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Locoregional recurrence risks in elderly breast cancer patients treated with mastectomy without adjuvant radiotherapy

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Abstract

This study examined tumour and treatment characteristics in elderly women treated with mastectomy without radiotherapy and compared their outcomes to younger counterparts. Data were analysed for 2362 women aged 50 years and older referred to the British Columbia Cancer Agency, Canada between 1989 and 1997. The women had invasive T1-4, N0–N3, M0 breast cancer treated with mastectomy without adjuvant radiotherapy. Clinical characteristics and patient outcomes were compared between two age cohorts: 50–69 ($n = 1423$) and 70+ years ($n = 939$). Median follow-up was 8.3 years. Tumours >5 cm were present in 5% of women aged 50–69 and 3.5% of women aged 70+, respectively. The distribution of nodal stage was similar in the two age cohorts but older women were more likely to have fewer axillary nodes removed ($P = 0.009$). Fewer women aged 70+ had grade III histology ($P = 0.002$) and estrogen receptor (ER)-negative status ($P < 0.001$). The rates of systemic therapy use were comparable in the two age groups. With tumours >5 cm, locoregional recurrence (LRR) were 13.7% and 30.0% in women aged 50–69 and 70+, respectively. With 1–3 positive nodes (N+), LRR were 14.8% and 13.0% in women aged 50–69 and 70+. In the presence of $\geqslant 4$ N+, LRR were 16.8% and 30.8% in women aged 50–69 and 70+. On multivariate analysis, age was not significantly associated with LRR ($P = 0.62$). Independent prognostic factors for LRR were grade III histology, lymphovascular invasion and positive nodal status. This study suggests that despite more favourable tumour characteristics and comparable systemic therapy use, women aged 70+ years have similar or higher postmastectomy LRR risks compared to younger women. Chronologic age alone should not preclude these women from consideration of adjuvant radiotherapy.

Keywords: Breast cancer; Locoregional recurrence; Mastectomy; Elderly; Age

1. Introduction

Women aged older than 70 years comprise approximately 30% of the breast cancer population [1] but are significantly under-represented in cancer therapy trials [2]. In particular, there is little data to guide adjuvant locoregional therapy decisions for older patients who choose to undergo mastectomy. Three recent randomised controlled trials demonstrated that in patients with advanced primary tumours or positive axillary nodes, postmastectomy radiotherapy (PMRT) improved not only locoregional control but also survival [3–5]. This evidence contributed to current guidelines recommending PMRT for women with tumours >5 cm or 4 or more positive nodes [6,7]. However, two of these PMRT trials enrolled only premenopausal patients [3,4] and one trial enrolled postmenopausal patients but excluded patients aged 70+ years [5] thus limiting the ability to formulate evidence-based guidelines for this population. Since

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some studies suggest that breast cancer may be less aggressive in older patients [8,9] whereas others do not [10], the magnitude of baseline locoregional recurrence (LRR) risks after mastectomy in older patients compared to younger counterparts warrants investigation.

The objective of this study was to examine tumour and treatment characteristics in a cohort of women treated with mastectomy without adjuvant radiotherapy and compare recurrence and survival outcomes by age and stage.

2. Methods and materials

The Breast Cancer Outcomes Unit Database was initiated in 1989 in the province of British Columbia, Canada, to prospectively record pathologic, therapeutic, and outcomes data on all breast cancer patients referred to the British Columbia Cancer Agency (BCCA). The database was used to identify 2362 women aged 50 years and older referred to the BCCA between January 1, 1989 and December 31, 1997 with invasive T1-4, N0–N3, M0 breast cancer treated with mastectomy and axillary dissection without adjuvant radiotherapy. Patients presenting with distant metastasis and patients with unknown pathologic nodal stage were excluded. During the study period, the institutional policy was to discuss PMRT with patients with advanced primary tumours >5 cm, 4 or more positive nodes, bulky nodes, or extracapsular nodal extension. Since the objective was to evaluate postmastectomy LRR in the absence of adjuvant radiotherapy, patients who received radiotherapy were excluded.

Data were extracted on each subject's age at diagnosis, date of pathologic diagnosis, date of relapse, and date of death as of December 1, 2003. Patients were followed at the BCCA and in the community. For patients who were discharged from the BCCA and followed by their primary care physicians, relapse information was obtained from the community physician on an annual basis. Death information was obtained from the Department of Vital Statistics on a monthly basis. Patients were censored 6 months prior to the date of data retrieval, thus ensuring that the majority of relapse and death information to that point has been received.

Tumour variables analysed included histologic type (ductal, lobular, other); tumour size ($\leqslant$2.0, 2.1–5.0, >5 cm, or unknown); grade (nuclear or histologic Scarff-Bloom-Richardon Grade I, II, III, or unknown); lymphovascular invasion (LVI) (present, absent, or unknown), estrogen receptor (ER) status (positive, negative, or unknown); pathologic nodal status (positive, negative); number of positive axillary nodes (0, 1–3, $\geqslant$4); number of nodes removed ($\leqslant$10, >10); and tumour involvement at surgical margins (positive, negative, or unknown). Adjuvant systemic therapy was analysed according to the following categories: systemic therapy use (yes or no); and systemic therapy type (hormone therapy alone, chemotherapy alone, both, or none).

The primary outcome was locoregional recurrence (LRR), defined as the first site of tumour recurrence involving the ipsilateral chest wall (local) and/or axillary, supra- or infraclavicular, and internal mammary nodes (regional). Secondary outcomes were distant recurrence (DR) and overall survival (OS).

2.1. Statistical analysis

Before analysis, a decision was made to categorise the study sample into two age cohorts (50–69 and 70+ years). This decision was based on the consensus that age 70 years may be considered the lower limit of senescence [11] and because the available randomised trials of postmastectomy adjuvant therapy excluded patients aged 70 years and older. Comparisons of tumour and treatment characteristics between the two age cohorts were performed using chi-square tests. To examine the effect of possible predictors of recurrence, 10-year Kaplan–Meier (KM) LRR and the associated 95% confidence interval (CI) were computed for each patient and tumour characteristic. Statistical significance of differences in outcomes was determined using the log-rank test. Test statistics were applied to known values only. Multivariate analyses of LRR, DR, and OS were performed using the Cox proportional hazards model. All statistical tests were two-tailed and performed using SPSS Version 11.0.1 (SPSS Inc, Chicago, IL).

3. Results

Of 2362 women analysed (median age 67 years; range: 50–95 years), 60% ($n = 1423$) were aged 50–69 years and 40% ($n = 939$) were aged 70+ years. The median follow-up times were 8.3 years (range: 0.12–14.7 years) in the entire cohort, 8.7 years in patients aged 50–69 and 7.8 years in patients aged 70+ years.

3.1. Tumour and treatment characteristics

Characteristics of the entire cohort and comparisons of tumour factors in the two age subgroups are presented in Table 1. Tumours >5 cm were present in 5% of women aged 50–69 and 3.5% of women aged 70+, respectively. Overall, 65% of patients had negative nodes (N0), 29% had 1–3 positive nodes (N+), and 6% had $\geqslant$4 N+. The distribution of nodal stage was similar in the two age cohorts. Compared to women aged 50–69, women aged 70+ had more favourable histologic characteristics with significantly fewer having Grade III disease (30% *vs.* 35%, $P = 0.002$) or ER-negative status (14% *vs.* 24%, $P < 0.001$).

Table 1
Tumour and treatment characteristics

	Entire cohort (n = 2362) n, %		Age 50–69 y (n = 1423) %	Age 70+ y (n = 939) %	P[a]
Histologic type					
Ductal cancer	2102	89.0	88.9	89.1	0.08
Lobular cancer	244	10.3	10.1	10.6	
Other	16	0.7	1.0	0.2	
Tumour size (cm)					
0.1–2.0	1333	56.4	57.7	54.5	0.05
2.1–5.0	905	38.3	36.8	40.6	
5.1–9.9	104	4.4	5.0	3.5	
Unknown	20	0.8	0.5	1.4	
Grade					
I and II	1305	55.2	52.6	59.3	0.002
III	787	33.3	35.4	30.1	
Unknown	270	11.4	12.0	10.5	
Lymphovascular invasion					
Absent	1456	61.6	61.6	61.7	0.66
Present	694	29.4	28.9	30.1	
Unknown	212	9.0	9.5	8.2	
ER status					
Positive	1521	64.4	60.5	70.3	<0.001
Negative	469	19.9	23.5	14.4	
Unknown	372	15.7	16.0	15.3	
Pathologic nodal status					
Positive	830	35.1	33.9	37.0	0.13
Negative	1532	64.9	66.1	63.0	
Number of positive nodes					
0	1532	64.9	66.1	63.0	0.29
1–3	683	28.9	27.8	30.7	
4 or more	147	6.2	6.2	6.3	
Number of nodes removed					
$\leqslant$10	1344	56.9	54.7	60.2	0.009
>10	1018	43.1	45.3	39.8	
Surgical margin status					
Positive	75	3.2	3.4	2.8	0.43
Negative	2007	85.0	85.8	83.7	
Unknown	280	11.9	10.8	13.5	
Systemic therapy					
Yes	1375	58.2	58.9	57.2	0.41
No	987	41.8	41.1	42.8	
Systemic therapy					
HT alone	1073	45.4	38.4	56.1	<0.001
CT alone	98	4.1	6.7	0.2	
Both	204	8.6	13.8	0.9	
None	987	41.8	41.1	42.8	

Abbreviations: ER = estrogen receptor; HT = hormone therapy; CT = chemotherapy.
[a] Test statistics applied to known values only.

All patients in this study cohort underwent axillary nodal staging. The median number of axillary nodes removed was 10 (range 1–40). The median number of nodes removed was 10 (range 1–40) in women aged 50–69 and 9 (range 1–36) in women aged 70+ years. Compared to younger counterparts, elderly women had fewer axillary nodes removed (60% of women aged 70+ years had $\leqslant$10 nodes removed compared to 55% of women aged 50–69, $P = 0.009$).

The rates of adjuvant systemic therapy use were similar in the two age groups (59% and 57% in age 50–69 and 70+, respectively, $P = 0.41$). Women aged 70+ were significantly more likely to receive hormone therapy (56% *vs.* 38%, $P < 0.001$) and less frequently received

chemotherapy (0.2% *vs.* 6.7%, $P < 0.001$), or combined hormone therapy and chemotherapy (1% *vs.* 14%, $P < 0.001$).

3.2. Recurrence and survival outcomes

Fig. 1 depicts LRR comparisons between the two age groups. Ten-year KM LRR was comparable between the two age cohorts, with risks of 10.0% for women aged 50–69 and 9.9% for women aged 70+ years, ($P > 0.05$). DR was also comparable between the two age cohorts, with risks of 22.9% for women aged 50–69 and 21.9% for women aged 70+ years ($P > 0.05$), and overall survival at 10 years was 72.0% for women aged 50–69 and 51.4% for women aged 70+ ($P < 0.0001$).

Table 2a summarises 10-year KM LRR outcomes according to nodal status (N0, 1–3 N+, ⩾4 N+) in the entire cohort and in each age-specific cohort. LRR was further separated into local chest wall recurrence (LR) and regional nodal recurrence (RR). In the entire cohort and within each age subgroup, LRR and RR significantly increased with increasing nodal involvement ($P < 0.05$). Chest wall recurrence increased with increasing nodal involvement in women aged 70+ ($P < 0.0001$) but not in women aged 50–69 years ($P = 0.19$). Within each nodal category, risks of LRR, LR and RR were similar in the two age groups ($P > 0.05$). The exception was in women with ⩾4 N+ where chest wall recurrence was observed to be higher in the older age group (LR 3.7% in women aged 50–69 and 16.0% in women aged 70+ years ($P = 0.04$).

Table 2b summarises 10-year KM DR and OS outcomes according to nodal status in the entire cohort and in each age-specific cohort. DR risks significantly increased with increased nodal involvement ($P < 0.05$) but the DR outcomes between the two age groups according to nodal stage were not significantly different

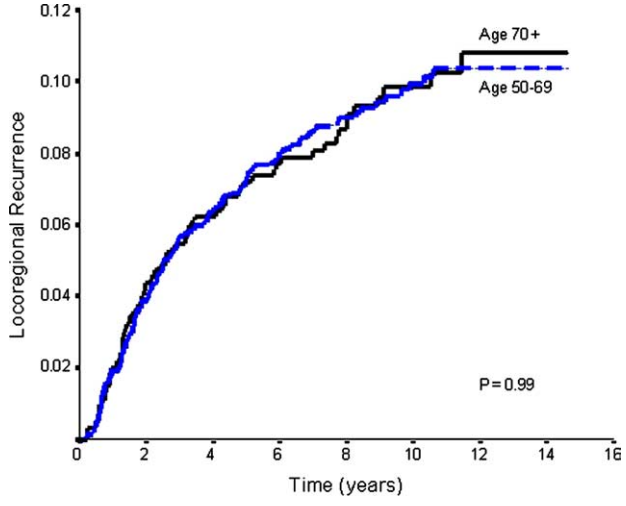

Fig. 1. Locoregional recurrence according to age.

Table 2a
Ten-year Kaplan–Meier locoregional recurrence (LRR), local recurrence (LR), and regional recurrence (RR) outcomes according to age and nodal status

	% LRR (95% CI)				% LR (95% CI)				% RR (95% CI)			
	N0	1–3 N+	⩾4 N+	*P*	N0	1–3 N+	⩾4 N+	*P*	N0	1–3 N+	⩾4 N+	*P*
Entire cohort	7.3 (6.0–9.0)	14.1 (11.3–17.5)	22.3 (15.0–32.3)	<0.0001	5.0 (3.9–6.4)	8.3 (6.2–11.0)	8.6 (4.7–15.5)	0.002	3.0 (2.2–4.1)	7.5 (5.4–10.3)	14.2 (8.2–24.0)	<0.0001
Age 50–69	7.6 (6.0–9.8)	14.8 (11.1–19.5)	16.8 (9.5–28.7)	0.0003	5.4 (4.0–7.3)	7.8 (5.3–11.3)	3.7 (1.2–11.2)	0.19	3.3 (2.3–4.8)	8.3 (5.5–12.5)	11.1 (5.4–21.9)	0.0002
Age 70+	6.8 (4.8–9.6)	13.0 (9.1–18.4)	30.8 (17.7–50.0)	<0.0001	4.3 (2.8–6.8)	8.9 (5.7–13.9)	16.0 (7.9–30.9)	<0.0001	2.5 (1.5–4.4)	6.3 (3.7–10.5)	20.5 (8.8–43.6)	<0.0001
P	0.39	1.00	0.14		0.20	0.76	0.04		0.43	0.66	0.53	

Abbreviations: CI = confidence interval; N+ = positive nodes.

Table 2b
Ten-year Kaplan–Meier distant recurrence (DR) and overall survival (OS) outcomes according to age and nodal status

	% DR (95% CI)				% OS (95% CI)			
	N0	1–3 N+	⩾4 N+	*P*	N0	1–3 N+	⩾4 N+	*P*
Entire Cohort	13.5 (11.7–15.5)	36.1 (32.2–40.3)	57.0 (48.6–66.8)	<0.0001	71.0 (68.5–73.4)	51.6 (47.4–55.6)	40.3 (32.0–48.4)	<0.0001
Age 50–69	14.2 (12.0–16.8)	36.0 (31.0–41.6)	57.8 (46.9–69.1)	<0.0001	79.0 (76.1–81.6)	60.6 (55.2–65.6)	47.7 (36.4–58.2)	<0.0001
Age 70+	12.2 (9.5–15.6)	36.2 (30.2–43.0)	52.8 (39.4–67.7)	<0.0001	59.0 (54.6–63.1)	40.3 (34.2–46.4)	29.4 (18.2–41.5)	<0.0001
P	0.20	0.84	0.77		<0.0001	<0.0001	0.0009	

Abbreviations: CI = confidence interval; N+ = positive nodes.

Table 3
Univariate analysis of locoregional recurrence according to tumour and treatment characteristics

	Entire cohort % (95% CI)	Age 50–69 y % (95% CI)	Age 70+ y % (95% CI)
Histologic type			
Ductal cancer	10.2 (8.8–11.8)	10.5 (8.8–12.6)	9.7 (7.6–12.3)
Lobular cancer	8.2 (5.1–13.2)	6.4 (3.2–12.4)	11.4 (5.7–21.9)
P	0.22	0.15	0.94
Tumour size (cm)			
0.1–2.0	7.0 (5.5–9.0)	7.8 (6.0–10.0)	5.7 (3.8–8.5)
2.1–5.0	13.7 (11.2–16.7)	13.3 (10.2–17.2)	14.3 (10.5–19.4)
>5	18.9 (12.0–29.1)	13.7 (7.0–25.6)	30.0 (16.2–51.3)
P	<0.0001	0.0095	<0.0001
Grade			
I/II	6.2 (4.9–7.9)	5.7 (4.1–7.9)	7.0 (4.9–10.0)
III	15.9 (13.2–19.2)	15.6 (12.3–19.6)	16.4 (11.9–22.5)
P	<0.0001	<0.0001	0.0001
Lymphovascular invasion			
Absent	7.6 (6.2–9.4)	8.5 (6.6–10.8)	6.3 (4.3–9.1)
Present	14.4 (11.6–17.7)	13.9 (10.5–18.4)	14.9 (10.8–20.4)
P	<0.0001	0.0071	<0.0001
Estrogen receptor status			
Positive	9.3 (7.7–11.2)	10.0 (7.9–12.6)	8.3 (6.1–11.3)
Negative	13.5 (10.5–17.3)	10.6 (7.5–14.8)	21.1 (14.4–30.4)
P	0.0015	0.30	< 0.0001
Pathologic nodal stage			
Negative	7.3 (6.0–9.0)	7.6 (6.0–9.8)	6.8 (4.8–9.6)
Positive	15.4 (12.7–18.6)	15.1 (11.7–19.3)	15.7 (11.6–21.0)
P	<0.0001	0.0001	<0.0001
Number of positive nodes			
0	7.3 (6.0–9.0)	7.6 (6.0–9.8)	6.8 (4.8–9.6)
1–3	14.1 (11.3–17.5)	14.8 (11.1–19.5)	13.0 (9.1–18.4)
⩾4	22.3 (15.0–32.3)	16.8 (9.5–28.7)	30.8 (17.7–50.0)
P	<0.0001	0.0003	<0.0001
Number of nodes removed			
⩽10	10.3 (8.6–12.3)	10.6 (8.4–13.3)	9.8 (7.3–13.0)
>10	9.5 (7.6–11.8)	9.2 (7.0–12.1)	10.0 (6.9–14.3)
P	0.56	0.44	0.99
Surgical margin status			
Positive	13.7 (7.4–24.9)	11.4 (4.9–25.4)	18.7 (7.4–42.9)
Negative	10.0 (8.6–11.7)	9.9 (8.1–12.1)	10.1 (7.9–12.9)
P	0.16	0.55	0.10
Systemic therapy			
Yes	11.6 (9.7–13.7)	11.5 (9.3–14.4)	11.5 (8.7–15.1)
No	7.8 (6.1–9.9)	7.9 (5.9–10.7)	7.8 (5.2–11.5)
P	0.005	0.09	0.02

Abbreviations: CI = confidence interval.

(all $P > 0.05$). Ten-year OS significantly decreased with increasing age and increasing nodal involvement (both $P < 0.0001$).

3.3. Univariate analysis of locoregional recurrence

Table 3 presents 10-year KM LRR stratified by tumour and treatment characteristics. Increasing tumour size was associated with higher LRR risks in both age groups (Fig. 2(a) and (b)). With tumours >5 cm, LRR were 13.7% and 30.0% in women aged 50–69 and 70+, respectively.

With respect to nodal status, the overall LRR risk was 7.3% among node-negative patients. Higher LRR risks of 14.1% and 22.3% were found in patients with 1–3 N+ and ⩾4 N+, respectively ($P < 0.0001$). Postmastectomy LRR risks increased with increased nodal burden in both age cohorts, 50–69 years (Fig. 3(a)) and 70+ years (Fig. 3(b)). With 1–3N+, LRR was similar in women aged 50–69 and 70+ years (14.8% and 13.0%, $P = 1.00$). In the presence of ⩾4N+, LRR was 16.8% in women aged 50–69 and 30.8% in women aged 70+ ($P = 0.14$).

In addition to tumour size and nodal involvement, other factors as shown in Table 3, associated with increased LRR approximating 15–20% were grade III histology and LVI in the entire cohort and in each age-specific cohort. Estrogen receptor-negative status and positive surgical margins were associated with increased LRR in women aged 70+ but not in women aged 50–69 years. The use of adjuvant systemic therapy was associated with higher LRR in both age groups. The number of axillary nodes removed was not significantly associated with LRR.

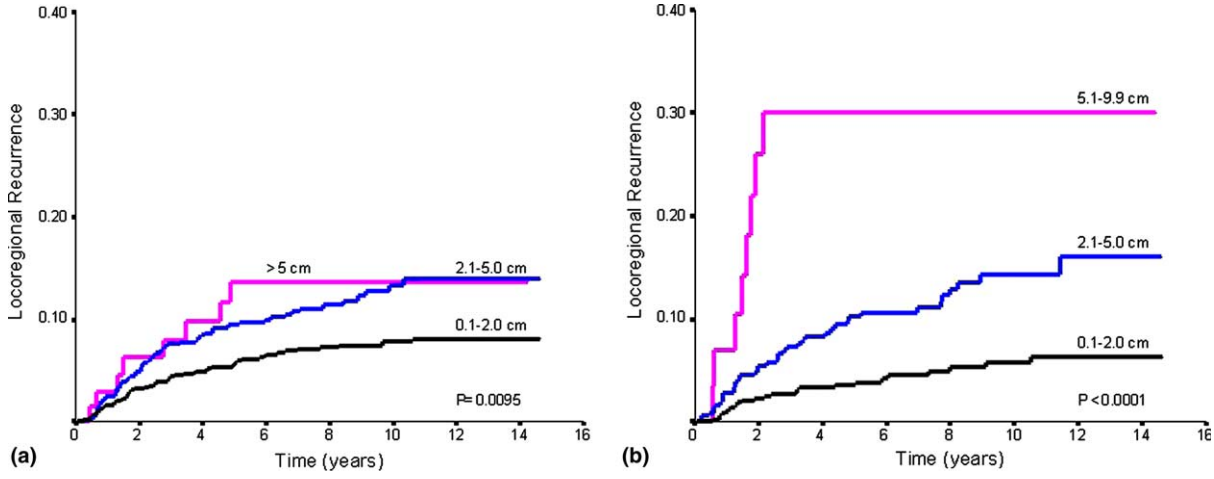

Fig. 2. Locoregional recurrence stratified by tumour size in: (a) women aged 50–69; (b) women aged 70+.

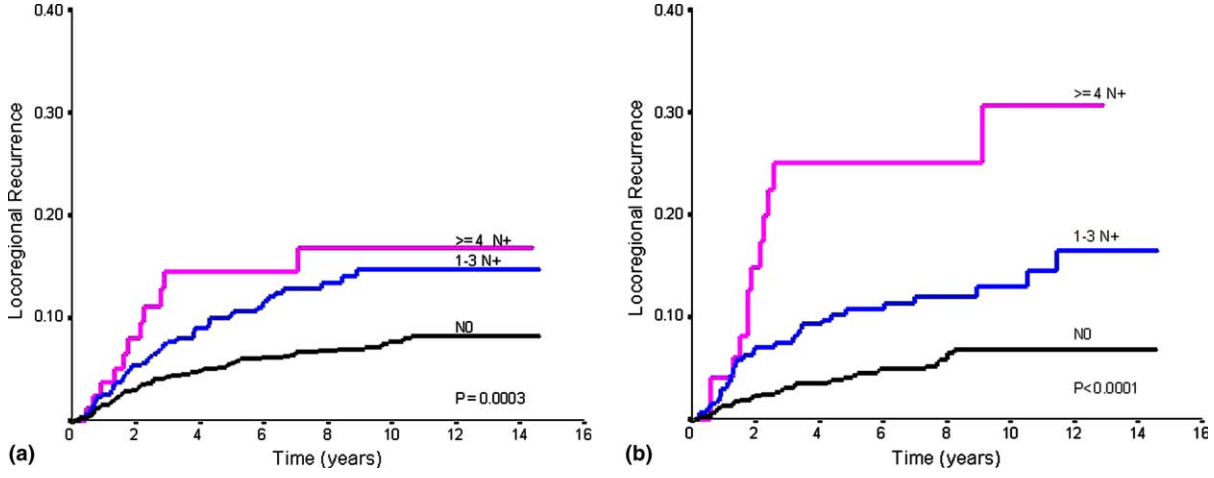

Fig. 3. Locoregional recurrence stratified by nodal status in: (a) women aged 50–69; (b) women aged 70+.

Table 4
Multivariate analysis

Variable	LRR *P* value HR (95% CI)	DR *P* value HR (95% CI)	OS *P* value HR (95% CI)
Age	0.62	0.56	<0.001
70+ *vs.* 50–69 y			2.24 (1.89–2.65)
Histologic type	0.88	0.42	0.26
Tumour size (cm)	0.26	<0.001	<0.001
2.1–5.0 *vs.* 0.1–2.0		1.56 (1.21–2.00)	1.40 (1.16–1.68)
>5 *vs.* 0.1–2.0		2.46 (1.56–3.90)	1.90 (1.28–2.82)
Grade	<0.001	0.002	0.010
III *vs.* I/II	2.40 (1.64–3.50)	1.45 (1.14–1.84)	1.27 (1.06–1.51)
Lymphovascular invasion	0.02	0.001	0.009
Present *vs.* absent	1.59 (1.08–2.33)	1.49 (1.17–1.91)	1.29 (1.07–1.55)
Estrogen receptor status	0.06	0.003	0.018
Negative *vs.* positive	1.47 (0.99–2.18)	1.49 (1.15–1.93)	1.28 (1.04–1.58)
Pathologic nodal status	0.02	<0.001	<0.001
Positive *vs.* negative	1.65 (1.10–2.47)	2.44 (1.87–3.19)	1.75 (1.43–2.14)
Number of nodes removed	0.25	0.35	0.99
Surgical margin status	0.46	0.001	0.003
Positive *vs.* negative		2.08 (1.34–3.24)	1.78 (1.22–2.60)
Systemic therapy use	0.48	0.34	0.15

Abbreviations: LRR = locoregional recurrence; DR = distant recurrence; OS = overall survival; HR = hazard ratio; CI = confidence interval.

3.4. Multivariate analysis

In the Cox regression analysis (Table 4), age was not significantly associated with LRR. Independent prognostic factors for LRR were grade III histology, the presence of LVI, and positive nodal status.

Age was significantly associated with OS, but not DR. Independent prognostic factors for DR and OS were increasing tumour size, grade III histology, presence of LVI, negative ER status, positive nodal status, and positive surgical margins.

4. Discussion

Postmastectomy locoregional management decisions require careful appraisal of baseline LRR risks to distinguish patients at high risks who may benefit from adjuvant therapy and those at low risks who may be spared therapy-related toxicities. The present study demonstrated that despite having more favourable tumour characteristics and comparable rates of systemic therapy use, women aged 70+ years were not at lower LRR risks compared to younger counterparts.

To date, there are few data pertaining to LRR risks in women aged 70 years and older who underwent definitive surgery with mastectomy and axillary dissection without radiotherapy. Table 5 summarises contemporary studies of postmastectomy LRR in patients treated without PMRT. Direct comparison with the current data is difficult since the studies varied in patient selection, sample size, follow-up time, and the use of surgical and systemic therapies. Not all studies reported outcomes stratified by age or nodal status. The numbers of elderly subjects in these studies were also not uniformly reported but were included when available.

In the Danish and BCCA randomised studies which excluded women aged 70+ years, patients with advanced primary tumours or node-positive disease treated with adjuvant systemic therapy were randomised to postmastectomy radiotherapy *vs.* no radiotherapy. In these trials, node-positive patients who did not receive radiotherapy experienced LRR risks of 30–45% at 10–15 years [3–5]. In the Danish 82c study of postmenopausal patients aged <70 years, patients with tumour size >5 cm experienced LRR risks of 34% without radiotherapy [5], a magnitude similar to that demonstrated in women aged 70+ in the current analysis.

Retrospective analyses of patients enrolled in randomised trials of systemic therapy also provide information on baseline LRR risks after mastectomy without radiotherapy. The Eastern Cooperative Oncology Group reported on 2016 patients entered in four randomized trials of systemic therapy without radiotherapy [12]. Of these, 247 were aged 65 years or older. The risks of LRR at 10 years were 13% in patients with 1–3 N+ and 29% for patients with $\geqslant$4 N+ [12], similar to the current study. Multivariate analysis identified increasing tumour size, increasing numbers of positive nodes, negative ER status and decreasing number of nodes examined as significant predictors of LRR.

The MD Anderson Cancer Centre analysed 1031 patients who participated in five trials of anthracycline-based chemotherapy. Of these, only 160 patients were aged 60 years or older. On multivariate analysis, the presence of four or more positive axillary nodes, tumour size of 5 cm or larger, close or positive surgical margins

Table 5
Literature summary of postmastectomy locoregional recurrence without adjuvant radiotherapy

	Number of patients	Number of patients aged 70+	Median follow-up (years)	% 10-year KM LRR		
				N0	1–3 N+	⩾4 N+
Prospective randomized trials						
BCCA, 1997 [3]	154	0	12.5	N/A	33 at 15 y	41
BCG 82b, 1997 [4]	856	0	9.5	17	30	42
DBCG 82c, 1999 [5]	689	0	10.2	23	31	46
EORTC 10850, 2003 [20,21][a]	222	222	10.5	NR	NR	NR
EORTC 10851, 2003 [22][b]	168	168	11	NR	NR	NR
Retrospective studies of patients enrolled on systemic therapy trials						
ECOG, 1999 [12]	2016	Age ⩾ 65 (n = 247)	12.1	N/A	13	29
MDACC, 2000 [13]	1031	Age > 60 (n = 160)	9.7	4	10	21–22
IBCSG, 2003 [14]	5352	Age ⩾ 60 (n = 1309)	14.5	Premenopausal: 11–17 for pT1-2; 30 for pT3 Postmenopausal: 10–13 for pT1-2; 14 for pT3	Premenopausal: 16–20 for pT1-2; 25 for pT3 Postmenopausal: 13–19 for pT1-2; 16 for pT3	Premenopausal: 28–41 for pT1-2; 33–35 for pT3 Postmenopausal: 26–34 for pT1-2; 35–48 for pT3
Retrospective population-based studies						
Taiwan, 2002 [24]	110	NR	4.5	N/A	10–21 (4-yr)	N/A
Ochsner Clinic, 2002 [25]	128	NR	4.1	N/A	N/A	11
Present Series, BCCA, 2004	2362	Age > 70 (n = 939)	8.3	7	14	22

Abbreviations: N/A = not applicable; NR = not reported; BCCA = British Columbia Cancer Agency; DBCG = Danish Breast Cancer Cooperative Group; EORTC = European Organization for Research and Treatment of Cancer; ECOG = Eastern Cooperative Study Group; MDACC = M.D. Anderson Cancer Center; IBCSG = International Breast Cancer Study Group.

[a] Overall LRR 15%.

[b] Overall LRR 11%.

or gross multicentric disease was found to be independent predictors of LRR [13].

A study from the International Breast Cancer Study Group included 5352 women in seven adjuvant systemic therapy trials, 1309 of whom were aged 60 years or older treated with mastectomy without radiotherapy [14]. Among postmenopausal women, the risk of LRR at 10 years was 10–14% in patients with node-negative disease, 13–19% in patients with 1–3 N+ and 26–48% in patients with $\geqslant$4 N+.

In contrast to these studies and the current analysis in which all subjects underwent definitive surgery with mastectomy and axillary nodal staging, other studies have evaluated the question of whether hormone therapy alone without definitive surgery is adequate therapy in elderly women. Two trials compared tamoxifen alone to surgery alone [15–17]. The trial from St. George's Hospital, which randomised 200 patients to surgery with wide excision or mastectomy without radiotherapy *vs.* tamoxifen alone without surgery, reported local relapse or progression in 44% and 56%, respectively, at a median follow up of 6 years [15]. Since the surgery arm of this study was not standardised and patients treated with breast conserving surgery did not receive radiotherapy, the ability to interpret these results and their applicability to current clinical practice is limited. Similarly, a trial from Nottingham demonstrated extreme local progression rates with tamoxifen alone (81%) compared to wedge resection without radiotherapy (38%) at 12-year follow up [16,17].

Two trials compared tamoxifen alone to surgery plus tamoxifen among elderly patients aged 70 years and older [18,19]. A trial from the United Kingdom demonstrated higher rates of cancer progression, breast cancer mortality, and overall mortality with tamoxifen alone [18]. A trial from the Italian Cooperative Group corroborated the findings of inferior local control with tamoxifen alone but no difference in survival compared to surgery and tamoxifen was observed [19].

The European Organization for Research and Treatment of Cancer (EORTC) recently published two trials specifically designed for elderly patients. The first trial (EORTC 10850) compared modified radical mastectomy with wide excision and tamoxifen [20–22]. Among 222 patients at a median follow up of 10.5 years, local surgery and tamoxifen resulted in a local recurrence rate of 27% compared to 15% with mastectomy [20]. Compared to mastectomy, the breast conservation approach was associated with fewer arm problems and a trend for improved body image [21]. The second trial (EORTC 10851) with 164 patients randomised mastectomy *vs.* tamoxifen alone [22]. In the absence of definitive surgery, tamoxifen alone resulted in a risk of local progression or relapse of 62% compared to 11% when mastectomy was used [22]. These findings thus clearly demonstrated that hormone therapy alone without surgery was inadequate therapy for elderly women with resectable breast cancer.

The breast cancer burden in the older population must be considered in the context of longer life expectancy among women in industrialised countries [11,23] and the individual's physiologic reserve and functional capacity rather than chronologic age alone [11,23]. Most studies of outcomes after mastectomy for breast cancer lacked data on the patients' comorbid diseases and functional status, which may exert considerable impact on adjuvant treatment selection and outcomes, particularly among elderly subjects. The current study is similarly limited by the lack of prospectively collected data on comorbidity and performance status. Due to its retrospective nature, the present study is subject to biases in patient and treatment selection. However, since the available data on postmastectomy LRR outcomes have largely been derived from younger subjects enrolled in prospective trials and from retrospective population-based studies limited by small numbers of patients and short follow-up times [24,25], the present analysis offers long-term follow-up information on a large patient cohort, and may be representative of older patients encountered in clinical practice.

Variations in surgical techniques among older patients have the potential to impact LRR risks. Although there is consensus that level I and II nodes, located lateral to and deep to the pectoralis minor muscle, should be removed for accurate staging and to reduce axillary recurrence, there is less agreement on the number of nodes that must be removed [26]. In the present study, older patients had fewer nodes removed compared to younger patients, a finding corroborated by other series [27]. However, the number of nodes removed did not emerge as a significant factor for LRR, DR, or OS in the univariate or multivariate analyses.

In addition to surgical factors, systemic therapy factors have the potential to impact recurrence and survival outcomes. While the rates of systemic therapy use were similar in the two age groups, elderly women were less likely to receive chemotherapy. Variations in systemic therapy use and different regimens could thus bias our findings even though this did not emerge as significant in the multivariate analysis.

With respect to pathological characteristics other than tumour and nodal stage, LRR risks approximately doubled in the presence of high grade histology or lymphovascular invasion in both age groups. In women aged 70+ years, LRR also approximately doubled with larger tumour size, ER-negative status, and positive margins. Age was not a significant independent predictor for LRR or DR. These findings thus challenge the perception that elderly breast cancer patients have lower risks of cancer recurrence compared to younger women.

While the thresholds of LRR risks at which clinicians should recommend adjuvant locoregional therapy are not well defined, we suggest that patients with 10-year LRR estimates <10% constitutes a low-risk subgroup who may be spared PMRT and that patients with LRR risks >30% constitutes a high-risk subgroup justifying PMRT recommendations. A LRR riskof 15–20% may arguably be a reasonable threshold at which PMRT should be consideredwith careful balancing of benefits, risks andthe patient's goals and preferences.

In the present study, 65% of patients had node-negative breast cancer with an overall LRR risk of less than 10%. However, the question of whether there are subsets of patients with node-negative disease who may have higher risks of LRR is currently unclear. In a recent study by our group using recursive partitioning analysis to evaluate this question, the concomitant presence of high grade histology and LVI was identified as a combination associated with LRR risks approximating 20% [28]. These findings require confirmation by other institutional series and by prospective research.

In the current study's examination of 10-year KM LRR risks, women aged 70+ with tumours >5 cm or $\geqslant$4 positive nodes were found to have LRR approximating 30%. This risk magnitude warrants consideration of adjuvant radiotherapy [6,7,29]. Among high-risk patients, establishing locoregional control is a priority since LRR may increase the risk of distant dissemination and compromise survival [30,31]. In addition, LRR can be physically and psychologically devastating with profound adverse effects on quality of life [32,33]. With modern techniques, adjuvant radiotherapy is a well tolerated procedure associated with few severe acute or late sequelae [6,7,29], including in elderly patients [34,35].

In conclusion, despite having more favourable tumour characteristics and similar rates of systemic therapy use, elderly women experienced locoregional recurrence risks similar or higher in magnitude compared to younger women, particularly with tumours >5 cm or with $\geqslant$4 positive nodes. In the presence of these high-risk features, breast cancer management should include consideration and discussion of the benefits and risks of postmastectomy radiotherapy. Ultimately, however, adjuvant therapy decisions must be based not only on locoregional control and survival endpoints but also on the patient's unique circumstances, goals, and expectations. For the elderly patient, functional capacity and quality of life may exert additional impact on decision-making [11,23]. These currently under-explored issues warrant future research.

Conflict of interest statement

None declared.

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