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Local recurrence in the breast after conservative surgery—a study of prognosis and prognostic factors in 391 women

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Abstract

In a population-based cohort of 6613 women with invasive breast cancer, who had breast-conserving surgery between 1981 and 1990, 391 recurrences in the operated breast were identified. The main aim of this study was to examine the prognosis and prognostic factors in different subgroups of local recurrences, characterised by the time to recurrence, location of recurrence and previously given radiotherapy. The median follow-up for women who had a local recurrence was 7.9 years. The life-table estimates for breast cancer-specific survival in women with local recurrences were 84.5% (standard error (S.E.) 1.8) at 5 years and 70.9% (S.E. 2.7) at 10 years. The risk of breast cancer death was highest among women who had an early ($\leqslant$2 years) recurrence in the same quadrant as the primary tumour, with a breast cancer-specific survival of 67.9% (S.E. 4.8) at 5 years and 56.0% (S.E. 5.9) at 10 years. There was a statistically significant difference in the probability of breast cancer-specific survival, as measured from the recurrence, between women who initially did or did not receive radiotherapy ($P=0.0123$). However, when measured from primary treatment, there was no significant difference, indicating that the difference in prognosis could be due to a lead-time bias. Independent prognostic factors for breast cancer-specific survival in women with local recurrences were time to local recurrence and the Nottingham Prognostic Index (NPI).

Keywords: Breast cancer; Conservative treatment; Local recurrence; Radiotherapy; Nottingham Prognostic Index; Prognosis; Survival analysis; Proportional hazards model

1. Introduction

Local recurrence is associated with an increased risk of distant metastasis [1–4] and death from breast cancer [5–7]. It is not clear whether this association is causal or whether a local recurrence merely indicates active disease, or both.

Clinically, local recurrences seem to have a heterogeneous tumour biology. The majority of recurrences occur in the area of the previous excision [6,8–11], and most likely are due to an incomplete removal of the index tumour. Recurrences in another quadrant of the breast often occur later and have been defined by some authors as new primaries [6,9–12]. Women with early recurrences have a worse prognosis than women with late recurrences [1–7,9,13]. Radiotherapy markedly reduces the number of local recurrences [4,7,14–18], but the recurrences that appear may be associated with a worse prognosis than those in patients who have not had

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irradiation [7]. Uncertainty about the biological and clinical implications of a local recurrence complicates therapeutic decisions, both as regards surgical procedures and more so with regard to systemic treatment.

We studied 391 women with local recurrences in the breast after breast-conserving surgery for invasive breast cancer. The aim was to study the prognosis and prognostic factors in different subgroups of local recurrences with regard to the time to recurrence, location of recurrence and previously given radiotherapy.

2. Patients and methods

A population-based cohort of 6613 women with invasive breast cancer from five of Sweden's six healthcare regions, operated upon with breast-conserving surgery between 1981 and 1990, was followed until 1997. In three healthcare regions, data were collected from regional breast cancer registers, in the other two from medical records. The design of the cohort study has been described in detail in Ref. [19], although with data on only 4694 women from four regions. The validity of the data from four regions was checked and found to be accurate by a detailed study of the records of 1332 controls, selected for a nested case–control study that aimed to analyse risk factors of local recurrence. In the fifth region, the number of person-years was incorrect, and data from this region were excluded in the cohort analysis.

During the study period, 391 women from the cohort experienced a local recurrence in the breast and they accordingly constitute the study base for this analysis. Local recurrence was defined here as the appearance of any morphologically-verified new breast tumour, invasive or *in situ*, in the operated breast parenchyma or in the overlying skin, prior to or at the same time as distant metastases. The median follow-up for the patients who had a local recurrence in the breast was 7.9 years, (range: 0.4–16.5 years) giving a total of 3068 person-years in the study.

Patient characteristics, data on the primary tumour and the local recurrence, follow-up data concerning distant disease, death and the date of each woman's latest clinical examination were collected from the medical records of all of the 391 women. Data concerning the cause of death were collected from the medical record. If cause of death was given as uncertain, or not given, in the medical record, the cause of death according to the National Causes of Death Register was used. The cause of death has been determined in a way that has been tested in a review of Swedish mammography trials and found to be accurate [20].

A clinically-, radiologically- or morphologically-verified distant recurrence (any recurrence in the infraclavicular nodes or beyond) and death from breast cancer not preceded by relapse were defined as events in the analysis of distant disease-free survival. Within 1 month after the appearance of the local recurrence, 11/391 were noted to have distant metastases, and 22/391 within 3 months. Breast cancer as an underlying or contributory cause of death was considered to be an event in the analysis of breast cancer-specific survival.

2.1. Histopathological re-evaluation

Data about Nottingham histological grade according to Elston [21] were obtained from a review of slides performed for a case–control study nested to the cohort where women with a local recurrence were the index cases. Slides of the primary tumour were available for 378 of the 391 women with local recurrence. The slides were reviewed by three pathologists using standardised forms and well-defined criteria for classification. The case–control status was unknown to the reviewing pathologists. The Nottingham Prognostic Index (NPI) was calculated for each case and control using the form NPI = 0.2 × tumour size (in cm) + nodal stage (1-3) + grade (1-3) [22].

2.2. Follow-up

The healthcare regions participating in this study had similar routines for follow-up. In the first 2 years, patients were seen three to four times a year and thereafter every 6 months up to 5 years. Yearly mammography was recommended. The routines after 5 years varied but, especially at the beginning of the period, it was recommended that patients have annual mammography up to 10 years after the operation. Most patients have also been checked at their local hospital or referred to their general practitioner for further clinical examinations after 5 years. Since the introduction of screening, all patients have been strongly encouraged to comply with the screening programme after their hospital-based check-ups had ended.

2.3. Surgical procedures

Breast-conserving surgery in Sweden has been performed as a segmental or sector resection aiming at local radicality [23], so that the tumour-bearing portion of the breast is removed by dissection of the breast parenchyma in the plane of Scarpa's fascia down to the pectoral muscle. Excision of the pectoral fascia has been recommended as part of the procedure. The skin incisions and the excision of overlying skin have varied. The routine for axillary dissection has been to dissect levels I and II [24].

2.4. Radiotherapy

During 1981–1990 postoperative radiotherapy to the breast up to 50–58 Gy was the standard treatment, but in the entire cohort only 70.2% of the patients received such

irradiation [19]. The women not receiving radiotherapy were mostly elderly, but 20.4% of the women aged less than 70 years also did not receive radiotherapy. For node-positive patients, the target volume included the residual breast, axillary, supraclavicular and infraclavicular nodes while, for node-negative patients, the target volume included only the residual breast. Boost has not been used to any extent in Sweden.

2.5. Adjuvant systemic therapy

Adjuvant systemic therapy was seldom used before 1985. After 1985, the larger central hospitals began to use postoperative adjuvant CMF (cyclophosphamide, methotrexate and 5-fluorouracil) for nine courses in premenopausal women with node-positive disease. For postmenopausal women with stage II disease, adjuvant tamoxifen therapy (20–40 mg daily) was used from 1985 on a full scale from approximately 1987. During the initial years of tamoxifen use, oestrogen receptor status did not generally guide treatment recommendations. The standard treatment period was 2 years, but some women were treated for up to 5 years in a randomised trial [25].

Only a small number of the women who experienced a local recurrence received adjuvant cytostatic treatment

Table 1
Characteristics of 391 patients[a] with local recurrence (LR) after breast-conserving surgery (BCS) from 1981 to 1990 for invasive breast cancer

	Number	Mean age (years)	Mean T-size (mm)	Node-positive (%)	Nottingham Prognostic Index (NPI)[b] <3.4 (%)	Primary tumours treated w/o RT (%)	LR re-operated with BCS (%)	LR treated with systemic therapy (%)
All LR	391	54.9	14.7	14.6	57.6	52.6	36.6	43.2
Early LR; same quad	102	55.8	16.3	13.7	49.4	70.6	51.0	39.2
Early LR; other quad[c]	7	49.6	15.0	28.6	14.3	57.1	57.1	42.9
Late LR; same quad	172	55.1	13.7	11.6	66.7	46.2	36.6	43.0
Late LR; other quad	37	53.4	12.8	16.2	67.6	35.1	32.4	35.1
Multifocal LR	59	54.5	14.9	18.6	53.3	54.2	8.5	49.2
LR after primary RT[d]	185	49.1	15.3	18.9	51.3	0.0	26.5	51.4
LR w/o primary RT	205	60.0	14.2	10.7	64.3	100.0	45.4	35.6

W/o, without; quad, quadrant; RT, radiotherapy; T-size, tumour size.
[a] Data about location of recurrence was missing for 14 patients, about radiotherapy for 1 patient.
[b] Based on 309 patients due to missing data.
[c] Limited possibility to interpret data due to few patients.
[d] 6 patients had RT in a dose less than 20 Gy; in these analyses they are included in the group LR after RT.

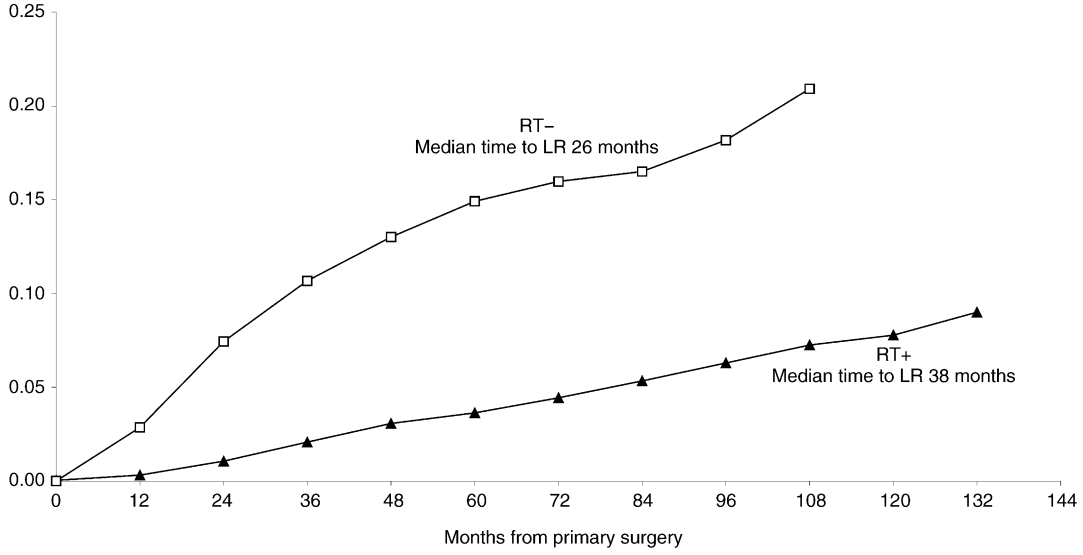

Fig. 1. Cumalative probability of local recurrence (LR) with or without prior radiotherapy ($n=123$ and $n=152$, respectively) in a cohort of 4383 women[a] operated upon with breast-conserving surgery from 1981 to 1990 for an invasive breast cancer ([a] data based on women from four healthcare regions, information about radiotherapy (RT) was lacking in 311 women).

(3.1%) and/or adjuvant hormonal treatment (5.4%) as treatment for the primary tumour. In comparison, 2.5% of the invasive controls selected for the nested case–control study from the cohort, were treated with adjuvant cytostatic treatment and 15.1% with adjuvant hormonal treatment.

2.6. Statistical analysis

The probabilities of distant disease-free and breast cancer-specific survival were estimated using the life-table method. The 5- and 10-year results are given together with the standard error (S.E.) of the life-table

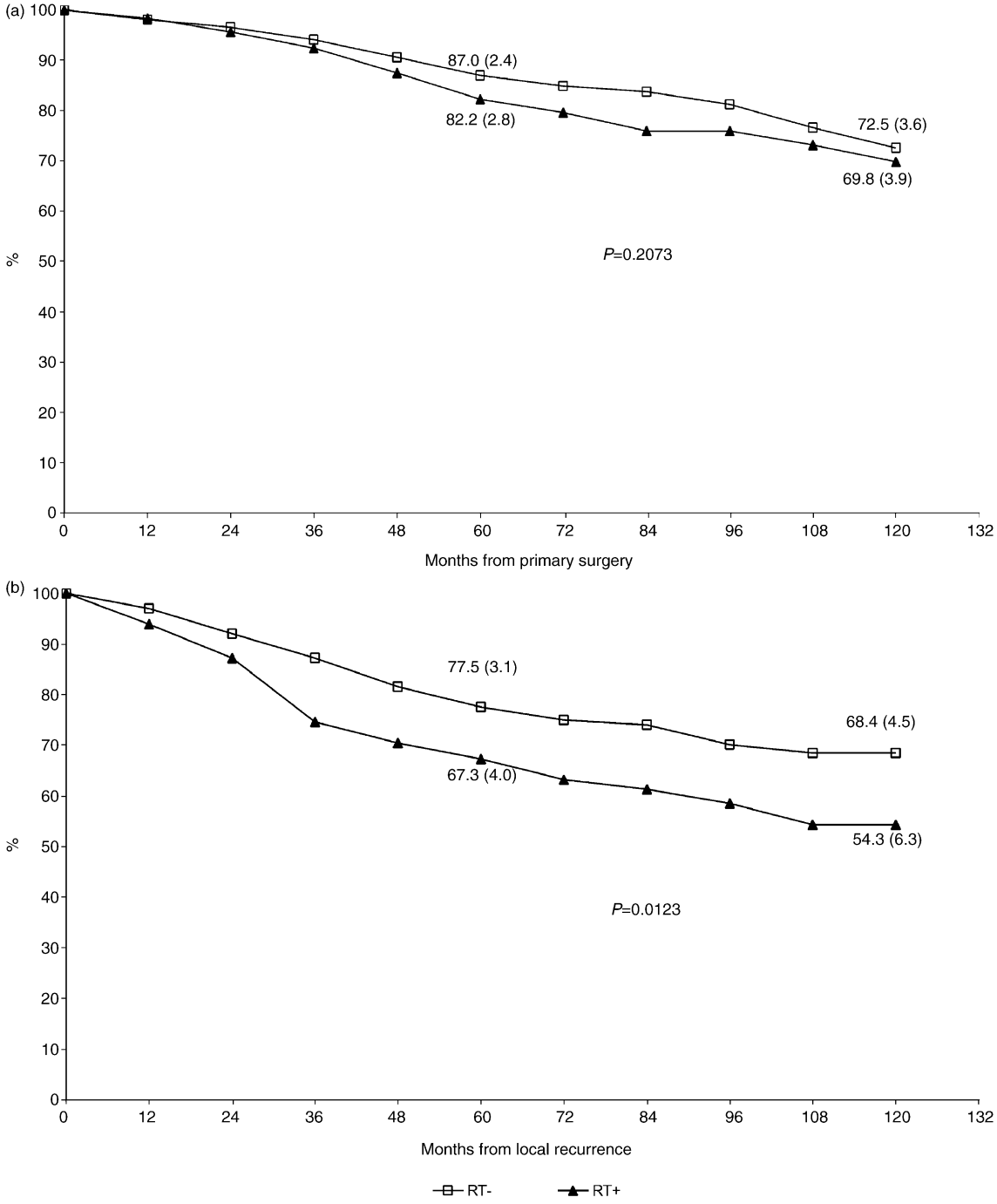

Fig. 2. Life-table curves showing estimated probabilities of breast cancer-specific survival in 391 women with local recurrence after breast-conserving surgery from 1981 to 1990 for invasive breast cancer, as measured from the primary operation (a) and from local recurrence (b). The analysis is stratified for radiotherapy at the primary surgery (5- and 10-year estimates are given with their standard errors).

estimate. The differences between survival curves were tested with a log rank test [26]. A Receiver Operating Characteristic (ROC) curve [27] was constructed to choose the optimal time, with regard to prognosis, for separating early from late recurrences. Different cut-off points were compared for analysing time between the primary operation and the recurrence as a marker of risk for breast cancer death. The ROC curve showed the best trade-off between specificity (66%] and sensitivity (62%) for a local recurrence to mark the risk of death to be at 2.3 years after the operation. In the prognostic models, the previously suggested cut-off point at 2 years was therefore used.

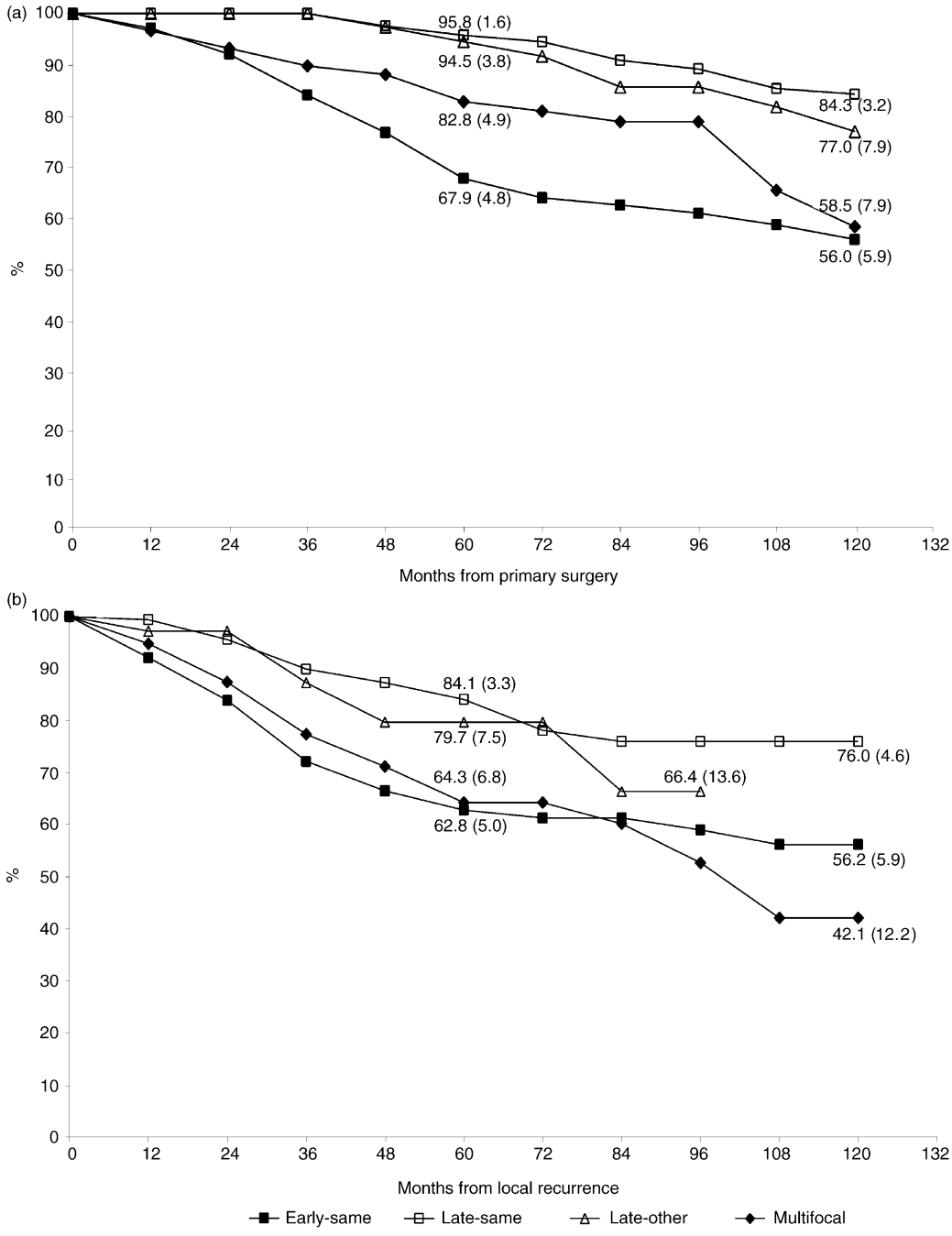

Fig. 3. Life-table curves showing estimated probabilities of breast cancer-specific survival in 391[a] women with local recurrence after breast-conserving surgery from 1981 to 1990 for invasive breast cancer, as measured from the primary operation (a) and from local recurrence (b). The analysis is stratified for time to and location of the recurrence (5- and 10-year estimates are given with their standard errors).

[a]Due to the low number of early recurrences in another quadrant than the primary tumour, the estimates of breast cancer-specific survival (71.4% (S.E. 17.1) at 5 and 10 years, respectively) are not shown in the figure.

In an attempt to study the joint effect of the different variables and, at least partially, deconfound the comparisons, multivariate proportional hazards analyses according to Cox were computed. Prognostic factors for breast cancer-specific survival in relation to location of local recurrence, time to local recurrence and previously given radiotherapy, adjusting for primary tumour detection mode, type of re-operation at local recurrence and systemic treatment at recurrence were studied. Since NPI includes a combination of tumour size and axillary node status, models with either NPI or tumour size and node status were computed one at a time in

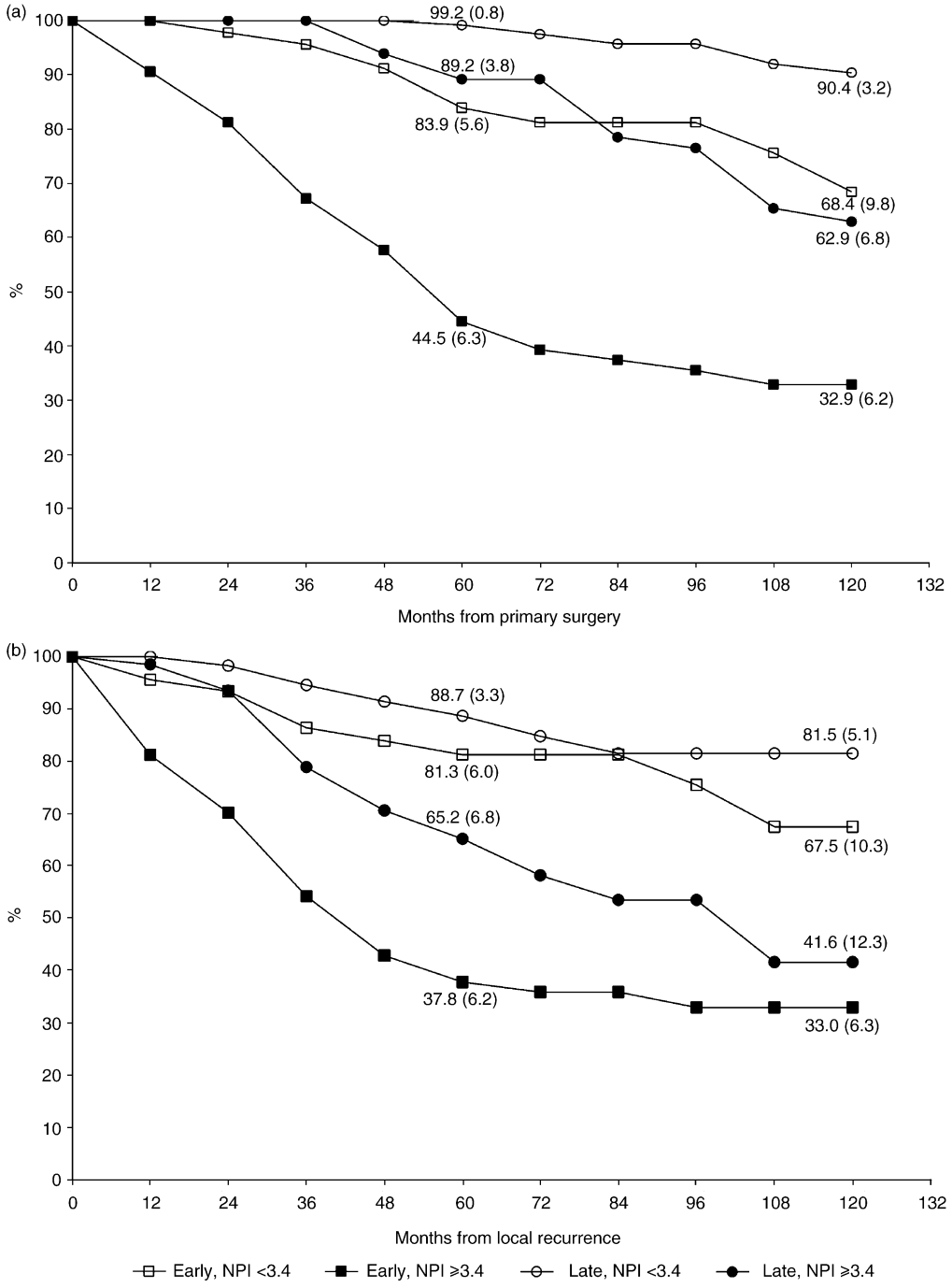

Fig. 4. Life-table curves showing estimated probabilities of breast cancer-specific survival in 391[a] women with local recurrence after breast-conserving surgery from 1981 to 1990 for invasive breast cancer, as measured from the primary operation (a) and from local recurrence (b). The analysis is stratified for time of appearance of local recurrence and the Nottingham Prognostic Index (NPI) (5- and 10-year estimates are given with their standard errors). [a]Due to missing data, these analyses are based on only 309 women.

the multivariate analysis of prognostic factors. By stepwise regression backwards, potential explanatory variables were studied to evaluate whether they contributed to the model fit or if the parameter estimates of the main variables of the study changed when they were removed [28]. The estimates of the models are given as relative hazards (RH) with 95% confidence intervals (95% CI).

3. Results

3.1. Patient characteristics

Table 1 shows characteristics of the 391 patients with local recurrence. Most of the recurrences appeared in the area of the previous excision (70.1%). In 59 women (15.1%) the recurrence was multicentric and in six women (1.5%) there were inflammatory signs. 34.5% of the recurrences appear early ($\leqslant 2$ years). Recurrences in the same quadrant as the primary tumour appeared earlier than those in another quadrant.

A comparison of the subgroups of local recurrences with respect to the time of occurrence and location (Table 1) showed that mean tumour size and proportion of primary tumours treated without radiotherapy differed between early recurrences in the same quadrant versus late recurrences in another quadrant. The proportion of women with a low NPI (<3.4) also differed between these two subgroups. The proportion of node-positive patients in the group of multicentric recurrences was higher than the average.

More than 50% of the recurrences came from the 30% of the cohort that was not irradiated (Table 1). A comparison of the subgroups of local recurrences with respect to radiotherapy showed that the women with local recurrences occurring without prior radiotherapy were older, were less likely to be node-positive and more likely to have a low NPI (<3.4).

Analysis of the cumulative probability of local recurrence in those given radiotherapy at the primary treatment (Fig. 1) shows that the probability for irradiated women is substantially lower throughout the observed period. Furthermore, women who had recurrences despite radiotherapy recurred later. The curves do not seem to level out for either group during the 10 years of follow-up.

3.2. Breast cancer-specific survival

During follow-up, 103 women died from breast cancer. The life-table estimates for breast cancer-specific survival as measured from primary treatment were 84.5% (S.E. 1.8) at 5 years and 70.9% (S.E. 2.7) at 10 years. Life-table analysis of breast cancer-specific survival *after* a local recurrence, using follow-up from the appearance of the recurrence, gave estimates of 72.5% (S.E. 2.5) at 5 years and 62.4% (S.E. 3.7) at 10 years for all recurrences.

3.3. Radiotherapy and breast cancer-specific survival

Life-table analysis of breast cancer-specific survival using follow-up from the primary operation, show a somewhat higher, but not statistically different ($P=0.2073$), risk of breast cancer death in women with a local recurrence presenting after irradiation compared with women with recurrences appearing without prior radiotherapy (Fig. 2a). The difference in the probability of breast cancer-specific survival *after* local recurrence between recurrences appearing with and without prior radiotherapy was, however, statistically significant ($P=0.0123$) (Fig. 2b).

Table 2
Multivariate Cox proportional hazards analysis of prognostic factors for breast cancer-specific survival, as measured from primary operation, in 391[a] patients with local recurrence after breast-conserving surgery from 1981 to 1990 for invasive breast cancer; stratified for the time of appearance of local recurrence

Age group (years)	Early LR ($n=135$)			Late LR ($n=256$)		
	Number	RH[b]	95% CI	Number	RH	(95% CI)
<40	17	1.1	(0.4–3.1)	24	1.5	(0.5–4.0)
40–49	33	0.9	(0.3–2.7)	49	0.7	(0.3–2.0)
50–59	19	1.0	Ref.	45	1.0	Ref.
60–69	21	0.6	(0.2–1.9)	49	1.3	(0.5–3.7)
70–79	12	1.8	(0.5–5.9)	26	1.8	(0.5–6.8)
⩾80	1	–	–	2	–	–
Total	103			196		
NPI						
<3.4	45	1.0	Ref.	131	1.0	Ref.
⩾3.4	58	**3.7**	**(1.6–8.7)**	64	3.1	**(1.5–6.2)**
Total	103			195		
Radiotherapy						
Yes	32	**2.3**	**(1.0–4.8)**	114	2.2	(0.9–5.3)
No	71	1.0	Ref.	81	1.0	Ref.
Total	103			195		
Location of LR						
Same quadrant	81	1.0	Ref.	131	1.0	Ref.
Other quadrant	7	0.4	(0.1–1.7)	34	0.9	(0.4–2.3)
Multifocal	15	**3.3**	**(1.5–7.5)**	30	1.4	(0.6–3.4)
Total	103			195		

RH, relative hazard; CI, confidence interval; Ref., reference; NPI, Nottingham Prognostic Index; LR, local recurrence; *n*, number.

[a] Due to missing data the full multivariate analyses are based on only 103 and 195 patients.

[b] Significant relative hazards are shown in bold.

3.4. Time and location of recurrence and breast cancer-specific survival

The risk of breast cancer death was highest among women who had an early (⩽2 years) recurrence in the same quadrant as the primary tumour (Fig. 3a), closely followed by multicentric recurrences that led to almost the same probability of death from breast cancer. Late recurrences (>2 years) were associated with a low probability of death. The corresponding life-table analyses of breast cancer-specific survival as measured from the recurrence are shown in Fig. 3b.

3.5. NPI, time to recurrence and breast cancer-specific survival

A stratification for NPI and time to recurrence gave a wide separation of the survival estimates (Fig. 4a and b). Between women with an early recurrence (⩽2 years) with a high NPI (⩾3.4) and those with a late recurrence with a low NPI (<3.4), there was an approximate 50% absolute difference in the ten year survival estimates (Fig. 4a). For the other two strata, survival prospects were similar.

3.6. Distant disease-free survival

Distant metastatic disease developed in 136 of the 391 women during follow-up. The probability of distant disease-free survival was 84.0% (S.E. 1.9) at 5 years and 65.1% (S.E. 2.8) at 10 years. An analysis of distant disease-free survival in the different groups of recurrences showed that the probabilities were distributed similarly to those for breast cancer-specific survival.

3.7. Cox proportional hazards analyses

In multivariate Cox analyses of prognostic factors for breast cancer-specific survival, tumour size and axillary node status did not show statistical significance for either variable in any of the constructed models (data not shown). However, NPI was an important prognostic factor in all subgroups of local recurrences and was therefore used in all of the multivariate models (Tables 2–4).

When the analyses were stratified for time to recurrence (⩽2 years or >2 years), to explore if early and late recurrences have different natural histories, a multicentric appearance of the recurrence was statistically significantly associated with an increased risk of death

Table 3
Multivariate Cox proportional hazards analysis of prognostic factors for breast cancer-specific survival, as measured from primary operation, in 391[a] patients with local recurrence after breast-conserving surgery from 1981 to 1990 for invasive breast cancer; stratified for the localisation of local recurrence

Age group (years)	Same quadrant ($n=274$[b])			Other quadrant ($n=44$[b])			Multifocal LR ($n=59$[b])		
	Number	RH	(95% CI)	Number	RH	(95% CI)	Number	RH	(95% CI)
<40	27	1.3	(0.6–2.8)	6	0.5	(0.03–8.9)	8	1.6	(0.1–18.2)
40–49	61	0.6	(0.3–1.4)	12	1.6	(0.2–16.1)	9	1.3	(0.1–13.3)
50–59	48	1.0	Ref.	9	1.0	Ref.	7	1.0	Ref.
60–69	45	0.6	(0.2–1.4)	11	3.6	(0.4–37.2)	14	2.1	(0.2–20.6)
70–79	29	1.8	(0.7–4.4)	3	–	–	6	3.9	(0.2–65.0)
>80	2	–	–	0	–	–	1	–	–
Total	212			41			45		
NPI									
<3.4	128	1.0	Ref.	24	1.0	Ref.	24	1.0	Ref.
⩾3.4	85	**2.6**	**(1.4–4.9)**	17	**10.3**	**(1.2–84.6)**	21	**8.8**	**(2.3–33.0)**
Total	212			41			45		
Radiotherapy									
Yes	100	**3.0**	**(1.6–5.9)**	25	0.5	(0.1–3.3)	21	2.3	(0.6–9.3)
No	112	1.0	Ref.	16	1.0	Ref.	24	1.0	Ref.
Total	212			41			45		
Appearance of LR									
Early (⩽2 years)	81	1.0	Ref.	7	1.0	Ref.	15	1.0	Ref.
Late (>2 years)	132	**0.2**	**(0.1–0.4)**	34	1.2	(0.1–10.4)	30	0.03	**(0.004–0.2)**
Total	212			41			45		

RH, relative hazard; CI, confidence interval; LR, local recurrence; Ref., reference; NPI, Nottingham Prognostic Index, *n*, number.
[a] Data about the location of recurrence was missing for 14 patients.
[b] Due to missing data, the full multivariate analyses are based on only 212, 41 and 45 patients, respectively.
Significant relative hazards are shown in bold.

Table 4
Multivariate Cox proportional hazards analysis of prognostic factors for breast cancer-specific survival, as measured from primary operation, in 391[a] women with local recurrence after breast-conserving surgery for invasive breast cancer; stratified for radiotherapy at primary surgery

Age group (years)	LR after primary RT ($n=185$)			LR without primary RT ($n=205$)		
	Number	RH	(95% CI)	Number	RH	(95% CI)
<40	28	0.5	(0.2–1.6)	11	2.4	(0.8–7.4)
40–49	51	0.6	(0.2–1.6)	29	1.2	(0.4–3.8)
50–59	29	1.0	Ref.	34	1.0	Ref.
60–69	26	1.4	(0.5–3.9)	43	0.8	(0.3–2.3)
70–79	6	0.9	(0.2–4.7)	32	2.8	(0.9–9.1)
⩾80	0	–	–	3	–	–
Total	140			152		
NPI						
<3.4	77	1.0	Ref.	98	1.0	Ref.
⩾3.4	63	**2.3**	**(1.2–4.7)**	54	**5.0**	**(2.2–11.2)**
Total	140			152		
Appearance of LR						
Early (⩽2 years)	27	1.0	Ref.	71	1.0	Ref.
Late (>2 years)	113	**0.1**	**(0.05–0.3)**	81	**0.2**	**(0.1–0.5)**
Total	140			152		
Location of LR						
Same quadrant	96	1.0	Ref.	112	1.0	Ref.
Other quadrant	25	0.4	(0.2–1.2)	16	1.1	(0.3–4.1)
Multifocal	19	1.2	(0.5–3.1)	24	**2.8**	**(1.2–6.5)**
Total	140			152		

RH, relative hazard; CI, confidence interval; RT, radiotherapy; NPI, Nottingham Prognostic Index; LR, local recurrence; Ref., reference, *n*, number.

[a] Due to missing data the full multivariate analyses was based on only 140 and 152 women.

Significant relative hazards are shown in bold.

from breast cancer for early recurrences (RH 3.3 (95% CI 1.5–7.5)) (Table 2). Both for early and late recurrences, radiotherapy was associated with a RH of approximately 2, these were on the verge of being statistically significant.

To further investigate if the location of the recurrence is a marker of recurrences with different types of clinical behaviour, we stratified analyses according to whether the recurrence appeared in the same quadrant, other quadrant or was multicentric. A late recurrence carried a markedly lower risk of death from breast cancer for recurrences in same quadrant (RH 0.2 (0.1–0.4)) and multicentric recurrences (RH 0.03 (0.004–0.2)) in contrast to recurrences located in other quadrants. A high NPI had a quantitatively larger impact in women with recurrences in other quadrants and multicentric tumours (Table 3).

Time of local recurrence was also, in an analysis stratified for radiotherapy, an important prognostic factor for breast cancer-specific survival. A late recurrence had a lower risk of death from breast cancer for recurrences after prior radiotherapy (RH 0.1 (0.05–0.3), as well as recurrences without prior radiotherapy (RH 0.2 (0.1–0.5)) (Table 4).

4. Discussion

In this study of prognosis after local breast recurrence, the first main finding is the clear prognostic impact of the time elapsed since the primary operation, which was stronger than the location of the recurrence in relation to the primary tumour. Secondly, radiotherapy saves a substantial proportion of the women from a local recurrence and may delay a recurrence for others, but has little influence on breast cancer-specific survival. The hitherto reported worse survival after local recurrences despite radiotherapy, as measured from the time of recurrence [7], may be partly due to a lead-time bias. Furthermore, in the different subgroups of women with local recurrence in the breast, defined by the time elapsed between the primary operation and recurrence and location of the recurrence, we found a prognostic impact of the NPI of the primary tumour.

Following the results of Whelan and colleagues [7], we expected a more sinister prognosis in women with local recurrence despite radiotherapy. There was only a tendency for this in the multivariate models. The findings concerning survival in this study in relation to radiotherapy should, however, be interpreted cautiously, since those not irradiated are a selected group concerning co-morbidity and risk of dying [19]. Only a small proportion of those not irradiated took part in randomised studies regarding radiotherapy or not after breast-conserving surgery. However, our previous cohort study [19] also revealed that the decision not to irradiate did not select a low-risk group concerning local recurrence. Thus, our findings which indicate a substantial reduction of local recurrences in absolute terms, a delay of local recurrences for some women, and a risk of local recurrence and/or new ipsilateral primary tumours that do not level off during 10 years of observation, should be generalisable. In addition, the selection mechanisms should not confound the comparison of the survival analyses as measured from the primary operation with those as measured from the local recurrence.

We found that a late recurrence and one located in another quadrant than the primary tumour was associated with a better prognosis in keeping with the notion that a large proportion of these recurrences may be new tumours. The prognosis after late local recurrences was similar to that expected after a contralateral cancer [29,30] also in our own source population of the recurrences (89.3 and 76.8% breast cancer-specific survival at 5 and 10 years, respectively) [19]. In this study, the time to recurrence was more closely associated with prognosis than the location of the recurrence. Multicentricity, however, was associated with a worse prognosis in several models. When we corrected for age and NPI, time to recurrence had a strong negative association with the risk of breast cancer death, whether we stratified for the location of the recurrence or previous radiotherapy.

The present study is to our knowledge the first to systematically test for the optimal, clinically meaningful cut-off point to distinguish between early and late recurrences with regard to prognosis for groups of women. The ROC curve (see Methods) clearly indicates that 2 years is a reasonable cut-off. However, low sensitivity and specificity indicate that, in decision-making for the individual, other prognostic markers should be taken into account. Interestingly, the addition of NPI separated out two groups at the extreme with a clinically highly relevant difference in prognosis in absolute terms: a good prognosis group with low NPIs and late recurrences and a bad prognosis group with high NPIs and early recurrences. However, there were no clear indications that effect of NPI varied quantitatively in the different strata according to the time or location of the recurrence. This pattern is in accordance with the fact that the behaviour of the metastases is associated with the characteristics of the primary, as well as the observation that the characteristics of the first tumour as well as the second—and the time interval between them—influence the prognosis in bilateral breast cancer [29].

In this setting, we cannot reliably tell which recurrences are 'true' recurrences and which are new primary tumours. However, from a clinical standpoint, we can conclude that the time to recurrence, NPI and location of the tumour (especially information on multicentricity) can help us to distinguish groups of women where the prognosis resembles either that of a more aggressive recurring disease or that after metachronous bilateral disease.

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