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Isolated loco-regional recurrence of breast cancer is more common in young patients and following breast conserving therapy: Long-term results of European Organisation for Research and Treatment of Cancer studies

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ABSTRACT

The aim of this study was to evaluate prognostic factors for isolated loco-regional recurrence in patients treated for invasive stage I or II breast cancer. The study population comprised 3602 women who had undergone primary surgery for early stage breast cancer, who were enrolled in European Organisation for Research and Treatment of Cancer (EORTC) trials 10801, 10854, or 10902, by breast conservation (55%) and mastectomy (45%). The median follow-up time varied from 5.3 (range: 0.6–9.5) to 11.9 years (range: 0.6–17.4). Main outcome was the occurrence of isolated loco-regional recurrence. The results of multivariate analysis showed that younger age and breast conservation were risk factors for isolated loco-regional recurrence (breast cancer under 35 years of age versus over 50 years of age: hazard ratio 2.80 (95% CI 1.41–5.60)); breast cancer age 35–50 years versus over 50 years: hazard ratio 1.72 (95% CI 1.17–2.54); breast conservation (hazard ratio: 1.82 (95% CI 1.17–2.86)). After perioperative chemotherapy, less isolated loco-regional recurrences were observed (hazard ratio 0.63 (95% CI 0.44–0.91)). No significant interaction effects were observed. It is concluded that young age and breast conserving therapy are both independent predictors for isolated loco-regional recurrence. As an isolated loco-regional recurrence is a potentially curable condition, women treated with breast conservation or diagnosed with breast cancer at a young age should be monitored closely to detect local recurrence at an early stage.

1. Introduction

Loco-regional recurrence of breast cancer is of concern in breast cancer treatment, as it is a well-established independent risk factor for distant metastases and death [1,2]. Many studies have looked for factors associated with the increased risk of loco-regional recurrence [3]. A well-known risk factor is breast conserving surgery, being associated

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with a higher risk of loco-regional recurrence, compared with mastectomy [4–8]. Risk factors for local recurrence frequently reported in patients treated with breast conserving therapy are: positive margin status, extensive intraductal component and young age of diagnosis of primary tumour [3,9–12]. Risk factors commonly reported for loco-regional recurrence in patients treated primarily with mastectomy are histological grade, and extensive axillary node involvement [13,14]. We studied risk factors at primary diagnosis of early breast cancer associated with isolated loco-regional recurrence and other recurrences, including distant metastases or death irrespective of primary treatment. We focused on isolated loco-regional recurrences, because these recurrences are not associated with distant metastases and are, in principle, curable, To do this, we re-analysed the data of 3602 patients with early stage breast cancer surgically treated and recruited in three European Organisation for Research and Treatment of Cancer (EORTC) trials (studies 10801, 10854 and 10902). Within all three studies patients were treated with mastectomy or with breast conserving therapy, which allowed us to study prognostic factors in relation to primary treatment.

2. Patients and methods

2.1. *Selection of trials and patients*

Patients were selected from trials that randomised early stage breast cancer patients. EORTC has conducted several large randomised phase III trials concerning the optimal management of breast cancer in patients with stage I or II breast cancer. A total of 4395 breast cancer patients have been enrolled for these trials; EORTC trials 10801, 10854 and 10902. Patients treated with pre-operative chemotherapy ($n = 377$), those not eligible for the study (due to false inclusion or severe protocol violation, $n = 88$), those with stage III breast cancer ($n = 238$) and those without full information on all co-variates ($n = 90$) were excluded from the analysis. A summary of the 3602 included patients is given in Table 1. For a short summary of the outcomes, the median overall follow-up times, and the median follow-up times to first event, see Table 2. A brief description of these trials follows.

EORTC trial 10801 (1980–1986) was conducted in order to assess the safety of breast conserving treatment. In this trial, patients were randomised between breast conserving surgery

Table 1 – Characteristics of the 3602 patients included in this analysis

Characteristics	Study			Total
	10801	10854	10902	
	n (%)	*n* (%)	*n* (%)	*n* (%)
Age at diagnosis (years)				
>50	502 (58.5)	1429 (56.8)	86 (37.7)	2017 (56.0)
35–50	317 (36.9)	970 (38.6)	122 (53.5)	1409 (39.1)
⩽35	39 (4.5)	117 (4.7)	20 (8.8)	176 (4.9)
Tumour size (cm)				
<2	167 (19.5)	801 (31.8)	38 (16.7)	1006 (27.9)
2–5	691 (80.5)	1715 (68.2)	190 (83.3)	2596 (72.1)
Nodal state				
Node-negative	502 (58.5)	1360 (54.1)	83 (36.4)	1945 (54.0)
Node-positive	356 (41.6)	1156 (45.9)	145 (63.6)	1657 (46.0)
Surgical therapy				
Mastectomy	414 (48.3)	1030 (40.9)	162 (71.1)	1606 (44.6)
Breast conserving therapy	444 (51.7)	1486 (59.1)	66 (28.9)	1996 (55.4)
Perioperative chemotherapy				
No	858 (100)	1261 (50.1)	228 (100)	2347 (65.2)
Yes	–	1255 (49.9)	–	1255 (34.8)
Adjuvant chemotherapy				
No	709 (82.6)	2061 (81.9)	–	2770 (76.9)
Yes	149 (17.4)	455 (18.1)	228 (100)	832 (23.1)
Adjuvant radiotherapy				
No	243 (28.3)	533 (21.2)	83 (36.4)	859 (23.8)
Yes	615 (71.7)	1983 (78.8)	145 (63.6)	2743 (76.2)
Tamoxifen				
No	858 (100)	1827 (72.6)	137 (60.1)	2822 (78.3)
Yes	–	689 (27.4)	91 (39.9)	780 (21.7)

Table 2 – Follow-up and first events for the patients included in this analysis

Outcomes (first events)	Study			Total
	10801	10854	10902	
	n (%)	*n* (%)	*n* (%)	*n* (%)
Isolated loco-regional recurrences, 2 years event-free[a]	47 (5.5)	122 (4.8)	3 (1.3)	172 (4.8)
Distant metastasis or death, or loco-regional recurrences with events in 2 years follow-up[b]	318 (37.1)	803 (31.9)	61 (26.8)	1182 (32.8)
Median (range) follow-up time (years)	11.9 (0.6–17.4)	10.2 (0.2–14.2)	5.3 (0.6–9.5)	10.2 (0.2–17.4)
Median (range) follow-up time to first event	11.0 (0.1–17.4)	9.5 (0.1–14.1)	4.9 (0.5–9.5)	9.2 (0.1–17.4)

a Without distant metastasis or death within 2 years of follow-up.
b With distant metastasis or death within 2 years of follow-up.

combined with radiotherapy, and modified radical mastectomy. Six cycles of adjuvant chemotherapy with cyclophosphamide (100 mg/m^2) given orally on days 1–14, methotrexate (40 mg/m^2) given intravenously on days 1 and 8, and 5-fluorouracil (600 mg/m^2) given intravenously on days 1 and 8, were indicated for all patients under the age of 55 years with positive nodes. No information was collected on hormonal therapy. In this study, 902 patients were randomised [5,15,16].

EORTC trial 10854 (1986–1991) considered the question of whether one course of perioperative chemotherapy given directly after surgery yields better results in terms of treatment outcome than surgery alone. Perioperative chemotherapy consisted of one single course of doxorubicin (50 mg/m^2), 5-fluorouracil (600 mg/m^2) and cyclophosphamide (600 mg/m^2) (FAC), administered intravenously within 36 h after surgery. It was recommended that axillary lymph node-positive pre-menopausal patients in the perioperative chemotherapy group received an extra five cycles of cyclophosphamide, methotrexate and 5-fluorouracil (CMF). The advice for node-positive patients, younger than 50 years, who did not receive perioperative chemotherapy, was one conventional course of FAC followed by five cycles of CMF after surgery. Patients were stratified for breast conserving therapy and modified radical mastectomy. Prolonged adjuvant systemic treatment was left to the discretion of the local investigators. A total of 2795 patients were included in this trial [17–19].

EORTC trial 10902 (1991–1999) was set up to determine the value of pre-operative chemotherapy. Patients were randomised to receive four cycles of chemotherapy either before or after surgery. Chemotherapy consisted of four cycles of 5-fluorouracil (600 mg/m^2), epirubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) (FEC) administered intravenously, at 3-weekly intervals. In the pre-operative chemotherapy group, surgical therapy followed within 4 weeks of the fourth course of chemotherapy. In the postoperative chemotherapy group, the first cycle was given within 36 h after surgery. A total of 698 patients were randomised [20].

2.2. *Assessments and statistical methods*

Endpoints for this study were: (i) isolated loco-regional recurrences, (ii) all other events, including distant metastases or death. Non-isolated loco-regional recurrences were considered as distant metastases. A loco-regional recurrence was defined as any recurrence in the ipsilateral breast, axilla or chest wall. A loco-regional recurrence was considered isolated if for a period of 2 years after the loco-regional recurrence occurred, no distant metastasis or death was observed. A loco-regional recurrence was considered non-isolated if distant metastasis was observed before, or concomitantly with, or within a period of 2 years after the occurrence of the loco-regional recurrence. In the database we could not discern breast cancer specific death from other causes of death, so all causes of death were considered as one group.

The following characteristics were considered: tumour size ($\leqslant$2 cm, 2–5 cm), axillary nodal status positivity (no, yes), oestrogen receptor positive (yes, no), age at diagnosis ($\leqslant$35, 36–50, >50 years), surgical therapy (mastectomy, breast conserving therapy), margins free (yes, no), perioperative chemotherapy (yes, no), adjuvant chemotherapy (yes, no), adjuvant radiotherapy (yes, no) and tamoxifen (yes, no) (see Table 1). The values for all characteristics were based on clinical observations.

Survival time was defined as the time between randomisation and the occurrence of the first events (loco-regional recurrence, distant metastasis or death from any cause) or last date of follow-up. Multivariate Cox proportional-hazard regression models were used to estimate hazard ratios with their 95% confidence intervals (CIs). All tests were two-sided. To test the assumption of proportional hazards, an interaction term of a prognostic variable and a time-dependent covariate was added [21]. To control for unmeasured possible differences in study populations, we added study as a factor in the multivariate Cox regression analysis.

Two years disease-free follow-up was taken as cut-off for an isolated loco-regional recurrence because the incidence of metastases lowers after that [22]. Because this point is not clear-cut, in a sensitivity analysis we varied this cut-off point between 3 months, 1 year and 5 years.

3. Results

In all, 55% of the patients underwent breast conserving therapy (Table 1). An isolated loco-regional recurrence without distant metastasis or death within 2 years of follow-up was observed in 172 (4.8%) of the patients (Table 2). Another event (a distant metastasis or death) occurred in 1182 (32.8%) of the patients. A total of 55 (32%) of the isolated loco-regional recurrences were seen in patients treated with mastectomy, and 117 (68%) were seen in patients treated with breast conserving therapy (data not in table).

Table 3 – Multivariate analyses of all patients related to outcomes (first events) (hazard ratios (HR) and 95% confidence interval (CI))

Characteristics	Isolated loco-regional recurrences, 2 years event-free[a] $n = 172$	Distant metastasis or death[b] $n = 1073$
	HR (95% CI)	HR (95% CI)
Age at diagnosis (years)		
>50	1	1
35–50	1.60 (1.14–2.25)	1.01 (0.87–1.16)
⩽35	2.34 (1.30–4.24)	1.55 (1.20–2.00)
Tumour size (cm)		
<2	1	1
2–5	1.12 (0.81–1.56)	1.56 (1.35–1.80)
Nodal state		
Node-negative	1	1
Node-positive	0.87 (0.55–1.38)	2.12 (1.81–2.47)
Surgical therapy		
Mastectomy	1	1
Breast conserving therapy	1.82 (1.17–2.86)	0.98 (0.86–1.13)
Perioperative chemotherapy		
No	1	1
Yes	0.63 (0.44–0.91)	0.94 (0.82–1.08)
Adjuvant chemotherapy		
No	1	1
Yes	0.63 (0.35–1.12)	0.66 (0.54–0.79)
Adjuvant radiotherapy		
No	1	1
Yes	0.66 (0.41–1.07)	1.00 (0.85–1.18)
Tamoxifen		
No	1	1
Yes	0.77 (0.42–1.41)	0.89 (0.73–1.07)

a Without distant metastasis or death within 2 years of follow-up.
b Including loco-regional recurrences with distant metastasis or death within 2 years of follow-up.

From the multivariate Cox regression analyses (Table 3) it appeared that significant risk factors for isolated loco-regional recurrence were: younger age at diagnosis of breast cancer, breast conserving therapy and no perioperative chemotherapy. Risk for isolated loco-regional recurrence for women under 35 years of age was compared with over 50 years of age: hazard ratio 2.34 (1.30–4.24); 35–50 years: hazard ratio 1.60 (1.14–2.25). Risk for loco-regional recurrence for breast conserving therapy compared with mastectomy: hazard ratio 1.82 (1.17–2.86). Less frequent isolated loco-regional recurrences were observed after perioperative chemotherapy (hazard ratio 0.63 (0.44–0.91)). In a model predicting loco-regional recurrence including age at diagnosis, surgical therapy and an interaction effect between these two, no statistically significant effects other than already reported, were observed (results not presented).

In the multivariate Cox regression analyses more distant metastases and deaths were observed in very young patients (under 30 years of age, hazard ratio: 1.55 (1.20–2.00)); in patients with larger tumour size (hazard ratio 1.56 (1.35–1.80)); and in patients with positive nodal status (hazard ratio 2.12 (1.81–2.47)). In patients treated with adjuvant chemotherapy less distant metastases or deaths were also observed (hazard ratio 0.66 (0.54–0.79)).

Subsequently the definition of an isolated loco-regional recurrence was varied: (a loco-regional recurrence was considered isolated if for a period of 3 months, 1 year and 5 years (instead of 2 years) after the loco-regional recurrence occurred, no distant metastasis or death was observed). It was found that a less restrictive definition (a shorter time-frame without any event after loco-regional recurrence was observed) reduced the prognostic effects of age and perioperative chemotherapy; meanwhile, it enhanced the prognostic effects of surgical therapy and adjuvant radiotherapy (see Table 4). A more restrictive definition (a longer time-frame after loco-regional recurrence without any event was observed) enhanced the prognostic effects of age and perioperative chemotherapy. Due to smaller numbers of patients, the confidence intervals are wider. With regard to distant metastasis, death, or non-isolated loco-regional recurrences, the hazards were not influenced, mainly due to the fact that the relative change in number was very small (results not presented).

4. Discussion

The major risk factor for an isolated loco-regional recurrence in this analysis was younger age as well as breast conservation (breast cancer under 35 years of age: hazard ratio 2.80 (1.41–5.60)); breast cancer between 35 and 50 years of age: hazard ratio 1.72 (1.17–2.54); breast conservation (hazard ratio: 1.82 (1.17–2.86)). No significant interaction effects between these two variables were observed. After perioperative chemotherapy, less isolated loco-regional recurrences were observed (hazard ratio 0.63 (0.44–0.91)), which has been published earlier [20]. Prognostic factors for distant metastases or deaths were larger tumour size (hazard ratio 1.56 (1.35–1.80)), positive nodal status (hazard ratio 2.12 (1.81–2.47)), and breast cancer under 35 years (hazard ratio 1.55 (1.20–2.00)). After adjuvant chemotherapy less distant metastases or death were observed (hazard ratio 0.66 (0.54–0.79)). No significant interaction effects were observed.

Young age (breast cancer diagnosed before 35 years) was a predictor for isolated loco-regional recurrence as well for other recurrences. Young age is generally accepted as being a prognostic factor for worse loco-regional control in breast cancer [3,9–12]. However, it has been reported that this is not the case for radical mastectomy [14]. Although the absolute number of isolated loco-regional recurrences was higher after breast conserving therapy than after mastectomy in our series, the effect of young age on the occurrence of isolated loco-regional recurrences was not different in patients treated with breast conserving therapy or mastectomy. Arriagada and colleagues found the same negative effect of young age as we did on loco-regional control irrespective of the type of surgery [14].

Table 4 – Results of sensitivity analysis; characteristics of all patients related to isolated loco-regional recurrences (multivariate, hazard ratios (HR) and 95% confidence interval (CI))

Characteristics	Isolated loco-regional recurrences, 3 months event-free[a] $n = 280$	Isolated loco-regional recurrences, 1 year event-free[b] $n = 228$	Isolated loco-regional recurrences, 5 years event-free[c] $n = 88$
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age at diagnosis (years)			
>50	1	1	1
35–50	1.46 (1.10–1.93)	1.47 (1.08–2.00)	2.04 (1.27–3.30)
⩽35	2.35 (1.48–3.74)	2.27 (1.36–3.80)	2.71 (1.17–6.28)
Tumour size (cm)			
<2	1	1	1
2–5	1.14 (0.88–1.49)	1.09 (0.82–1.45)	1.04 (0.66–1.64)
Nodal state			
Node-negative	1	1	1
Node-positive	1.14 (0.81–1.61)	1.08 (0.73–1.58)	0.66 (0.35–1.27)
Surgical therapy			
Mastectomy	1	1	1
Breast conserving therapy	2.14 (1.52–3.00)	2.10 (1.43–3.09)	1.85 (0.99–3.47)
Perioperative chemotherapy			
No	1	1	1
Yes	0.69 (0.53–0.93)	0.67 (0.49–0.92)	0.50 (0.29–0.87)
Adjuvant chemotherapy			
No	1	1	1
Yes	0.81 (0.53–1.22)	0.72 (0.47–1.15)	1.03 (0.43–2.47)
Adjuvant radiotherapy			
No	1	1	1
Yes	0.60 (0.41–0.87)	0.60 (0.40–0.91)	0.56 (0.29–1.09)
Tamoxifen			
No	1	1	1
Yes	1.01 (0.66–1.54)	0.88 (0.54–1.42)	1.34 (0.60–2.96)

a Without distant metastasis or death within 3 months of follow-up.
b Without distant metastasis or death within 1 year of follow-up.
c Without distant metastasis or death within 5 years of follow-up.

Other reported risk factors for local recurrences in patients treated with breast conserving therapy are positive margin status and extensive intraductal component [3,9–12]. Because these measurements were not consistently assessed in the included studies, they could not be studied. Risk factors reported for loco-regional recurrences in patients primarily treated with mastectomy are histological grade, and extensive axillary node involvement (10 nodes or more) [13,14]. We could not confirm these findings in our study, which might be explained by the more restricted definition of loco-regional recurrences we used (i.e., not followed by distant metastases within 2 years of follow-up). The impact of loco-regional recurrences on overall survival has not been demonstrated in trials which randomised between breast conserving therapy and mastectomy [13,23,24]. This means that some loco-regional recurrences are potentially curable, as they are not followed by further distant spread of the disease. Whether adjuvant chemotherapy is effective in these women is the subject of a randomised trial of the National Cancer Institute and the Breast International Group [25].

As outlined earlier, more loco-regional recurrences were observed after breast conserving therapy. It can be expected that, due to improvement in patient selection and treatment techniques, the differences will decrease between breast conserving therapy and mastectomy, with regard to the occurrence of loco-regional recurrences after breast conserving therapy [26]. This is also in accordance with the results of the EORTC trial that randomised between a conventional therapeutic regimen and an extra boost to the tumour bed after breast conserving surgery [27]. Local control was significantly improved by adding a radiation boost for patients with breast conservation.

This analysis shows that young age and breast conserving therapy are both independent predictors for isolated loco-regional recurrences. To reach optimal local control, young women and patients treated with breast conserving therapy should be monitored closely to detect local breast cancer recurrences at an early stage.

Conflict of interest statement

None declared.

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