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Radiotherapy After Surgery for Small Breast Cancers of Stellate Appearance

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1. Introduction

Radiotherapy is widely used in breast cancer treatment, particularly in patients undergoing breast conserving surgery, principally in order to reduce risk of local recurrence (Liljegren et al. 1999; Fisher et al. 2002). Although radiation therapy has been observed in a major meta-analysis to confer a net survival benefit (Clarke et al. 2005), it is not without side-effects. It has been observed to confer increased risks of cardiovascular events and lung tumours (Clarke et al. 2005; Darby et al. 2005). The fact that radiation therapy confers both benefits and harms raises issues pertinent to all treatments, i.e., the importance of selecting patient populations for which the balance of benefits to harms is optimised, and of excluding those patients who will not benefit from the treatment, or at least not sufficiently to outweigh the risk of adverse effects. Given the current lack of confidence that the prognostic indicators for such selection exist, conservative therapy includes post-surgical radiotherapy as a standard of care.

It has been reported that patients with invasive breast tumours less than 15 mm in size have mammographic tumour features that are good indicators of prognosis, and in particular, good long term survival has been observed in stellate lesions of this size without accompanying calcifications or with only non-specific calcifications (Smith et al. 2004; Tabar et al. 2000). The large majority of these patients did not receive adjuvant therapy other than radiotherapy, and since long-term survival was very high, the potential for modern adjuvant therapies to further improve upon the survival of these cases is very small. However, the extent to which these patients benefited from radiotherapy, in terms of reduction of risk of local recurrence, is not known. In this paper, we review the treatment and tumour features of 425 stellate invasive breast cancers of

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maximum diameter less than 15 mm, with a view to developing an index of risk of local recurrence and possibly of identifying patient populations suitable and unsuitable for radiotherapy. The research was approved by the Ethics Committee of Falun Central Hospital.

2. Patient data obtained for analysis

Mammograms were retrieved of all tumours of pathological size less than 15 mm, diagnosed in women aged 40-69 between 1977 and 1998 in Falun Central Hospital, Sweden. Of these, 425 were identified to have stellate appearance and either no calcifications or non-specific calcifications on the mammogram. Patient charts were retrieved and additional pathological information was obtained on exact tumor size in mm, node status, tumor grade and histological type. Treatment details with respect to surgery, adjuvant radiotherapy, chemotherapy and hormonal therapy were also retrieved. In addition, we recorded age, date of diagnosis, mode of detection (screening or symptomatic) and follow-up details including dates of local recurrence, death from breast cancer and death from other causes.

There was an average follow-up of 10.4 years to recurrence, death or last known date alive and disease-free, and a maximum follow-up of 27.9 years. The most recent date of follow-up was 20th March 2006. Local recurrence was defined as the occurrence of a histologically confirmed *in situ* or invasive carcinoma in the ipsilateral breast after treatment of the first breast cancer was completed.

3. Radiotherapy treatment regimens

For women who had breast conserving surgery for an invasive breast cancer, radiotherapy was regarded as standard treatment and computer dose-planned photon beam (6 and/or 15 MV) treatment was used. Care was taken not to treat the ipsilateral lung and, in the case of left-sided breast cancers, the heart. The whole breast parenchyma was defined as the target and 2 Gray per fraction times 25 was delivered over 5 weeks. If the patient was younger than age 45 yrs or if extensive DCIS (>25% of tumor) was present, additional photon-boost was used against the tumor bed. The boost-target was treated with 2 Gy per fraction to a total of 10 - 16 Gray. If one or more lymph nodes were engaged with cancer, separate fields were directed to the ipsilateral axilla and supraclavicular fossa, 2 Gray per fraction x 25 was used. Treatment of the intramammary lymph nodes was considered if 4 or more of the axillary nodes were metastasized.

Computer dose-planned radiotherapy was used also for some patients treated with a mastectomy. The thoracic wall was treated with opposed tangential photon fields if the tumor was > 30 mm or multifocal or N1. Regional lymph nodes were treated according the rules described above. Boost treatment was given only in the rare instances when surgical radicality could not be achieved.

4. Multifactor score of risk of recurrence

Data were analysed by stepwise Cox proportional hazards regression to build up a multifactor score of risk of recurrence. Analyses were adjusted for age and epoch of diagnosis, as radiotherapy practices depended on these factors. After exclusion of those factors that were not statistically significant when adjusted for other variables, we used the final Cox regression model to estimate the absolute reductions in 15-year risk of recurrence (only 22% of subjects had follow-up in excess of 15 years).

5. Recurrence rates in patients with small stellate breast cancers

Survival in this group was generally excellent. Figure 1 shows survival by size group (1-9 mm and 10-14 mm) and radiotherapy. In all four groups, long-term survival was 90% or greater. There was no significant effect of radiotherapy on survival.

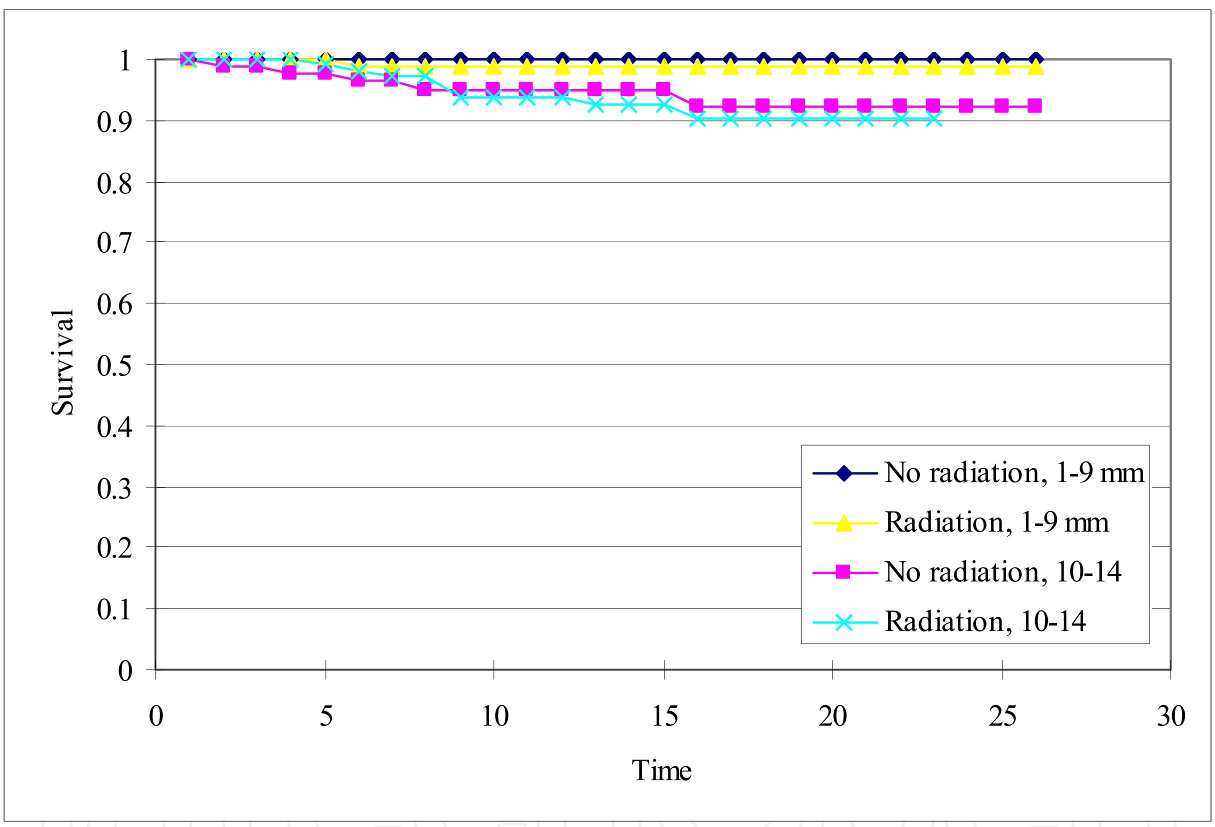

Fig. 1. Breast cancer specific survival of 425 1-14 mm stellate invasive breast cancers by size group and radiotherapy.

Table 1 shows the study subjects and recurrence rates by tumour, host, diagnostic and treatment features. There were 70 local recurrences in 425 patients. Overall, the average rate of recurrence was 1.6% per annum. Notably high recurrence rates were observed in grade 3 tumours and lobular carcinoma cases. Because 51% of the cases were diagnosed before 1990, the proportions of subjects treated with breast conserving surgery and with hormone therapy were considerably smaller than would be the case in tumours diagnosed at the present time.

Factor	Category	Cases (%)	Recurrences	Crude annual % recurrence rate
Epoch of diagnosis	1977-84	117 (28)	20	1.4
	1985-89	99 (23)	18	1.5
	1990-94	99 (23)	19	2.0
	1995-98	110 (26)	3	1.7
Age group	<55	142 (33)	26	1.5
	55+	283 (67)	44	1.6
Tumour size (mm)	1-9	156 (37)	25	1.6
	10-14	269 (63)	45	1.6
Node status	Negative	341 (80)	55	1.5
	Positive	45 (11)	10	2.0
	Not examined	39 (9)	5	1.7
Grade	1	204 (50)	24	1.1
	2	173 (42)	31	1.8
	3	34 (8)	10	2.9
	Unknown	14	5	4.1
Surgery	Mastectomy	136 (32)	21	1.3
	BCS*	289 (68)	49	1.7
Radiotherapy	No	168 (40)	31	1.7
	Yes	254 (60)	38	1.5
	Unknown	3	1	3.3
Chemotherapy	No	411 (97)	67	1.6
	Yes	12 (3)	3	2.9
	Unknown	2	0	0.0
Hormone therapy	No	391 (92)	64	1.5
	Yes	32 (8)	6	2.4
	Unknown	2	0	0.0
Histological type	Ductal	286 (67)	47	1.6
	Lobular	52 (12)	14	2.8
	Tubular	80 (19)	7	0.8
	Other	7 (2)	2	2.9
Detection mode	Symptomatic	102 (24)	22	2.0
	Screening	323 (76)	48	1.4

* BCS=breast conserving surgery

Table 1. Host, tumour and treatment characteristics, with the corresponding rates of local recurrence.

Table 2 shows the final model from the stepwise Cox regression for prediction of recurrence. Age and epoch of diagnosis were included regardless of significance. A highly significant increase in risk of recurrence was noted with grade (HR=1.93, 95% CI 1.31-2.85, p=0.001, trend test). Although the main effect of radiotherapy was not significant, it had a significant interaction with age (p=0.03), associated with lower rates of recurrence in patients aged 55 and over (HR=0.26, 95% CI 0.07-0.88), but not in patients aged less than 55. It also had a borderline significant interaction with histological type (p=0.07) with a high rate of recurrence in lobular carcinoma cases treated with radiotherapy (HR=3.58, 95%CI 0.90-14.13). The effects of BCS (p=0.01) and histological type (p=0.04) were significant before adjustment for these interactions, so these factors were retained in the model. No other variables had significant effects on risk of recurrence after adjustment for the factors in Table 2.

Factor	Category	Cox regression RR*	95% CI
Age group	<55	1.00	-
	55+	2.53	0.93-6.87
Epoch of diagnosis	1977-84	1.00	-
	1985-89	1.19	0.55-2.53
	1990-94	2.15	0.95-4.82
	1995-98	1.42	0.55-3.04
Surgery	Mastectomy	1.00	-
	BCS	1.81	0.93-3.51
Histology	Ductal, other	1.00	-
	Lobular	0.92	0.31-2.76
Grade	Trend	1.93	1.31-2.85
Radiotherapy	No	1.00	-
	Yes	1.21	0.40-3.62
Interaction	Lobular AND radiotherapy	3.58	0.90-14.13
Interaction	Age 55+ AND radiotherapy	0.26	0.07-0.88

* RR=rate ratio

Table 2. Relative hazards and 95% confidence intervals from the final Cox regression model after stepwise regression.

Table 3 shows the results from the final Cox regression model, in terms of estimated annual rates of recurrence in the absence of radiotherapy and absolute reductions in cumulative 15-year recurrence associated with radiotherapy. Overall, absolute effects were small. For example, for grade 1, non-lobular tumours, in women aged 55 or older, treated with mastectomy, the absolute reduction in risk of local recurrence associated with radiotherapy was 1.87%. Substantial reductions in recurrence rates were observed only for cases aged 55 or more at diagnosis, of grade 2 or 3 and of non-lobular histological type. For some combinations of factors, notably lobular carcinoma cases younger than age 55, the reductions were negative, i.e. showing increases in recurrence in those treated with radiotherapy. For lobular carcinoma cases age 55 or over, and for non-lobular cases younger than age 55, no substantial benefit of radiotherapy was observed.

6. Expert commentary

This study pertains to a very special subgroup of good prognosis tumours, i.e. stellate lesions less than 15 mm in size without calcifications. Within this group, our results suggest that radiotherapy was substantially beneficial only in terms of preventing local recurrence in women aged 55 and older diagnosed with non-lobular carcinoma grade 2 or 3, a subgroup constituting 31% of the subjects (131 out of 425). Of the remaining 294 cases, 183 (63%) received radiotherapy, and based on these results not only did not substantially benefit from it, but may indeed have had their risk of recurrence increased. It might be argued that in modern treatment practice, very few of the mastectomy cases would receive radiotherapy. Where margins are close, the NCCN recommends that radiotherapy should be considered (NCCN 2009). However, also in modern therapeutic practice, a large proportion of these cases, being smaller than 15 mm, would receive wide local excision.

Radiotherapy is primarily aimed at reducing the risk of local recurrence (Liljegren 2002). It has been suggested that radiotherapy might be dispensed with for low-risk patients (e.g.

Surgery	Age	Lobular histology	Grade	Estimated % annual recurrence rate without radiotherapy	Absolute reduction in 15-year probability of recurrence with radiotherapy
Mastectomy	<55	No	1	0.5	-0.0007
			2	0.9	-0.0026
			3	1.7	-0.0115
		Yes	1	0.4	-0.0114
			2	0.9	-0.0360
			3	1.7	-0.0748
	55+	No	1	1.2	0.0187
			2	2.3	0.0570
			3	4.5	0.1470
		Yes	1	1.1	-0.0030
			2	2.2	-0.0084
			3	4.2	-0.0235
Breast conserving surgery	<55	No	1	0.9	-0.0036
			2	1.7	-0.0088
			3	3.2	-0.0228
		Yes	1	0.8	-0.0319
			2	1.6	-0.0882
			3	3.0	-0.1800
	55+	No	1	2.2	0.0504
			2	4.2	0.1363
			3	8.3	0.2769
		Yes	1	2.0	-0.0078
			2	3.9	-0.0220
			3	7.6	-0.0340

Table 3. Estimated recurrence rates in the absence of radiotherapy and absolute reduction in 15-year risk of recurrence by surgery, age, histological type and grade of tumours, from the final Cox regression model.

older patients with lower stage non-lobular tumours) (Liljegren 2002; Liljegren et al. 1997). One study has found risk of recurrence to be particularly low in those with non-dense breast tissue (Cil et al. 2009). The results here suggest that a significant proportion of patients with small stellate lesions can be considered at low risk, and that some higher risk patients, such as lobular carcinoma cases, may have high local recurrence rates despite radiotherapy. These results are observational, and need to be validated.

Another observational study has found, contrary to our results, that radiotherapy is associated with substantially reduced risk of local recurrence in lobular carcinoma (Diepenmaat et al. 2009). There was, however, a comparatively shorter follow up time (median of 7.2 years). Issues such as this may be resolved by delineating the tumour populations in radiotherapy trials which have already been conducted, or by carrying out new prospective trials.

The point has already been made that small stellate lesions are a good candidate for less aggressive therapy (Smith et al. 2004; Alexander, Yankaskas, and Biesemier 2006). The potential to save almost 70% of patients in this group from the hazards of radiation therapy is a goal worth pursuing.

7. Five year view

The results of this observational study suggest that contrary to standard practice, post-operative radiotherapy may not be the ideal treatment for all breast cancers treated with breast conserving surgery, particularly those with good prognosis. This is not to deny the results of the randomised trials and meta-analyses. There is clear evidence from these that radiotherapy reduces local recurrence and improves survival. However, this does not necessarily imply that it is needed in all cases. There is potential for utilising patient and tumour information to assign treatment based on that which is appropriate for the subgroup. This tailored therapeutic approach uses simply obtained specifics, e.g patient age, radiological appearance and tumour histology/grade. It would enable a more accurate risk-benefit analysis to be calculated before prescription of therapies with adverse side-effects such as radiotherapy. It is therefore attractive in comparison with universal provision of radiotherapy to all patients. Before such policies can be implemented, it is essential that we are certain of the risks:benefit ratio for each patient subgroup and therefore these findings must be validated. This approach of investigating the level of benefit to different patient populations may be useful for other cancer therapies with adverse side-effects, with the objective of identifying other areas for improvement as medical oncology progresses to an era of individually tailored treatments.

8. Conclusion

Radiotherapy is widely used to reduce the risk of local recurrence of breast cancer, particularly after breast conserving surgery. However, radiotherapy to the breast has adverse long-term side effects (risk of heart disease, lung cancer, angiosarcoma, deformation), and therefore it would be useful to identify subsets of patients for whom this treatment is unnecessary. Patients with stellate tumours of 1-14mm have a good prognosis and a high proportion of them might benefit from omitting radiotherapy. A Cox regression was applied to follow up data from 425 such patients and a comparison of local recurrence rates made for different patient groups/tumour stages receiving or not receiving radiotherapy post surgery. These observations suggest that the only group of patients within the 1-14 mm stellate lesions to benefit from radiotherapy are those aged 55 or more, with high grade (2 or 3) disease and non-lobular histology. Radiotherapy may not be beneficial to certain groups with higher risk of recurrence (e.g. younger women or lobular carcinoma) and some groups with low risk of recurrence (e.g. low grade tumours). Further validation using subgroup analyses of trials already performed would be useful.

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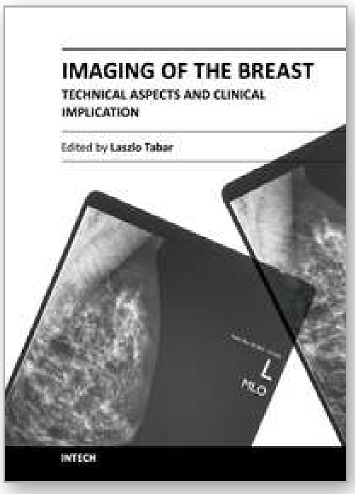

Imaging of the Breast - Technical Aspects and Clinical Implication

Edited by Dr. Laszlo Tabar

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Early detection of breast cancer combined with targeted therapy offers the best outcome for breast cancer patients. This volume deal with a wide range of new technical innovations for improving breast cancer detection, diagnosis and therapy. There is a special focus on improvements in mammographic image quality, image analysis, magnetic resonance imaging of the breast and molecular imaging. A chapter on targeted therapy explores the option of less radical postoperative therapy for women with early, screen-detected breast cancers.

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