Risk factors for late relapse and death in patients with early breast cancer

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Adjuvant treatments reduce the risk for recurrence and death from breast cancer; but even 10-15 years after diagnosis, these risks persist. The aim of our study was to identify prognostic factors for relapse and death in the second decade after primary surgery. Patients with early breast cancer treated from 1983-1987 (n=1035) were included. Patients' characteristics, tumor prognostic factors, treatments, data on recurrence and death were obtained from patients' charts and our cancer registry. Median follow-up was 17 (1-23) years. At 10 years after surgery, 515 (49.8%) patients were alive and of them 432 (41.7%) were relapse-free. Of the 432 patients being alive and relapse-free at 10 years 153 (35.4%) had an event thereafter, of them 38 (25%, 9% of all) had a relapse of breast cancer. For this period only the presence of lymphovascular invasion (LVI) and positive estrogen receptors (ER) were found as independent unfavorable prognostic factors for relapse-free (HR 2.09, p=0.007; HR 1.50, p=0.021, respectively) and overall survival (HR 2.15, p=0.006; HR 1.41, p=0.05, respectively) while tumor size, grade and nodal status had no prognostic significance. Positive ER and LVI are independent prognostic factors for relapse and death in the second decade after surgery in patients with early breast cancer.

Key words: breast cancer, estrogen receptors, late relapse, lymphovascular invasion

The peak annual hazard of relapse of early breast cancer is within the interval of 1 to 2 years and decreases consistently within the interval of 2 to 5 years but a substantial risk exists even many years after the primary treatment [1–3]. The peak hazard of relapse in estrogen receptor (ER) positive tumors occure later than in corresponding ER-negative tumors [1, 4]. Adjuvant hormonal treatment with tamoxifen diminishes the risk for relapse and death in ER-positive tumors. With 5 years of adjuvant tamoxifen the annual relapse rate was diminished by 41% (hazard ratio 0.59; SE 0.03) and the breast cancer mortality rate was reduced by 34% (hazard ratio 0.66; SE 0.04), as reported by Early Breast Cancer Trialists' Collaborative Group [5]. In ER-positive and ER-unknown group vs. corresponding control group the relative gain of 5 years of tamoxifen for relapse was 11.4%, 13.6% and 11.8% at 5, 10 and 15 years, respectively. The relative gain for mortality in tamoxifen-treated vs. non-treated group steadily increased being 3.6%, 7.9% and 9.2% at 5, 10 and 15 years, respectively [5]. As more than half of relapses occurred after 5 years of adjuvant tamoxifen, trials of extended adjuvant treatments started. Trial with letrozole vs. placebo after finishing approximately 5 years of tamoxifen (MA.17), conducted by National Cancer Institute of Canada Clinical Trials Group, already showed benefit in reducing 4-year DFS by 42% and even mortality by 18% in node positive patients [6]. Extended adjuvant hormonal therapy beyond 5 years in high risk (node positive) patients is therefore already evidence based. The question remains what is the appropriate duration of the extended therapy in order to reduce the relapse rate to minimum, and if there are possible additional prognostic factors associated with these late relapses that could be targeted. More in depth knowledge of the natural history of breast cancer (long term relapse rate) could be obtained from databases of patients with long term follow-up data.

The aim of our study was to identify risk factors for late relapse and death (in the second decade after primary surgery) in patients with early breast cancer.

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Patients and methods

Patients, staging procedures and treatments. Charts of all consecutive female breast cancer patients surgically treated at the Institute of Oncology, Ljubljana, Slovenia, between January the 1st 1983 and December the 31st 1987, were reviewed and included in our analysis. Data of patients' characteristics, tumor prognostic factors (tumor size, grade, lymphovascular invasion (LVI), estrogen receptors (ER), progesterone receptors (PgR), histology and nodal status), adjuvant treatments, data of relapse and death were collected from the patients' records and our national tumor registry.

In the staging procedure before surgery, chest x-ray and laboratory blood examination was performed. If the clinical or laboratory findings were suspicious, a bone or liver scan was performed to exclude bone or liver metastases. The lymph node status was determined by histological examination of all removed axillary lymph nodes. Histological grading was performed according to the Scarff-Bloom-Richardson method and was applied only for tumors of ductal type. Lymphovascular invasion was assessed in the peritumoral tissue on haematoxylin and eosin sections. It was defined as carcinoma cells present within a definite endothelial lined space (blood vessels or lymphatics) [7]. The assessment of steroid receptors status was done biochemically [8]. The cut-off value was 10 fmol/mg proteins for both ER and PgR receptors. Data about the type of surgery and adjuvant chemotherapy were collected. Chemotherapy consisted of Cyclophosphamide 600 mg/m2, Methotrexate 40 mg/m2, 5-flourouracil 600 mg/m2 on either day 1 and day 8 every 4 weeks or day 1 every 3 weeks (CMF schedule). The patients were followed-up regularly at our Institute. If the disease recurred, the patients were treated with chemotherapy (anthracyclines) and/or hormonal therapy if the tumor was ER and/or PgR positive.

Statistical analysis. Relapse-free survival (RFS) and overall survival (OS) were analyzed for the whole follow-up period and additionally for the period starting 10 years after surgery. Relapse-free survival was calculated as time from definitive surgery to (1) local or distal relapse or (2) death without relapse, or (3) last follow-up (censored observations). Overall survival was calculated as time between definitive surgery and the time of death of any cause or the time of last follow-up for living patients (censored observations).

The univariate statistical analysis was performed with Mann-Whitney U test, chi-square test, Kaplan-Meier survival analysis and log-rank test. Multivariate analysis was performed with Cox model. All statistical analyses were carried out with SPSS software v. 13.

Results

In the observed period 1035 female breast cancer patients with early breast cancer were treated with primary surgery. Median age was 57 years (min. 20, max. 87). Patients' and tumor characteristics are shown in Table1. Local therapy was the modified radical mastectomy in most cases (87%). Of patients treated with breast conserving surgery, only half were irradiated to the operated breast. An axillary dissection was performed in all 1035 patients, and a median of 16 (2-32) lymphnodes were removed. Adjuvant chemotherapy according to CMF schedule received 314 (30.3%) patients. Only 33 (6.8%) of node negative patients received adjuvant chemotherapy. It was used mainly in patients with positive axillary lymph nodes (in 81.9% of premenopausal and 34.6% of postmenopausal patients). Of all patients with ER and/or PgR positive tumors only 18% received adjuvant hormonal therapy with tamoxifen that was applied exclusively in postmenopausal

Table 1 Tumor characteristics and type of primary treatment in all patients at surgery and in patients relapse free at 10 years after surgery

	At surgery (n=1035)		Relapse free at 10 years (n=432)	
	n	%	n	%
Tumor size				
≤2 cm	447	43.2	242	56.0
>2 and ≤5 cm	523	50.5	177	41.0
>5 cm	65	6.3	13	3.0
Histology				
IDC	738	71.3	314	72.7
ILC	137	13.2	40	9.3
Other	160	15.5	78	18.1
Tumor grade				
Grade 1	186	18.0	112	25.9
Grade 2	409	39.5	148	34.3
Grade 3	222	21.4	94	21.8
Unknown	218	21.1	78	18.1
Lymphovascular invasion				
Absent	877	84.7	403	93.3
Present	158	15.3	29	6.7
Nodal involvement				
0	486	47.0	264	61.1
1-3	306	29.5	132	30.6
4-9	141	13.6	28	6.5
10 or more	102	9.8	7	1.6
Missing data	1	0.1	1	0.2
Hormone receptors				
ER neg	444	42.9	204	47.2
ER pos	515	49.8	199	46.1
Unknown	76	7.3	29	6.7
PR neg	552	53.3	235	54.4
PR pos	308	29.8	115	26.6
Unknown	175	16.9	82	19.0
Menopausal status				
Premenopausal	372	35.9	179	41.4
Postmenopausal	663	64.1	253	58.6

IDC – invasive ductal carcinoma, ILC – invasive lobular carcinoma, ER – estrogen receptors; PR – progesterone receptors

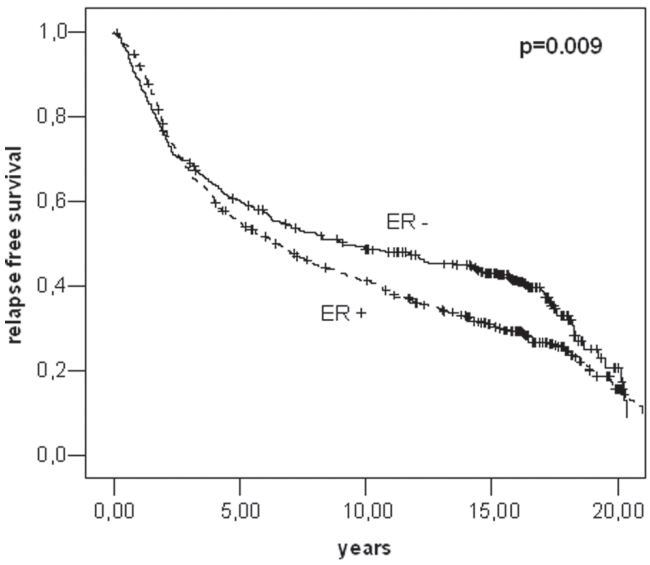

Figure 1. Relapse-free survival according to negative (-) or positive (+) estrogen receptors (ER).

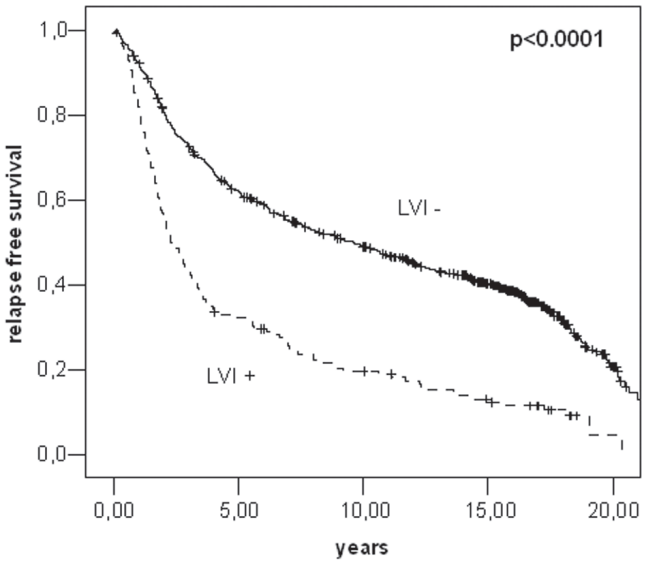

Figure 2. Relapse-free survival according to absent (-) or present (+) lymphovascular invasion (LVI).

patients. Median duration of hormonal therapy was 20 months (minimum 1, maximum 72). Median follow-up time was 17 (1-23) years. At 10 years after surgery, 515 (49.8%) patients were alive and of them 432 (41.7%) were relapse-free. Of the 432 patients being alive and relapse-free at 10 years 153 (35.4%) had an event thereafter, of them 38 (25%, 9% of all) had a relapse of breast cancer.

In Tables 2 and 3 results of multivariate analysis of independent risk factors for RFS and OS for the whole observation period and for patients being relapse-free at 10 years after surgery are presented. Nodal and tumor stage, LVI and ER were independent prognostic factors for both RFS and OS for the whole observation period. For patients being relapse-free at 10 years, thereafter only positive ER and the presence of LVI in the primary tumor were independent prognostic factors for RFS and OS. Kaplan-Meier survival curves illustrate the impact of ER and LVI on RFS and OS (Figures 1–4).

Table 2. Multivariate analysis – relapse-free survival for the whole observation period and ≥10 years after surgery

	Whole observation period		≥10 years after surgery	
	HR (95% CI)	p	HR (95% CI)	p
Nodal stage	1.56 (1.33-1.83)	<0.0001	NS	
Tumor stage	1.51 (1.32-1.73)	<0.0001	NS	
LVI	1.98 (1.63-2.40)	<0.0001	2.09 (1.22-3.59)	0.007
ER	1.24 (1.06-1.44)	0.008	1.50 (1.07-2.12)	0.021

HR – hazard ratio, CI – confidence interval, NS – non significant
Nodal stage: positive vs. negative axillary lymphnodes
Tumor stage: T3, T2 vs. T1
LVI: lymphovascular invasion present vs. absent
ER: positive vs. negative estrogen receptors

Both pre- and postmenopausal patients with ER-positive tumors had worse RFS and OS than those with ER–negative tumors. Due to a smaller number of patients in each group the difference was not significant.

Discussion

The purpose of this analysis was to identify possible risk factors for late relapse and death among patients with early breast cancer. We found that positive ER and the presence of LVI in primary tumors are the only risk factors with a significant impact on RFS and OS after 10 years after primary treatment.

More than one third of patients being relapse-free at 10 years had an event thereafter, 25% of them (9% of all) being relapses of breast cancer. In the report of Karrison et al [9], who analyzed the pattern of long-term relapses of patients treated and followed up from 1945–1987, 41 of 828 (5%) patients relapsed from 10–20 years post-operatively. They found stage III patients (tumors >5 cm with positive axillary nodes) to be at slightly higher risk for relapse in the second decade than lower stages. On the contrary, our results did not indicate, that nodal and tumor stage is a prognostic factor for RFS and OS after 10 years after surgery (Tables 2 and 3). The reason for this discrepancy could be because in the report of Karrison et al [9] ER and LVI were not studied because of older patients series.

Patients with ER-positive tumors had significantly lower RFS than those with ER-negative tumors. The difference began at 3 years post-surgery and curves diverged thereafter (Figure 1). The hazard ratio for relapse in ER-positive vs. ER-negative patients being relapse-free at 10 years after sur-

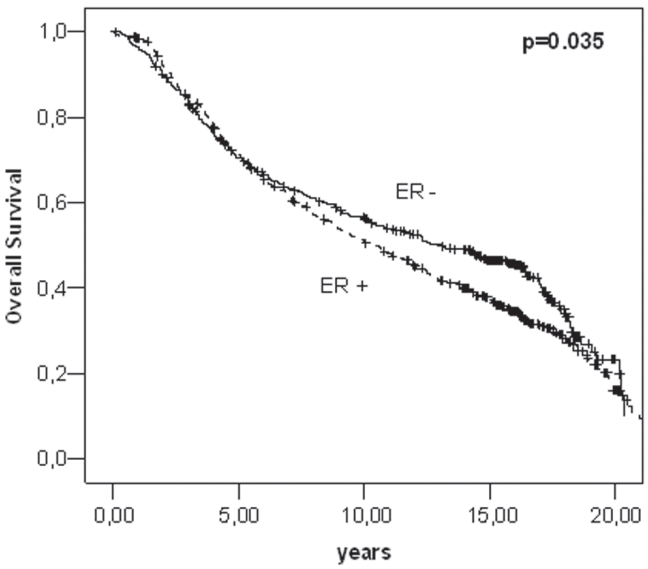

Figure 3. Overall survival according to negative (-) or positive (+) estrogen receptors (ER).

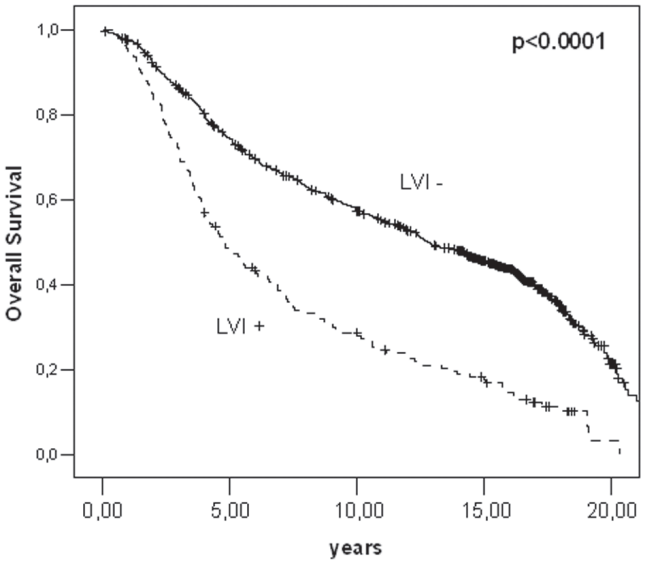

Figure 4. Overall survival according to absent (-) or present (+) lymphovascular invasion (LVI).

gery was 1.50, p=0.021 (Table 2). For OS, the difference among ER-positive and ER-negative patients occurred later (from 5th year on) and was less pronounced (Figure 3) and the hazard ratio for patients being relapse-free at 10 years after surgery was 1.41, p=0.05 (Table 3). This was probably because ER-positive patients received 2–3 lines of hormonal treatments in the metastatic setting since only 18% of our patients with ER-positive tumors received adjuvant hormonal therapy. Saphner et al [1] found an increased hazard of relapse in ER-negative patients in the interval of 1–3 years, thereafter hazard for ER-negative and ER-positive patients crossed and the hazard was higher in ER-positive patients. Our findings are similar to their data. Hortobagyi et al [2] also reported higher residual risk of ER-positive and/or PgR-positive tumors than hormone receptor negative tumors after 10 and 15 years after primary treatment in patients being relapse-free at 5 years. In concordance to our report they also reported that nodal status was not prognostic for relapse at 10 and 15 years after surgery. Hilsebeck et al [4] analyzed the time-dependence of hazard ratios for prognostic factors in large series of primary breast cancer patients (n=2875). For ER they found that ER-positivity is protective for early relapse, but switched to poor prognosis after 3 years. Studies with short follow-up (3–4 years) would therefore show only early effects of ER, while studies with longer follow-up (until 7–8 years) would show no effects of ER, because early and late effects cancel each other out. This was probably the reason, why ER were not prognostic for disease-free interval in the report of Trudeau et al [10] with 8 years of follow-up. In concordance with our series, Quiet et al [11] (826 node negative patients, median follow-up of 13.3 years) found that patients with ER-negative or borderline ER-positive tumors had an improved DFS and OS as compared with those with ER-positive tumors.

In our present work, LVI was an independent prognostic factor for the whole observation period with even stronger hazard ratio than nodal stage for both RFS and OS (Tables 2 and 3). Kaplan-Meier curves for RFS and OS (Figure 2 and 4) showed extremely dismal survival if tumors were LVI-positive. We should also take into account that only 15% of our patients had the presence of LVI in their tumors, which is in the range otherwise reported in node negative patients [10, 12]. The pathological assessment of LVI is to some extent subjective and both over- and under diagnosis is possible; this may in part explain the differences in the frequency of LVI observed in various series. It seems likely, however, that LVI was underreported in our series as pathology reports were not standardized in that period and the notion on absence or presence of LVI was not an obligatory part of the report. Even

Table 3. Multivariate analysis – overall survival for the whole observation period and ≥10 years after surgery

	Whole observation period		≥10 years after surgery	
	HR (95% CI)	p	HR (95% CI)	p
Nodal stage	1.58 (1.37-1.99)	<0.0001	NS	
Tumor stage	1.57 (1.36-1.81)	<0.0001	NS	
LVI	1.91 (1.57-2.34)	<0.0001	2.15 (1.25-3.69)	0.006
ER	1.19 (102-1.40)	0.032	1.41 (1.01-2.15)	0.05

HR – hazard ratio, CI – confidence interval, NS – non significant
Nodal stage: positive vs. negative axillary lymphnodes
Tumor stage: T3,T2 vs. T1
LVI: lymphovascular invasion present vs. absent
ER: positive vs. negative estrogen receptors

nowadays we do not have a standard method for LVI determination or a specific marker for lymphatic endothelium. In the future this might be podoplanin [13]. Nevertheless, Lauria et al [14] reported LVI as a strong poor prognostic factor in both lymph node negative and lymph node positive patients. Similarly, LVI was shown to be an independent prognostic factor in node-negative patients by Yildirim et al [15] and Trudeau et al [10] and added prognostic significance to the Nottingham prognostic index in women with lymph node-negative breast cancer. According to the latest St. Gallen recommendations [16, 17], node-negative patients with the presence of LVI fall into intermediate or high risk group of patients. For even better selection of patients for adjuvant treatments, the extent of LVI should be considered [17].

On the contrary to nodal and tumor stage, LVI remained as independent prognostic factor also after 10 years in our patients. However, as only 29 patients with LVI positive tumors were disease free at 10 years, and 11 events occurred in these patients thereafter we cannot make any firm conclusions of prognostic significance of LVI for this period.

In conclusion, positive ER and the presence of LVI are unfavorable prognostic factors for RFS and OS in the second decade after surgery for patients with early breast cancer. Patients with ER-positive tumors had more events than patients with ER-negative tumors after 10 years after surgery (HR=1.50). Positive ER may predict for slowly progressive tumors, that need longer time for relapse and probably need prolonged adjuvant hormonal therapy maybe even 10 years or more, irrespective of tumor or nodal stage at surgery.

The presence of LVI is a very strong unfavorable prognostic factor for the whole observation period; however its real role in the second decade is speculative because of the small number of LVI-positive cases remaining in this period. What is the exact mechanism of LVI is not yet known. The role of VEGF-C is proposed in lymphangiogenesis and also in lymphangiovascular invasion [18]. The presence of LVI could be therefore also a predictive factor for antiangiogenesis treatment.

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