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REVIEW

Radiation Therapy and Breast Conservative Surgery: A Concise Review

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ABSTRACT

Radiotherapy has an established role in reducing the local relapses in breast cancer patients. The objective of this review was to investigate whether radiotherapy or its omission after breast surgery has measurable consequences on local tumor recurrence and patient survival. The late excess of cardiac deaths has also been published in various reports but important advances in the delivery of radiotherapy have overcome this problem to the extent that, excess cardiac deaths do not appear to be occurring in more recent trials. In this article some recent data, suggesting that radiotherapy following mastectomy and/or breast conserving surgery has a beneficial effect on survival is reviewed. Omission of radiotherapy is associated with a large increase in risk of ipsilateral breast tumor recurrence and with a small increase in the risk of patient's mortality.

Key Words: Radiotherapy, Breast cancer, Recurrence, Mortality

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Introduction

The role of radiation therapy in the treatment of early breast cancer is changing. Breast-conserving therapy has been used in an increasing proportion of patients with early-stage disease beginning in the 1980s. At the same time as breast-conserving surgery (BCS) therapy was reducing the number of mastectomies, the use of post mastectomy irradiation was decreasing due to the perception that it did not improve survival. The role of radiotherapy to the breast for treatment of early-stage breast cancer has recently been challenged because routine radiotherapy after conservative surgery in early-stage breast cancer may be complicated by not only treatment-related morbidity but also limited radiotherapy resources. Therefore, assessment of the role of radiotherapy for patients diagnosed with early-stage breast cancer is needed. This article is written to re-evaluate the role of radiotherapy in early-stage breast cancer by performing an independent pooled analysis of published trials in the literature.

Review of literature

Role of radiotherapy in the treatment of breast cancer has a long and controversial history. [1] Till date there is enough evidence available, this demonstrates that radiotherapy reduces the local relapse. However the reduction in relapse rates did not translate to a reduction in mortality. Many explanations have been suggested for this disparity including detrimental effect of radiotherapy or immune system. [2] The first evaluation of mortality concerns in an individual patient data overview [3] showed that radiotherapy has little effect on mortality in first

ten years of follow up, but was potentially detrimental in longer term. Reports for Rutqvist *etal*[4] and Cuzik J *etal* [5] clearly demonstrated that there was a late excess of cardiac deaths that was masking a potential reduction in deaths from breast cancers. Further confirmation of these findings was provided by many larger subsequent trials[6]. The consensus of these published data does not mean to dismiss radiotherapy as a treatment modality for breast cancer, but to make clear that changes in its administration were needed if its benefit in terms of late breast cancer deaths was not to be nullified by increased mortality. Radiation oncologists have accepted this challenge, and important modifications to the fields used and individual patient planning have greatly reduced the cardiac doses. Excess cardiac deaths do not appear to be occurring in more recent trials, and breast cancer deaths are indeed reduced. [7], [8]

Some recent data suggests that radiotherapy following mastectomy and / or breast-conserving surgery has a beneficial effect on survival.[9] Three randomized clinical trials of post-mastectomy radiotherapy [7], [10], [11] from Canada and Denmark , have shown a 9 – 10% improvement in overall survival at 10 years for patients that received radiotherapy compared with those who did not receive radiotherapy. These results contrast with those of a patient-based meta-analysis of randomized clinical trials [12], in which radiotherapy was shown to be associated with a reduced risk of dying of breast cancer; however, this reduced risk was offset by increased mortality from vascular causes. There are several possible explanations for this apparent discrepancy. Many of the trials included in the patient-based meta-analysis, were initiated a long time ago, and these trials were often small and involved radiotherapy techniques and fractionation schedules that resulted in higher doses to heart than are obtained with modern radiotherapy techniques. In a reanalysis of data from these trials, a substantial reduction was found in the risk of mortality associated with radiotherapy of 12.4% ($p < .001$) when only recent trials were included[13]. In addition patients treated in Canadian and Danish trials received adjuvant chemotherapy and or / tamoxifen in conjunction with radiotherapy. Hence if the burden of distant micrometastasis can be reduced by systemic therapy, then radiotherapy given to the locoregional sites might prevent secondary dissemination, thus being potentially curative. This hypoythesis is supported by results of meta-analysis of randomized clinical trials of adjuvant radiotherapy[14], in which patients also received systemic therapy. In these trials, adjuvant radiotherapy statistically significantly reduced the risk of mortality (odds ratio = 0.83, 95% confidence interval [Cl] =0.74 to 0.94; p=.04). These results have led to the general acceptance that radiotherapy given after breast conservative surgery among patients at moderate or high risk of dying from breast cancer has favourable effects on survival. The updated recommendations[15] for breast irradiation after Breast conservative therapy are as per Table/Fig - 1

Multiple trials have shown a substantial risk of local recurrence if radiotherapy is omitted after breast conserving surgery. Given the evidence in favor of an association of radiotherapy after mastectomy with an impact on survival, similar benefits might be expected for radiotherapy after breast conserving surgery. A literature based Meta analysis of 15 clinical trials [Table/Fig 2] between 1976 and 2000 is presented by Vin-Hungh et. Al[9]. The combined data from 13 trials for which mortality were available indicated a relative risk of mortality of 1.086 (95%CI = 1.003 to 1.175) in patients not receiving radiotherapy after breast conserving surgery. This relative risk of mortality of 1.086 implies an absolute increase in survival due to administration of radiotherapy, but the values are much lower than those found in Danish and Canadian trials. [7], [10], [11] For example patients undergoing mastectomy tend to have poorer prognostic factors, and radiotherapy is usually administered to the regional lymph nodes and chest wall, whereas radiotherapy is often given to the residual breast in patients undergoing breast-conserving surgery (BCS). The most likely explanation for improved survival from the use of radiotherapy after breast-conserving surgery is that local failure may result in secondary dissemination of disease. Local failure is known to predict for poorer survival compared with non-failure, both after mastectomy and breast conserving surgery.

Given that none of the individual trials of breast-conserving surgery with or without radiotherapy has shown a statistically significant association between survival and radiotherapy, then how reliable are the results of current meta-analysis? All but two of the trials included in the meta-analysis by Vinh-Hungh et al[9] showed a trend in survival benefit from radiotherapy, hence the meta-analysis is internally consistent. One weakness in the meta-analysis is that it was based

on published data and not on survival data for individual patients included in the trials.

In contrast to the results of individual trials and the relatively small benefit in survival with radiotherapy demonstrated in meta-analysis by Vinh-Hungh et al[9]. It is intriguing that analysis of registry data by the some authors[9], [16], [17] suggests a large survival benefit from use of radiotherapy after breast-conserving surgery. Guidelines for evidence based- medicine assign highest priority to large, randomized clinical trials and meta-analysis of these trials. Randomised clinical trials have the advantage of ensuring a balance of prognostic factors between the groups that are compared, but suffer from the disadvantage of a selected patient population. Population-based studies suffer from potential imbalances in prognostic factors between patients that do and do not receive an intervention; however they do have the advantage of large size and the inclusion of a less selected patient/subject population. These two different types of studies should be regarded as complementary, and the results of the registry lend credence to the current mata-analysis[17] by supporting the role of radiotherapy in improving survival of the breast conserving surgery. (BCS) Radiotherapy to the conserved breast (using modern techniques} probably carries a minimal risk for cardiac toxicity. [18] In addition, the emergence high-precision radiotherapy techniques, such as intensity- modulated radiotherapy and partial breast irradiation, will help avoid irradiation of heart, with further improvement in risk-benefit ratio of using radiotherapy. There are probably groups of patients with good prognostic factors such that radiotherapy might not be necessary for reducing the rate of disease recurrence after breast conserving surgery. Moreover, these same patients are also likely to have high rates of survival, and any gains in absolute survival from radiotherapy would probably be small. In general, however, the mata-analysis presented by Vinh-Hungh, reinforces the view that the large majority of patients undergoing breast-conserving surgery should also receive radiotherapy. A major advancement in the use of this modality has already emerged, but it is still too early to declare an absolute victory.

Conclusion

In summary, trials of breast irradiation following BCS continue to support the evidence that irradiation substantially reduces not only the risk of local recurrence but also improves the survival. This also prevents the need of mastectomy and improves the cosmesis among the breast cancer patients. The various acute and long term morbidity negative effects described in literature appear to be limited. This review supports the role of radiotherapy among the patients with breast cancer after breast conserving surgery (BCS).

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Table/Fig 1

SERIAL NO.	CLINICAL GUIDELINES FOR RADIOTHERAPY (RT) AFTER BEAST CONSERVING SURGERY
1.	Women who under go breast conserving surgery (BCS) should be advised for RT. Omission of RT after BCS increases the risk of local recurrence
2.	Contraindications are pregnancy, previous RT including mantle RT in Hodgkin's disease, unable to abduct arm, scleroderma, systemic lupus erythematosus.
3.	Dose of RT fractionation schedule is 50 Gy (Gray) in 25 fractions
4.	Boost to breast should be considered in women at high risk to local recurrence
5.	Optimal sequencing of chemotherapy and breast RT is not clearly defined. Most centres favor the administration of chemotherapy before radiotherapy.
6.	Breast RT should be started as soon as possible after surgery and not later than 121 weeks after, except for patient whom RT is preceded by chemotherapy
7.	Patient must aware about the acute and late complication of the RT
8.	Patients should be offered the opportunity to participate in clinical trials whenever possible.

Table/Fig 2: Various clinical trials studying breast cancer patients with breast surgery with or with out Radiotherapy

Trials	No. of Patients	Median Follow up	Tumor size	Node positive %	% Local relapse		Relative Risk (95% CI)
					NO RT	RT	
NSABP B-06	1137	20.7	≤4	37 Node +	39.2	14.3	1.07 (0.96 TO 1.20)
Uppsala-Orebro	381	8.8	2	None	24	8.5	0.98 (0.67 to 1.42)
St. George's	418	6.1	5	38	35	13	1.15 (0.74 to 0.79)
Ontario	837	7.6	4	None	33.5	10.6	1.12 (0.87 to 1.45)
Scottish	585	5.3	4	23	24.5	5.8	1.01 (0.69 to 1.49)
Tokyo	113	4.6	5	40	9.4	7.1	
St. Petersburg	360	9.9	2.5	20	14.2	5.8	1.18 (0.84 to 1.65)
CRC UK	518	9.7			21.2	6.6	1.03 (0.78–1.36)
Milan III	579	9.1	<2.5	31	23.5	5.8	1.18 (0.84 to 1.66)
NSABP B-21	673	7.2	1	None	13.5	2.7	0.91 (0.51 to 1.63)
Tampere	152	6.7	<2	None	18.1	7.5	1.85 (0.46 to 7.48)
Swe BCG	1187	7	5	None	13.3	4.4	1.15 (0.74 to 1.79)
Toronto	769	3.4	5		5.7	0.5	1.40 (0.81 to 2.45)
BASO II	1172	2.9	2	None	3.6	1.3	
CALGB 9343	647	2.3	2		1.3	0	1.05 (0.57 to 1.92)

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