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Does adjuvant radiation therapy benefit women with small mammography-detected breast cancers?

K. Jerzak MD,* N. Dudalski,† K. Pritchard MD,‡§ P. Sun PhD,|| and S.A. Narod MD§||

ABSTRACT

Background Women with small nonpalpable breast tumours have an excellent prognosis. The benefit of radiotherapy in this group of low-risk women is unknown.

Methods A cohort of 1595 women with stages I–III invasive breast cancer treated with breast-conserving surgery were followed for local recurrence. Using t-tests, baseline demographic data and tumour characteristics were compared for the women who had palpable ($n = 1023$) and mammography-detected ($n = 572$) breast cancers. The 15-year actuarial risk of local recurrence was estimated using a Kaplan–Meier method, stratified for adjuvant radiation therapy (yes or no), tumour palpability (palpable or not), and tumour size (≤1 cm or >1 cm). Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated using a multivariate Cox regression model. Results were considered statistically significant if 2-tailed p values were less than 0.05.

Results Among women with a nonpalpable tumour, the 15-year actuarial rates of local recurrence were, respectively, 13.9% and 18.3% for those treated and not treated with adjuvant radiation therapy (HR: 0.65; 95% CI: 0.40 to 1.06; $p = 0.08$). Among women with small nonpalpable breast cancers (≤1.0 cm), the rates were 14.6% and 13.4% respectively ($p = 0.67$). The absolute reduction in 15-year local recurrence was 11.0% for women with palpable tumours.

Conclusions Our results suggest that women with small (<1 cm) screen-detected nonpalpable breast cancers likely derive little benefit from adjuvant radiotherapy; however, an adequately powered randomized trial would be required to make definitive conclusions.

Key Words Breast cancer, radiation therapy, palpable breast tumours

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BACKGROUND

In women with early-stage breast cancer who are treated with breast-conserving surgery, radiotherapy (RT) reduces the risk of local recurrence. In the individual patient meta-analysis from the Early Breast Cancer Trialists' Collaborative Group, RT was associated with a reduction in the 10-year risk of local or distant recurrence to 19.3% from 35.0%, an absolute reduction of 15.7%[1]. However, the extent of the absolute reduction varied depending on the patient subgroup. For example, the absolute reduction in 10-year local recurrence associated with RT was 21.2% (to 42.5% from 63.7%) for women with node-positive disease and 15.4% (to 15.6% from 31.0%) for those with node-negative disease[1]. The proportional reductions were similar in both scenarios[1]. Further, younger women and those with grade 3 tumours were at higher risk of local recurrence than were older women and those with low-grade tumours; consequently, the former group derived a greater absolute benefit from radiation therapy[1].

With the advent of screening mammography, breast cancers are increasingly being diagnosed when they are small, nonpalpable, and node-negative. Many are diagnosed at 1 cm or less. In a previous study, we showed that tumour palpability is an adverse prognostic factor in terms of breast cancer–specific survival; however, in that study, we did not report on palpability as a risk factor for local recurrence[2].

Compared with nonpalpable tumours, palpable tumours are more likely to be large and node-positive[3–5].

Correspondence to: Steven A. Narod, Women's College Research Institute, 76 Grenville Street, Toronto, Ontario M5S 1B2.
E-mail: steven.narod@wchospital.ca ■ **DOI:** https://doi.org/10.3747/co.24.3089

Although some evidence suggests that, independent of their size at initial presentation, palpable tumours might be inherently more aggressive than nonpalpable tumours, the association between palpability and local recurrence has not been well studied. Further, whether women with small nonpalpable breast tumours derive a benefit from adjuvant RT similar to that for women with palpable cancers remains unknown.

In the present study, we sought to determine whether tumour palpability is an independent risk factor for in-breast recurrence. We also quantified the absolute benefit of adjuvant RT for women with palpable and nonpalpable breast cancers.

METHODS

We used the Henrietta Banting Breast Centre database to conduct a prospective cohort study of women with early breast cancer treated with breast-conserving surgery. All women underwent primary surgical therapy at Women's College Hospital (Toronto, ON) between January 1987 and December 2000. Of 2452 patients identified in the database, 857 were excluded because of noninvasive disease, treatment with mastectomy, bilateral breast cancer, or lack of relevant clinical or pathologic data. The remaining 1595 women were included in the analysis.

Details about patient age at diagnosis, pathologic features of the tumour (grade, hormone receptor status, nodal status, tumour size), and treatment (chemotherapy, RT, and hormonal therapy) were systematically recorded. A palpable tumour was defined as one that was first detected by the patient or her physician. In contrast, a nonpalpable tumour was first detected by imaging.

The primary clinical outcome of local recurrence has been updated in database at least once annually, with some records having up to 28 years of follow-up (median: 14 years). Local or regional recurrences within 90 days of surgery were not considered to be true relapses, but rather part of the primary presentation. Women who had a distant relapse within 90 days of surgery were excluded.

Statistical Analysis

Using the t-test for means and the chi-square statistic for frequencies, baseline demographic data and tumour characteristics were compared for women who had palpable (n = 1023) and mammography-detected (n = 572) breast cancers. A Kaplan–Meier analysis was used to estimate the 15-year actuarial risk of local recurrence. Patients were stratified based on treatment with adjuvant RT (yes or no), the palpability of the primary tumour (palpable or not), and tumour size (≤1 cm or >1 cm). The log-rank test was used to determine statistical differences between those groups of women.

A multivariate Cox regression model was used to calculate hazard ratios (HRS) and 95% confidence intervals (95% CIS) associated with RT. The model was adjusted for age, tumour size (≤1 cm, 1.1–2 cm, or >2 cm), nodal status (positive or negative), tumour grade (1, 2, or 3), chemotherapy (yes or no), hormonal therapy (yes or no), estrogen receptor (ER) status (positive or negative), and progesterone receptor status (positive or negative). Results were considered statistically significant if 2-tailed p values were less than 0.05.

RESULTS

Of the early-stage breast cancers in this patient cohort, 1023 (64.1%) were detected by palpation; the remaining 572 were detected by screening mammography alone. On average, palpable tumours were larger than nonpalpable tumours (2.1 cm vs. 1.3 cm, $p < 0.0001$), more likely to be node-positive (38.8% vs. 24.2%, $p < 0.0001$), and more likely to be ER-negative (29.4% vs. 22.3%, $p = 0.003$) and progesterone receptor–negative (42.7% vs. 28.6%, $p < 0.0001$; Table I). Compared with women whose cancer was detected only by mammography, those with a palpable breast cancer were more likely to receive chemotherapy (33.9% vs. 12.8%, $p < 0.0001$); they were also more likely to receive RT (77.6% vs. 71.0%, $p = 0.003$; Table I). All patients were treated with breast-conserving surgery.

The 15-year risk of local recurrence in women after breast-conserving surgery was 22.1% in the overall population, 26.2% for women with palpable cancers, and 15.2% for women with nonpalpable cancers ($p < 0.0001$). In the univariable analysis, predictors of local recurrence included grade 3 disease, tumour size greater than 2 cm, lymph node positivity, positive expression of ER, and treatment with RT, tamoxifen, and chemotherapy (Table II). In a multivariable model, tumour palpability was associated with a 1.45 HR for local recurrence (95%: 1.08 to 1.95), and RT was associated with a 0.55 HR (95% CI: 0.42 to 0.73).

In the overall cohort, the 15-year risks of local recurrence were, respectively, 20.4% and 27.5% for those treated and not treated with adjuvant RT (HR: 0.63; 95% CI: 0.49 to 0.80; p = 0.0002). Among women with nonpalpable mammography-detected tumours, the 15-year actuarial rates of local recurrence were 13.9% was 18.3% for those treated with and without adjuvant RT (HR: 0.65; 95% CI: 0.40 to 1.06; $p = 0.08$). For women with palpable tumours, the 15-year actuarial risks of local recurrence were, respectively, 23.8% and 34.8% with and without RT (HR: 0.55; 95% CI: 0.41 to 0.74; $p < 0.0001$). Hence, the absolute net reductions in local recurrence at 15 years were 4.4% for women with a nonpalpable cancer and 11.0% for women with a palpable cancer.

After stratification by tumour size, palpability, and RT, the benefit of RT was estimated for various subgroups (Figures 1–4). Radiotherapy was beneficial for all women with palpable cancers and for all women with cancers measuring more than 1.0 cm. Among women with small (≤1.0 cm) nonpalpable breast cancers, the 15-year risks of local recurrence were, respectively, 14.6% and 13.4% for women who received and did not receive RT (p = 0.67, Figure 3).

In a multivariable model, the HRS with RT were, respectively, 0.57 (95% CI: 0.26 to 1.24; $p = 0.15$) and 0.26 (95% CI: 0.12 to 0.57; p = 0.0007) for nonpalpable breast cancers 1 cm or less in size and more than 1 cm in size.

DISCUSSION

Since the late 1980s, screening mammography has been promoted throughout Ontario in the context of the

TABLE I Characteristics of women with palpable or mammography-detected early breast cancer

Variable	Detection method		*p* Value
	Mammography	Palpation	
Patients (*n*)	572	1023	
Age at diagnosis (years)			
Median	60.2	54.4	<0.0001
Range	29–89	32–94	
Tumour size (cm)			
Average	1.28	2.10	<0.0001
Range	0–5	0–5	
Nodal status [*n* (%)]			
Negative	344 (60.1)	556 (54.4)	<0.0001
Positive	110 (19.2)	352 (34.4)	
Missing	118 (20.6)	115 (11.2)	
Receptor status [*n* (%)]			
Estrogen			
Negative	118 (20.6)	287 (28.3)	0.003
Positive	411 (71.9)	689 (67.4)	
Missing	43 (7.5)	47 (4.6)	
Progesterone			
Negative	144 (25.2)	411 (40.2)	<0.0001
Positive	360 (62.9)	551 (53.9)	
Missing	68 (11.9)	61 (6.0)	
HER2			
Negative	241 (42.1)	511 (50.0)	0.004
Positive	41 (7.2)	150 (14.7)	
Missing	290 (50.7)	362 (35.4)	
Radiotherapy			
No	406 (71.0)	794 (77.6)	0.003
Yes	166 (29.0)	229 (22.4)	
Missing	0 (0)	0 (0)	
Chemotherapy			
No	496 (86.7)	672 (65.7)	<0.0001
Yes	73 (12.8)	345 (33.7)	
Missing	3 (0.5)	6 (0.6)	
Tamoxifen therapy			
No	229 (40.0)	547 (53.5)	<0.0001
Yes	338 (59.1)	469 (45.9)	
Missing	5 (0.9)	7 (0.7)	
Local recurrence			
No	495 (86.5)	789 (77.1)	<0.0001
Yes	77 (13.5)	234 (22.9)	
Missing	0 (0)	0 (0)	
Time to local recurrence (years)			
Median	12.2	10.3	<0.0001
Range	0.3–18	0–18	

Ontario Breast Screening Program and through various other screening clinics. As a consequence of those intensified screening efforts, increasing numbers of women are being diagnosed with breast cancers at an early stage (ductal carcinoma *in situ* or stage I) and before clinical presentation. In many cases, screen-detected cancers are nonpalpable. Public interest in understanding the clinical outcomes of patients with screen-detected cancers is increasing, including the possibility of overtreatment with systemic therapies and local or regional adjuvant radiation. Hence, we studied the absolute benefit of adjuvant RT in preventing local relapse among women with screen-detected breast cancers.

In this retrospective study of 1595 women with early-stage breast cancer, we found that women with palpable breast cancers were more likely than women with nonpalpable cancers to experience a local recurrence (HR: 1.94; 95% CI: 1.49 to 2.51; $p < 0.0001$); however, after adjustment for tumour size, grade, tumour subtype, and treatment variables, the association between palpability and lymph node status was attenuated (HR: 1.45; 95% CI: 1.08 to 1.95; $p = 0.01$).

Prior studies suggest that, compared with nonpalpable tumours, palpable tumours might represent disease that is inherently more aggressive; however, the relative benefit of RT in the two groups of women was not assessed[4,5]. Tafra *et al.*[5] found that, compared with mammography-detected tumours ($n = 120$), palpable tumours ($n = 225$) were larger (2 cm vs. 1 cm, $p < 0.001$) and more likely to be node-positive (46% vs. 19%, $p < 0.01$). The rates of local recurrence after breast-conserving therapy were similar for women with palpable and nonpalpable tumours, but the study was likely underpowered for assessment of recurrence outcomes. In another cohort of 649 women, palpable breast tumours were, compared with mammography-detected cancers, larger, higher grade, more likely to be node-positive, and more likely to be ER-negative[4]. Although women with palpable tumours received more aggressive systemic and surgical therapies, they were still more likely than their counterparts with nonpalpable disease to experience a recurrence (24% vs. 11%)[4]. Those results strengthen our findings that women with nonpalpable and small breast cancers might have a lower risk of recurrence and, therefore, a lower absolute risk reduction with RT.

In the Banting database, 67% of women with small (≤1 cm) nonpalpable lesions and 0% of women with small palpable cancers were given RT. Of women with mammography-detected disease, 14% experienced a local recurrence, thus excluding the possibility of overdiagnosis. Nevertheless, we find that women with particularly small (≤1 cm) mammography-detected cancers might be appropriate candidates to forgo RT.

Strengths of our study include its large sample size, prospective recruitment, and long-term follow-up data (approaching 20 years). However, the retrospective analysis at a single institution, the predominant use of non-anthracycline chemotherapy regimens, and a lack of data related to the use of aromatase inhibitors and HER2-targeted therapy are limitations. Hence, further study and prospective validation are required, particularly in the context of newer gene-expression assays, which have shown promise for further personalizing RT for women with breast cancer[6–9].

TABLE II Relative risk (RR) of local recurrence for palpable or mammography-detected early breast cancer

Variable	Univariate analysis			Multivariate analysis [a]		
	RR	95% CI	*p* Value	RR	95% CI	*p* Value
Grade						
1		1			1	
2	1.33	0.92 to 1.92	0.13	1.26	0.86 to 1.83	0.23
3	2.08	1.44 to 3.00	<0.0001	1.50	1.00 to 2.25	0.05
Tumour size						
0–1 cm		1			1	
1.1–2 cm	1.26	0.94 to 1.68	0.13	1.16	0.84 to 1.60	0.37
>2 cm	1.65	1.22 to 2.22	0.001	1.23	0.86 to 1.75	0.26
Tamoxifen						
No		1			1	
Yes	0.49	0.39 to 0.62	<0.0001	0.57	0.43 to 0.75	<0.0001
Chemotherapy						
No		1			1	
Yes	1.28	1.00 to 1.63	0.05	0.63	0.44 to 0.90	0.01
Nodal status						
Negative		1			1	
Positive	1.58	1.24 to 2.01	0.0002	1.89	1.40 to 2.56	<0.0001
Receptor status						
Estrogen						
Negative		1			1	
Positive	0.67	0.53 to 0.86	0.002	0.88	0.64 to 1.21	0.45
Progesterone						
Negative		1			1	
Positive	0.74	0.59 to 0.94	0.01	0.99	0.74 to 1.33	0.94
HER2						
Negative		1			1	
Positive	1.34	0.96 to 1.85	0.08	1.06	0.76 to 1.49	0.75
Radiotherapy						
No		1			1	
Yes	0.64	0.51 to 0.82	0.0006	0.55	0.42 to 0.73	<0.0001
Palpable						
No		1			1	
Yes	1.94	1.49 to 2.51	0.0001	1.45	1.08 to 1.95	0.01

[a] Adjusted for all the variables and for year of birth.
CI = confidence interval.

CONCLUSIONS

The results of the present study suggest that women with small screen-detected nonpalpable breast cancers derive little benefit from adjuvant RT. Those results must be confirmed in a large randomized controlled trial before clinical recommendations can be made. Given the excellent outcomes among women with low-risk nonpalpable breast cancers, the de-escalation of RT, with possible reductions in short- and long-term toxicities, warrants further attention.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

*Department of Medicine, University of Toronto, Toronto; †McMaster University, Hamilton; ‡Department of Medicine, Sunnybrook Odette Cancer Centre, Toronto; §Dalla Lana School of Public Health, University of Toronto, Toronto; and ||Women's College Research Institute, Women's College Hospital, Toronto, ON.

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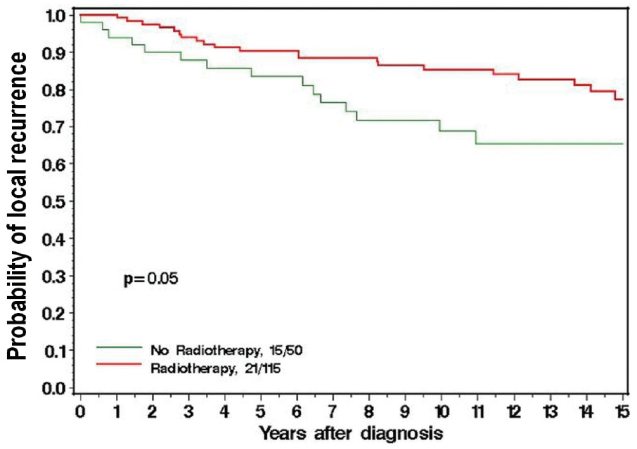

FIGURE 1 Local recurrence rates in women with palpable breast cancers 1 cm or less in size.

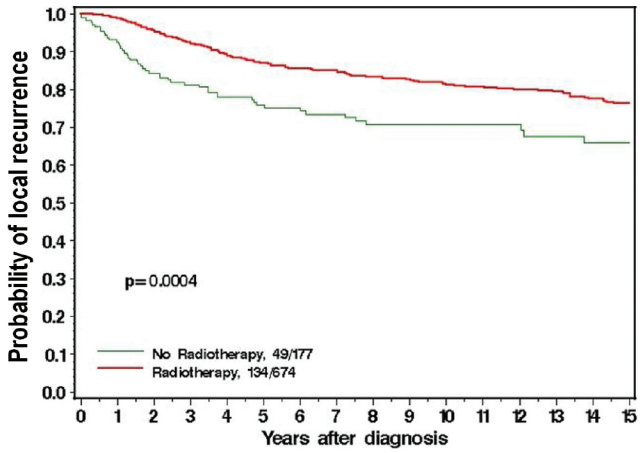

FIGURE 2 Local recurrence rates in women with palpable breast cancers more than 1 cm in size.

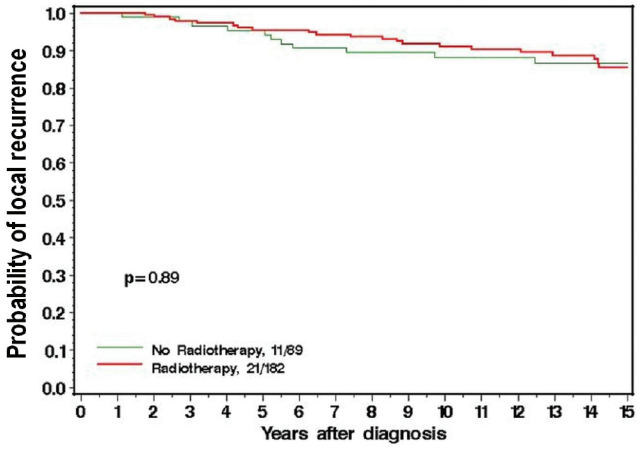

FIGURE 3 Local recurrence rates in women with nonpalpable breast cancers 1 cm or less in size.

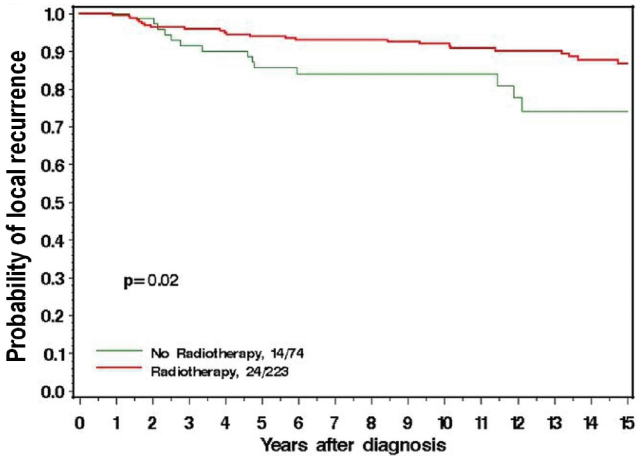

FIGURE 4 Local recurrence rates in women with nonpalpable breast cancers more than 1 cm in size.

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