based on published evidence and practical experience in real life management of such patients. The expert group discussions were moderated by Dr Dinesh Singh and Dr Gagan Saini. The core expert group consisted of Dr Vaneet Gupta, Dr Deepak Abrol, Dr Sudarshan De and Dr Piyusha Kulshrestha. Members of the panel were also allowed to share their personal experiences and make comments. This manuscript is the outcome of the expert group discussion and consensus arrived at in 2017.

Defining Clinical Cohort and Practice of Expert Group Panel Members

The primary objective was to provide a consensus statement for community oncologists that could be applicable as ready-to-use practical recommendations. Hence, the applicable setting was outlined by defining the clinical cohort and current practice of the participating delegates and expert group panel members – on the basis of which this document was prepared. The experts discussed a case of a 40 year old

premenopausal lady who was diagnosed with infiltrating duct carcinoma in left breast inner quadrant. She underwent Breast Conservation Surgery (BCS). HPE results were – T1N1M0 (well differentiated tumor, single node positive out of twenty) ER-80%, PR-80%, HER2/neu-negative and Ki 67-3%. Metastatic workup was negative. Based on this case, a series of questions were put up for poll upon which the expert group discussed and aimed to reach a consensus. Each question had multiple choice options from which participants were to select the one most appropriate for their clinical practice setting. The expert group then formed the practical consensus recommendations for the community oncologists.

Radiotherapy Postbreast Conservation Surgery

A total of 100% of the polled oncologists were in support of recommending radiotherapy post BCS in early node positive (pT1N1) breast cancers [Table 1]. There have been many studies and Meta-analyses which back up the poll results. It has been observed that administering radiotherapy after quadrantectomy reduces the risk of local recurrence in women with small cancers of the breast.^[6] A meta-analysis by the Early Breast Cancer Trialists' Collaborative Group suggests that radiation therapy after breast-conserving surgery substantially reduces the risk of cancer recurring in the breast and moderately reduces the risk of death from the disease.^[7] The results were based on data from nearly 11,000 women who participated in 17 randomized trials that compared breast-conserving surgery with and without radiation therapy. Overall, radiation therapy was associated with a 16 percent drop in the absolute risk of breast cancer recurring in the first decade (from 35 percent to 19 percent); it was also associated with a 4 percent drop in the absolute risk of dying from breast cancer in the first 15 years after surgery (from 25 percent to 21 percent). The largest individual trial evaluating the use of radiation after breast conservation surgery was the NSABP B-06 trial^[8] in which 12-year actuarial local recurrence data revealed an ipsilateral breast recurrence rate of 35% in the lumpectomy-alone group compared to 10% in the lumpectomy plus radiation group.

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The expert group was in agreement with the polled oncologists and recommended post BCS radiation therapy for patients with early node positive (pT1N1) breast cancers. It was also discussed that omission of radiotherapy has also been associated with a large increase in risk of ipsilateral breast tumor recurrence and with a small increase in the risk of patient mortality.^[9] The expert group suggested that the use of radiation therapy also reduces the risk of recurrence due to any residual cancer cells at the site of tumor or any microscopic disease that may be present in the remaining breast.

Need for Hypofractionation

Recently, it has been shown that less frequent but higher-dose radiotherapy regimens are as safe and effective as the standard regimen of more frequent lower doses for women with early breast cancer post-surgery.^[10] The results of the two UK Standardisation of Breast Radiotherapy (START) trials showed that 3 weeks of radiotherapy is as good as 5 weeks of radiotherapy with less damage to nearby healthy tissue. Breast shrinkage, telangiectasia, and breast edema were less common in the 3-week regimen compared with the 5-week schedule. Two more randomized trials—the Royal Marsden Hospital/Gloucestershire Oncology Centre (RMH/GOC) trial^[11,12] and the Canadian trial^[13]—have supported the establishment of Hypofractionated whole breast irradiation (HF-WBI) with recent publication of 10-year outcomes.

Majority of the oncologists (80%) gave affirmative answer when asked if they would recommend Hypofractionation [Table 2]. The expert panel was slightly divided regarding the recommendation of hypofractionation. Concerns about cardio-toxicity were raised although there have been studies which have showed that cardiac mortality is not statistically different among left sided breast cancer patients treated with Hypofractionated radiotherapy or conventional radiotherapy.^[14,15] A large Canadian trial enrolled 1234 women with invasive, lymph node-negative breast cancer treated by lumpectomy with negative pathologic margins.^[16] The trial randomized women to receive hypofractionated whole breast irradiation of 42.5 Gy in 16 fractions over 22 days versus standard whole breast irradiation of 50 Gy in 25 fractions over 35 days. Acute toxicity was low and was similar between the arms. Long-term outcomes also were similar between the arms. The 10-year risk of local recurrence was 6.2% in the hypofractionated arm and 6.7% in the standard arm.^[13] Thus, hypofractionated whole breast irradiation has been shown to yield similar disease control, with considerably greater convenience, in patients with characteristics similar to those of patients entered on that study. It was also pointed out that HF-WBI has already been adopted in parts of UK and Canada as well as some parts of USA, as the standard of care for women requiring adjuvant radiotherapy for invasive early breast cancer.^[10,17,18] A recent Indian study by Nandi *et al.*^[19] has suggested that Hypofractionated RT is well tolerated in Indian population with reduced acute skin toxicity and good cosmetic outcome. The expert panel concluded that hypofractionation can be given to patients based on recent reports of its equivalent efficacy in comparison with standard schedules in terms of local control and cosmesis.

Importance of Boost

The technique of giving a radiation boost at the end of treatment has been very effective in keeping breast cancer from coming back. Radiation boost treatments are given after the regular sessions of radiation are complete.^[20] The polled oncologists unanimously agreed that boost should be given in this case as indicated by Table 3. There is enough published evidence to suggest that radiation boost is beneficial for early breast cancer patients in reducing the chance of local recurrence. Two randomized trials compared 50 Gy to the breast alone with 50 Gy given to the breast followed by a tumor bed boost.^[21,22] Both trials demonstrated a lower risk for breast recurrences in the arm treated with the boost dose. In the trial conducted by the European Organisation for Research and Treatment of Cancer (EORTC), the greatest benefit was noted in young patients.^[21] However, patients in all age categories achieved a statistically significant benefit. An international multicenter retrospective study was performed on 373 patients, aged 45 years or less, treated in 18 institutions.^[23] Forty five percent of them underwent WBI, 40% underwent WBI plus a boost, and 15% had no radiotherapy. The relapse-free survival rates at ten years were 46% without radiotherapy, 72% in the WBI group, and 86% in the WBI plus boost group. Differences were statistically significant with an overall risk reduction for local relapse of 66% with WBI and 85% with WBI and boost. Another study by Wong *et al.*^[24] confirmed the favorable effect of the radiation boost, with no local relapse observed among 79 patients receiving a boost, whereas 8 out of 141 patients in the “no-boost” group experienced in-breast local recurrence. Looking at all the evidence, the expert panel was of the opinion that radiation boost should be given to early breast cancer patients. Although, boost has been shown to be more effective for younger patients, it still has a beneficial effect on older patients.

Role of Radiotherapy to Axilla

When asked whether they would recommend axillary radiotherapy upon breast surgery in early breast cancer patients, a total of 91.7% of the polled oncologists were not in its support as indicated in Table 4. Axillary lymph

Table 1: Question 1 - Following breast conservation surgery, is radiotherapy necessary in early stage disease?

Options	Yes	No
Percentage of polled oncologists	100	0

Expert group consensus: Post-BCS radiotherapy is recommended for patients with early node positive (pT1N1) breast cancers. BCS=Breast conservation surgery

Table 2: Question 2 - Can radiation therapy be given with hypofractionation?

Options	Yes	No
Percentage of polled oncologists	80	20

Expert group consensus: Hypofractionation can be given but is not mandatory. Recent reports showed equivalent efficacy in comparison with standard schedules in terms of local control and cosmetic outcome

Table 3: Question 3: Is radiation boost recommended to tumor bed?

Options	Yes	No
Percentage of polled oncologists	100	0

Expert group consensus: Boost is beneficial and should be given to early breast cancer patients irrespective of age

node dissection has been the standard mode of management of axilla in invasive breast cancer. It is controversial as to whether axillary radiotherapy can displace axillary lymph node dissection. A meta-analysis performed to compare axillary radiotherapy and axillary dissection showed no significant difference in disease free survival and overall survival between the radiation group and the dissection group.^[25] There was also no significant difference in either the axillary recurrence or the local recurrence between the two groups. A study by Recht *et al.*^[26] analyzed the likelihood of regional nodal failure (RNF) for 1,624 patients with stage I or II invasive breast carcinoma treated with conservative surgery and radiotherapy (RT). They concluded that RNF is uncommon in patients treated to the breast alone following an adequate axillary dissection when the axillary nodes are negative or when one to three positive nodes were present. The expert group was of the opinion that radiation therapy to axilla in patients with less than 3 nodes positive does not seem to have much benefit over axillary dissection. The panel suggested that currently there is no role of axillary radiation therapy in patients with an adequately dissected axilla. It was also suggested that axillary radiation therapy may be an option for patients with four or more positive lymph nodes, but more evidence is required for it to become the standard treatment.

Inclusion of Internal Mammary Chain

To the question whether they would include the internal mammary chain in the radiation field, the polled oncologists were fairly divided as indicated by Table 5. While 62.5% gave an affirmative answer, 37.5% were against recommending the inclusion of the internal mammary chain in the field. There is no general consensus concerning irradiation of internal mammary nodes. Many studies and meta-analyses have been done regarding the benefit of irradiating the internal mammary chain with conflicting results. According to a study by Courdi *et al.*^[28] internal mammary chain irradiation in node-negative tumours is associated with increase in overall survival and cancer specific survival in patients with inner or centrally located lesions. Two large studies, each with about 10 years of follow-up, have shown that Irradiation of the internal mammary lymph nodes, even in patients with left-sided breast cancer, improves outcomes without significantly increasing cardiac or lung toxicity.^[29,30] The European study, known as the Internal Mammary Irradiation Trial, was conducted by the EORTC Radiation Oncology Group and Breast Cancer Group. A total of 4004 patients were randomized into two groups: the nodal-irradiation group and the control group. At 10 years, overall survival was 82.3% in the nodal-irradiation group and 80.7% in the control group. The rate of disease-free

survival was 72.1% in the nodal-irradiation group and 69.1% in the control group and the rate of distant disease-free survival was 78.0% in the nodal-irradiation group and 75.0% in the control group. In the Danish study conducted by the Danish Breast Cancer Cooperative Group (DBCG), a total of 3,089 patients were included. Of these, 1,492 patients were allocated to internal mammary node irradiation (IMNI), whereas 1,597 patients were allocated to no IMNI. The 8-year overall survival rates were 75.9% with IMNI versus 72.2% without IMNI, breast cancer mortality was 20.9% with IMNI versus 23.4% without IMNI and the risk of distant recurrence at 8 years was 27.4% with IMNI versus 29.7% without IMNI. On the contrary, there have also been some studies which have shown that no benefit could be attributed to IMNI in conservatively-treated breast cancer patients in terms of distant metastases or cause-specific survival for the entire patient population.^[31,32]

The expert panel considered the available evidence and recommended that internal mammary radiation may be given only to a select group of breast cancer patients. The panelists noted that the EORTC study has addressed this issue in a randomized design, and its results are encouraging. The panel also suggested that other factors such as pulmonary and cardiac co-morbidities should be taken into account before delivering internal mammary radiation and radiation of this field is best omitted in patients with cardiac concerns.

Take Home Message

1. Post BCS radiation therapy can be given to patients with early node positive (pT1N1) breast cancers
2. Hypofractionation can be given to patients based on recent reports of its equivalent efficacy in comparison with standard schedules in terms of local control and cosmesis
3. Boost is beneficial and should be given to early breast cancer patients. It has been shown to be more effective in younger patients but it is still beneficial in older patients
4. Currently there is no role for axillary radiation therapy in patients with an adequately dissected axilla
5. Internal mammary radiation may be given only to a select group of breast cancer patients. It is usually omitted in patients with significant pulmonary or cardiac concerns

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Conflicts of interest

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Table 4: Question 4: Will you include axilla in the field of radiation?

Options	Yes	No
Percentage of polled oncologists	8.3	91.7

Expert group consensus: Currently there is no role for axillary radiation therapy in patients with an adequately dissected axilla

Table 5: Question 5 - Will you include internal mammary chain in the field?

Options	Yes	No
Percentage of polled oncologists	62.5	37.5

Expert group consensus: Internal mammary radiation may be given only to a select group of breast cancer patients

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