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The impact of loco-regional recurrences on metastatic progression in early-stage breast cancer: a multistate model

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Abstract To study whether the effects of prognostic factors associated with the occurrence of distant metastases (DM) at primary diagnosis change after the incidence of loco-regional recurrences (LRR) among women treated for invasive stage I or II breast cancer. The study population consisted of 3,601 women, enrolled in EORTC trials 10801, 10854, or 10902 treated for early-stage breast cancer. Data were analysed in a multivariate, multistate model by using multivariate Cox regression models, including a state-dependent covariate. The presence of a LRR in itself is a significant prognostic risk factor (HR: 3.64; 95%-CI: 2.02–6.5) for the occurrence of DM. Main prognostic risk factors for a DM are young age at diagnosis (≤40: HR: 1.79; 95%-CI: 1.28–2.51), larger tumour size (HR: 1.58; 95%-CI: 1.35–1.84) and node positivity (HR: 2.00; 95%-CI: 1.74–2.30). Adjuvant chemotherapy is protective for a DM (HR: 0.66; 95%-CI: 0.55–0.80). After the occurrence of a LRR the latter protective effect has disappeared ($P = 0.009$). The presence of LRR in itself is a significant risk factor for DM. For patients who are at risk of developing LRR, effective local control should be the main target of therapy.

Keywords Breast cancer · Follow-up studies · Women · Local recurrences · Distant metastasis · Prognostic factors · Survival analysis · Meta-analysis · Multistate model

Introduction

Breast-conserving surgery is associated with a higher risk of loco-regional recurrences (LRR), as compared to mastectomy [1–5]. However, the impact of LRR on overall survival has not been demonstrated in trials which randomized between breast-conserving therapy and mastectomy [6–8]. A common explanation of these data is that the most important therapy in breast cancer is effective systemic therapy. Another explanation is that local control is a very important in the treatment of breast cancer, but that these trials did not have the power to study the impact of LRR on overall survival, due to the low incidence of LRR as compared to distant metastases (DM). It is reasonable to suppose that there is a group of LRR after primary treatment that are not associated with DM or death and that are potentially curable. In these recurrences early diagnosis can prevent the development of distant metastasis [9]. In addition, in a recent meta-analysis it was found

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that avoiding LRR lead to the avoidance of DM and breast cancer-specific death [10]. On this basis it might be useful if at the time of primary treatment we could identify prognostic risk factors associated with an increased risk of developing LRR followed by DM. Therefore, we studied whether the effects of prognostic risk factors associated with DM at primary diagnosis change after the incidence of LRR.

The aim of this analysis was to study the effect of prognostic factors known at primary diagnosis on the occurrence of DM. The effects were estimated for patients without any occurrence of LRR and for patients after the occurrence of LRR. In this way we were able perform a formal test on the equality of these effects, and to test the effect of LRR on the occurrence of DM. To do this, using a multivariate multistate model, we reanalysed the data of 3,601 patients with early-stage breast cancer who were surgically recruited in three EORTC trials (studies 10801, 10854 and 10902). Using this approach, we discerned three outcomes (no recurrence, LLR and DM) over the course of the disease after primary surgery, and using one model we studied the effect of all prognostic factors for each outcome.

Methods

Selection of trials and patients

Patients were selected from trials that randomized early-stage breast cancer patients. The European Organisation for Research and Treatment has conducted several large randomized phase III trials concerned with the optimal management of breast cancer in patients with stage I or II breast cancer. A total number of 4,395 breast cancer patients were enrolled for these trials, EORTC trial 10801, 10854 and 10902. Patients treated with preoperative chemotherapy ($n = 377$), patients not eligible for the study (due to false inclusion or severe protocol violation, $n = 88$), patients with stage III breast cancer ($n = 238$), and patients without full information on all covariates ($n = 91$) were excluded from the analysis. A summary of the 3,601 patients included is provided in Table 1. For a short summary of the events and the median follow-up times, see Table 2. A brief description of these trials follows.

EORTC trial 10801 (1980–1986, median follow-up 13.4 years) was conducted in order to assess the safety of

Table 1 Characteristics of patients, for all studies and total

Characteristics	Study			Total *N* (%)
	10801 *N* (%)	10854 *N* (%)	10902 *N* (%)	
Age at diagnosis				
≥50	530 (61.8)	1,512 (60.1)	93 (40.8)	2,135 (59.3)
40–50	244 (28.5)	720 (28.6)	96 (42.1)	1,060 (29.4)
<40	83 (9.7)	284 (11.3)	39 (17.1)	406 (11.3)
Tumour size				
<2 cm	167 (19.5)	801 (31.8)	38 (16.7)	1,006 (27.9)
2–5 cm	690 (80.5)	1,715 (68.2)	190 (83.3)	2,595 (72.1)
Nodal state				
Node-negative	501 (58.5)	1,360 (54.1)	83 (36.4)	1,944 (54.0)
Node-positive	356 (41.6)	1,156 (45.9)	145 (63.6)	1,657 (46.0)
Surgical therapy				
Mastectomy	413 (48.3)	1,030 (40.9)	162 (71.1)	1,605 (44.6)
Breast-conserving therapy	444 (51.7)	1,486 (59.1)	66 (28.9)	1,996 (55.4)
Perioperative chemotherapy				
No	857 (100)	1,261 (50.1)	228 (100)	2,346 (65.2)
Yes	–	1,255 (49.9)	–	1,255 (34.8)
Adjuvant chemotherapy				
No	708 (82.6)	2,061 (81.9)	–	2,769 (76.9)
Yes	149 (17.4)	455 (18.1)	228 (100)	832 (23.1)
Adjuvant radiotherapy				
No	242 (28.3)	533 (21.2)	83 (36.4)	858 (23.8)
Yes	615 (71.7)	1,983 (78.8)	145 (63.6)	2,743 (76.2)

Table 2 Follow-up and events for the patients included in this analysis per study and in total

	Study			Total
	10801	10854	10902	
Total number of patients	857	2,516	228	3,601
Events	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Loco-regional recurrences	78 (9.1)	221 (8.7)	11 (4.8)	310 (8.6)
Distant metastases				
All distant metastases	330 (38.5)	833 (33.1)	61 (26.7)	1,224 (40.0)
Distant metastases after loco-regional recurrences	36 (4.2)	90 (3.5)	3 (1.3)	129 (3.5)
Median (range) follow-up time in years for the patients included in this analysis	11.9 (0.6–17.4)	10.2 (0.2–14.2)	5.3 (0.6–9.5)	10.2 (0.2–17.4)

breast-conserving treatment. In this trial, patients were randomized between breast-conserving surgery 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 with positive nodes. In this study, 902 patients were randomized [2, 11, 12].

EORTC trial 10854 (1986–1991, median follow-up 10.8 years) studied the question 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 of surgery. It was recommended that axillary lymph node-positive premenopausal patients in the perioperative chemotherapy group receive an extra five cycles of cyclophosphamide, methotrexate and 5-fluorouracil (CMF). Node-positive patients younger than 50 years who did not receive perioperative chemotherapy were advised to take 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. The trial included 2,795 patients [13–15].

EORTC trial 10902 (1991–1999, median follow-up 6.1 years) was set up to determine the value of preoperative chemotherapy. Patients were randomized 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-week intervals. In the preoperative 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 number of 698 patients were randomized [16].

Assessments and statistical methods

We modelled breast cancer disease progression as a multistate model. In this approach, transitions are assessed during the course of the disease and prognostic factors for each transition are studied [17, 18]. In our model there are three possible outcomes or states in which a patient may be at any time (see Fig. 1). After surgery, a patient may be without any recurrences due to the primary breast cancer, a patient may experience a LRR, or a patient may develop metastatic breast cancer disease. The directions of the arrows in Fig. 1 indicate the transitions between the three states that are logically possible. Transition 1 indicates the transition from 'without any recurrence' to 'LRR'; transition 2 indicates the transition from 'without any recurrence' to 'DM'; transition 3 indicates the transition from 'LRR' to 'DM'.

A LRR was defined as any recurrence in the breast, the chest wall, the axillary or supraclavicular lymph nodes. In

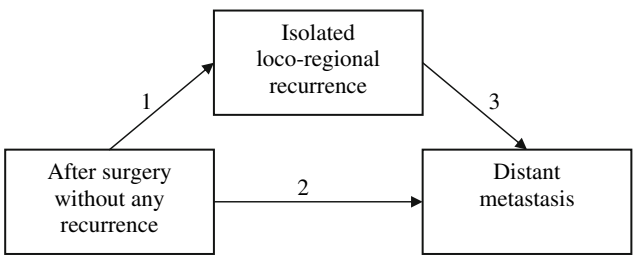

Fig. 1 Breast cancer disease progression as a multistate model. There are three possible states in which a patient may be at any time. After surgery, without any recurrence, loco-regional recurrence (LRR), distant metastasis (DM). *Arrow 1* indicates the transition from 'without any recurrence' to 'LRR'. *Arrow 2* indicates the transition from 'without any recurrence' to 'DM'. *Arrow 3* indicates the transition from 'LRR' to 'DM'

patients experiencing LRR after the diagnosis of DM, the LRR was not used as outcome. In the analyses, all primary sites of LRR were combined into one group of recurrences. Death was not considered as a separate outcome because all metastatic breast cancer disease will inevitably lead to death. In addition, the database did not allow us to discern breast cancer-specific death from other causes of death.

The following characteristics were considered for each transition: age at diagnosis (<40, 40–50, ≥50), tumour size (≤2 cm, 2–5 cm), axillary nodal status (0, ≥1), surgical therapy (mastectomy, breast-conserving therapy), perioperative chemotherapy (yes, no), adjuvant chemotherapy (yes, no), and adjuvant radiotherapy (yes, no), see Table 1. The values for all characteristics were based on clinical observations.

The beginning of follow-up corresponded to the time of randomization (close to the date of surgery). The end of follow-up corresponded to the incidence of distant metastases or the last date of follow-up (due to death, being lost to follow-up, or end of study).

The prognostic effect of all independent variables was measured by adjusted hazard ratios (HR) with 95% confidence intervals (95%-CI). To control for unmeasured possible differences in study populations, study group was added as a factor in all models. All analyses were performed with SPSS12.01. A significance level of 0.05 was used.

To estimate the adjusted hazard ratios for the transitions from surgery to LRR, a multivariate Cox proportional-hazard regression model was performed (results in Table 3, column 1).

Because we wanted to compare the transition from surgery to DM with the transition from LRR to DM, a multivariate Cox regression proportional-hazard model, including a time-dependent covariate, was performed to estimate the adjusted hazard ratios in tests related to these two transitions. As this time-dependent covariate refers to a state, it is further named a state-dependent covariate.

To estimate the adjusted hazard ratios for distant metastases after surgery, the state-dependent covariate was

Table 3 Characteristics of all patients with respect to parameter estimates related to each transition

Characteristics	Transition 1: from surgery to LRR	Transition 2: from surgery to DM	Transition 3: from LRR to DM	*P*-values for testing transition 2 versus transition 3
Numbers at risk	3,601	3,601	310	
Numbers of events	310	1,115	129	
Age at diagnosis	***P* = 0.001**	***P* < 0.001**	$P = 0.82$	0.17
≥50	1	1	1	
40–50	**1.42 (1.09–1.85)**	0.95 (0.81–1.11)	0.94 (0.62–1.41)	
<40	**1.79 (1.28–2.51)**	**1.45 (1.19–1.76)**	0.85 (0.51–1.42)	
Tumour size				
<2 cm	1	1	1	
2–5 cm	1.07 (0.83–1.37)	**1.58 (1.35–1.84)**	1.12 (0.74–1.69)	0.19
Nodal state				
Node-negative	1	1	1	
Node-positive	1.17 (0.89–1.55)	**2.00 (1.74–2.30)**	1.69 (0.13–2.53)	0.49
Surgical therapy				
Mastectomy	1	1	1	
Breast-conserving therapy	**2.26 (1.63–3.12)**	0.93 (0.81–1.07)	1.22 (0.70–2.11)	0.42
Perioperative chemotherapy				
No	1	1	1	
Yes	**0.68 (0.52–0.90)**	0.95 (0.82–1.09)	1.20 (0.81–1.77)	0.28
Adjuvant chemotherapy				
No	1	1	1	
Yes	0.82 (0.57–1.19)	**0.66 (0.55–0.80)**	1.35 (0.83–2.21)	**0.009**
Adjuvant radiotherapy				
No	1	1	1	
Yes	**0.59 (0.41–0.84)**	1.05 (0.88–1.25)	1.27 (0.70–2.32)	0.67
Loco-regional recurrence present			**3.64 (2.02–6.55)**	
Time to loco-regional recurrence			1.44 (0.99–2.10)	

Bold values refer to significant values

0 for patients without LRR. For patients with a LRR, this state-dependent covariate was 0 before the incidence of a LRR, and became 1 after the incidence of a LRR. This model allows an interpretation of the effects of the covariates as adjusted hazard ratios for DM without any LRR (results in Table 3, column 2).

To estimate the adjusted hazard ratios for DM after LRR, the state-dependent covariate was 1 for patients without a LRR. For patients with a LRR, it was 1 before the incidence of a LRR and became 0 afterwards, allowing the interpretation of the effects of the covariates as adjusted hazard ratios for DM after a LRR (results in Table 3, column 3).

In these two models, the state-dependent covariate itself indicates the prognostic risk of DM after LRR. The interaction of the state-dependent covariate with the other covariates provides a test of the changes in the effects of prognostic factors after LRR [18].

All prognostic factors were included, as well as the interaction of the prognostic factors with a state-dependent covariate. Finally, the model was extended with a second time-dependent covariate. This time-dependent covariate was 0 before the incidence of a LRR, and equivalent to the time (in years from randomization) of LRR. Incorporation of this second time-dependent covariate allowed us to study changes in the hazard ratio that might be related to the timing of the LRR.

Results

A LRR was observed in 310 (8.6%) of the patients, 1,224 (40.0%) of the patients had DM without LRR, while 129 (3.5%) of the patients had DM after LRR (Table 2).

The main prognostic risk factors for LRR were breast-conserving therapy (HR: 2.26; 95%-CI: 1.63–3.12) and young age at diagnosis (<40: HR: 1.79; 95%-CI: 1.28–2.51; 40–50: HR: 1.42; 95%-CI: 1.09–1.85) (Table 3). Perioperative chemotherapy (HR: 0.68; 95%-CI: 0.52–0.90) and adjuvant radiotherapy (HR: 0.59; 95%-CI: 0.41–0.84) lowered the risk of LRR.

Young age at diagnosis (<40: HR: 1.45; 95%-CI: 1.19–1.76), larger tumour size (HR: 1.58; 95%-CI: 1.35–1.84), and positive nodal state (HR: 2.00; 95%-CI: 1.74–2.30) were significant prognostic risk factors for DM. Adjuvant chemotherapy (HR: 0.66; 95%-CI: 0.55–0.80) lowered the risk of DM.

The presence of a LRR in itself was a significant prognostic risk factor (HR: 3.64; 95%-CI: 2.02–6.55) for DM. The longer time until the LRR was a borderline significant prognostic factor (HR: 1.44; 95%-CI: 0.99–2.10).

When testing the equality of the HRs related to the transition from surgery to DM and those related to the transition from LRR to DM, the HR for adjuvant chemotherapy was significantly different, indicating that after primary surgery adjuvant chemotherapy was statistically significant associated with a favourable prognostic effect on the incidence of DM, whereas after the incidence of the LRR primary adjuvant chemotherapy was no more statistically significant associated with an unfavourable prognosis (P-value for difference in the prognostic role of primary adjuvant chemotherapy: 0.009).

Discussion

We studied whether the effects of prognostic risk factors associated with DM at primary diagnosis change after the incidence of LRR among women treated for invasive stage I or II breast cancer. The presence of LRR in itself is a significant prognostic risk factor (HR: 3.64; 95%-CI: 2.02–6.5) for the occurrence of DM. Other main prognostic risk factors for DM are young age at diagnosis (≤40: HR: 1.79; 95%-CI: 1.28–2.51), larger tumour size (HR: 1.58; 95%-CI: 1.35–1.84) and node positivity (HR: 2.00; 95%-CI: 1.74–2.30). Adjuvant chemotherapy is protective for DM (HR: 0.66; 95%-CI: 0.55–0.80). After the occurrence of LRR this protective effect is no longer present ($P = 0.009$).

Young age, larger tumour size and nodal status are the most important prognostic factors for the occurrence of DM [for example, 19, 20]. Young age and breast-conserving therapy are often mentioned as risk factors for the incidence of LRR [for example, 21–23]. Other studies also report that patients with a LRR are at an increased risk of developing DM as compared to patients who develop no LRR [for example, 24–27]. We found that time from surgery until the loco-regional recurrence was not a significant prognostic factor, whereas in the literature there are many indications that earlier loco-regional recurrences are associated with worse patient outcome [28–30].

The effect of LRR on the occurrence of DM has been debated for decades [31]. On the one hand there is the view that breast cancer is a local disease that spreads over time to develop DM [32]. On the other hand there is the view that breast cancer is a systemic disease from the outset with DM present before primary diagnosis [33]. Though it is clear that the first view on the biology of breast cancer is not correct for all breast cancers, the systemic view is not entirely correct for all breast cancers either [31]. In this paper we hypothesised a model that is at least partly based on the first view of distant spread. Our finding that the presence of LRR in itself is a significant prognostic risk factor for the occurrence of DM gives some support for this hypothesis. Other data supporting this hypothesis are derived from randomized clinical trials demonstrating a link between local control and overall survival in breast

cancer [e.g., 10, 34, 35]. The statistical analysis presented in this paper is just an argument in the discussion on the effect of LRR on the occurrence of DM. However, it never can proof a causal relation.

The current analysis was based on a database of three trials with complete information on crucial parameters and long-term follow-up for more than 3,500 patients. The trials concerned patients treated for early breast cancer, and the patient, disease and treatment characteristics as well as the outcomes were registered in a comparable way, which allowed us to meta-analyse these three studies. Patients treated with preoperative chemotherapy were excluded because the pT-size of the tumours of these patients may not have been comparable to the pT-size of patients without this treatment.

To control for factors such as treatment (e.g., mastectomy versus breast-conserving therapy) only the results of the multivariate multistate analyses were presented. The various types of treatment were analyzed as separate components, due to the fact that in the older studies included not all patients were treated among the current pre-defined treatment schemes.

The aim of this analysis was to study the effect of prognostic factors known at primary diagnosis on the occurrence of DM. These effects were estimated for patients without any occurrence of LRR and for patients after the occurrence of LRR. In this way we were able perform a formal test on the equality of these effects, and to test the effect of LRR on the occurrence of DM. One of the strongest points of the multivariate multistate model applied in this paper is that all data are summarized in one model instead of presenting many separate analyses. Presenting many separate analyses will lower the power of the estimated effects or may result in false positive findings. Such an analysis can only be performed on a large cohort of patients with a long follow-up time. Only in such a cohort there are enough events of LRR and DM after the occurrence of LRR. For that reason we chose to analyse studies with the longest follow-up available.

A shortcoming of this study is that some data recognised as being related to important prognostic and predictive factors were missing from the database. Hormonal status was unknown for most patients, as was the use of Tamoxifen. Recording the number of positive nodes or a more detailed T stage, grade, margin status and lymphovascular invasion was not part of the protocol in these EORTC studies, so we were not able to include this information in our meta-analysis. This can be considered a limitation of our study because these factors allow the breast cancers to be further categorized with respect to risks which might influence the occurrence of LRR. Tailored systemic treatment making use of ER and PR receptors and HER2 is now state of the art [10]. Only the newer studies will include the newer predictive and prognostic factors, but these studies will not allow us to perform such long-term analyses due to their shorter follow-up.

The main finding of this study is that patients with a LRR have a more than three times increased risk of developing DM as compared to patients who develop no LRR. Due to a lowering incidence of LRR, especially after adjuvant therapy in node negative patients, this might be an overestimation of the effect of LRR on the occurrence of DM after LRR [36]. However, in a recent meta-analysis of the long-term effects of LRR on breast cancer mortality, it was concluded that for every four LRR that were avoided, one breast cancer death over the next 15 years could be avoided, and that this should reduce 15-year overall mortality [10]. Our study confirms these findings, as we found a strong association between the occurrence of a loco-regional recurrence and a distant metastasis (HR: 3.64; 95%-CI: 2.02–6.55).

This study again stresses the point that breast-conserving therapy is a risk factor for local recurrence and that patients with a loco-regional recurrence are at an increased risk of developing distant metastases as compared to patients who develop no loco-regional recurrence. This is also reported in other studies [for example, 25, 26]. Young patients are more at risk of developing local recurrences than older patients. Treatment selection at time of diagnosis, especially in young patients, should therefore focus on improvement of local control. Improvement of systemic treatment regimens will improve this local control, as will the provision of systemic adjuvant therapy [for example, 10, 37, 38] or an increase in the radiation dose on the tumour bed [for example, 36, 39].

A prediction of the risk of LRR at the time of diagnosis can guide treatment decisions and lead to optimal local control. These prognostic risk factors could be incorporated into a web-based tool and guide primary treatment choices, similarly to the web-based models that guide the optimal choice of adjuvant therapy by making use of prognostic factors for DM in predicting the outcome of early breast cancer (http://www.adjuvantonline.com/). Breast cancer before the age of 50 and breast-conserving therapy should be included in such a model as risk factors for the incidence of LRR. To build such a system, large databases with long follow-up times are needed.

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