

## Letters to the Editor

## Radiotherapy for early stage favourable breast cancers

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## Sir

We read with great interest the results of a randomized trial investigating the omission of radiation as a component of breast conservation therapy for a favourable subset of women with stage I breast cancer (Holli *et al*, 2001). The data demonstrated that the locoregional recurrence was reduced in the patients randomized to radiotherapy (6.2% (radiation) vs 14.1% (no radiation) ( $P=0.029$ )), but there was no difference in rates of distant metastases or breast cancer deaths. In addition, because the patients who recurred after lumpectomy alone were most often treated with a second lumpectomy and radiation, the final rates of breast conservation were equivalent between the two arms.

A number of points should be considered when interpreting the data of this trial, particularly because these data have the potential of leading to a further decline in the use of radiation following breast conservation surgery. The first point is that the population studied represents a very small subset of women with early stage breast cancer. Despite the study's highly selective eligibility criteria, radiation clearly reduced the risk of local-regional recurrences. These data are consistent with those from previously published prospective trials that also studied highly selected favourable patients and found increased rates of breast recurrences when radiation was omitted (Veronesi *et al*, 1993; Schnitt *et al*, 1996; Liljegren *et al*, 1997; Wollmark *et al*, 2000).

The new twist of this trial is the assertion that breast preservation rates and survival may be equivalent without initial radiation because of the availability of re-excision and radiation as a salvage therapy for those initially treated with surgery alone. In the Holli *et al* (2001) trial, rates of breast preservation does not appear to have been a predetermined endpoint of the study. The choice of salvage therapy apparently was not determined by the protocol and therefore was likely affected by a number of biases. In addition, the length of follow-up after salvage treatment was not provided and the long-term efficacy of re-excision with or without radiation has not been established. Therefore, we feel that this endpoint should not have been reported.

The goals of all breast cancer therapies are to minimize the risk of breast cancer death and provide the patient with the best quality of life. The authors acknowledge that developing a potentially

avoidable local recurrence, even if it is curable with salvage therapy, has a significant negative impact on the quality of life of a patient. A second factor that impacts the quality of life of patients is the final aesthetic outcome of the treatment. The authors stated that radiation can have a negative impact on aesthetics and in their study was avoided in 87.5% of those randomized to the no radiation arm. Aesthetic results are also highly dependent of the extent of surgery. To be eligible for this trial a 1-cm negative microscopic margin was needed. This degree of normal tissue margins requires a considerable volume of breast to be resected and is not necessary for patients receiving radiation. Furthermore, for patients undergoing additional conservative surgery for recurrence, the aesthetic results are likely to be significantly compromised. No reports of aesthetics outcomes are reported for this study.

Finally, a critical question for patients and practitioners to consider is whether increased rates of local recurrences predispose patients to higher rates of distant metastases. This study suggested rates were equivalent, but because of the small number of patients in the study, there were only nine total metastatic events. Furthermore, the authors reported the distribution of these events between the two arms differently in the text of their results section compared to the same data presented in their Figure 2. A large number of patients with a long follow-up period are required to properly study the relationship between locoregional recurrence and distant failure. A recently published meta-analysis that evaluated the outcome of 2091 women treated on breast conservation randomized trials reported that those receiving radiation had a 14% lower relative risk of dying from breast cancer than those patients randomized to not receive radiation (Early Breast Cancer Trialists' Collaborative Group, 2000). This benefit suggests that some local-regional recurrences are associated with new distant metastases and this relationship should be considered when deciding the optimal manner in which early stage breast cancer should be treated.

It is our opinion that sufficient randomized data is available to recommend radiation therapy as a standard after lumpectomy for all women with invasive breast cancers. We feel that omission of radiation should not be offered outside the context of a clinical study.

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## Reply

## Relative harms and merits of postoperative radiation following conservative surgery for low risk breast cancer

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## Sir

Buchholz and Singletary raise the following issues in their commentary to our study (Holli *et al*, 2001):

- the breast preservation rate should not have been reported as an endpoint as it was not predetermined by the protocol and, therefore, it is subject to bias
- no aesthetic outcomes were reported
- loco-regional recurrences are likely to be associated with distant metastases and an increased risk of death. Hence, longer follow-up after salvage therapy is needed.

The mastectomy rate following conservative surgery depends on a number of factors, such as the relative size of the recurrent tumour with respect to the breast size, location of the tumour, availability of breast reconstruction, skill and experience of the surgeon, and patient preference. Therefore, we preferred not to give strict guidelines in the study protocol for the type of breast surgery used following recurrence, nor did we select the breast preservation rate as a study endpoint. Had the breast preservation rate been predetermined as an endpoint, the attitudes of the clinicians might have influenced the choice of the type of surgery more than in the present design, where no emphasis was given on the issue prospectively. Hence, it is possible that our study design may have been even less biased than after predetermining the breast preservation rate as an endpoint.

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**Table 1** Relative harms and merits associated with breast radiation in low risk breast cancer patients treated with conservative surgery

End point	Radiation (n=80)		No radiation (n=72)		Relative harm ratio
	n	(%)	n	(%)	
Poor cosmesis (6 months after surgery)	11	14	9	13	1.1
Recurrence	6	8	13	18	0.4
Distant metastasis	7	9	2	3	3.1
Recurrence leading to mastectomy	4	5	4	6	0.9
Death	2	3	2	3	0.9

Cosmetic outcome was not reported in our article, but we did study it by asking the subjective opinions of the patient and the physician. The results on the cosmetic outcome are shown in Table 1. We considered the cosmetic result poor only when both the patient and physician regarded the result as such. There was no difference between the study arms in the cosmetic outcome 6 months following surgery. The cosmetic result following removal of the recurrent tumour was not assessed formally.

It is generally accepted that loco-regional recurrences are associated with an increased risk for distant metastases and death. However, the data is scanty in the subset of very low risk patients. We intentionally selected a very low risk subgroup for the study, and when looking at the 6-year survival rates it is evident that

we truly succeeded in determining such a group. Nevertheless, as we emphasized in our article, the risk for local relapse is quite high (18% in our study) even in this very low risk group when radiotherapy is omitted. We fully agree with Buchholz and Singletary that a long follow-up time is needed in this low risk group, because the tumours, in particular, are likely to have a slow cell proliferation rate, and both local and distant metastases may need a long time to appear. We plan to perform a new analysis after 10-year follow-up of the patient cohort. Seven patients in the post-operative radiation group and two in the non-radiation group have recurred distally, and we apologize for the incorrect numbers in Figure 2 of our previous paper (Holli *et al*, 2001).

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The main message from the study is that radiotherapy decreases the risk for local relapse even in low risk patients after conservative breast surgery. However, it remains to be confirmed that radiotherapy decreases the rate of mastectomies in this carefully selected and closely followed subgroup of patients, where the option for reexcision and radiotherapy may still be available when radiotherapy has not been given primarily. In general our recommendation is to give radiotherapy to all patients with invasive breast cancer after conservative surgery to avoid local relapses, and we agree that omission of radiotherapy should be done only in the context of a clinical study.