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Predictors of Loco-Regional Recurrence and Cancer-Related Death after Breast Cancer Surgery

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■ **Abstract:** To determine which tumor-related factors might predispose the patient to loco-regional recurrence or death and the impact of these factors on the different types of events. We retrospectively analyzed the data of 1991 women between January 1998 and March 2010 for a first primary nonmetastatic breast cancer and treated with surgery and neo-adjuvant/adjuvant therapy. The overall survival distribution was estimated using the Kaplan–Meier method. The prognostic impact of several factors on cumulative overall and loco-regional recurrence free survival was evaluated by univariate (log-rank test) and multivariate analysis (Cox regression). At log-rank test, pT, nodal status, histotype, grading, lymphangioinvasive growth, tumor diameter, estrogen receptors (ER) status, progesterone receptors (PR) status, expression of Ki67, and expression of Her2/neu had a prognostic value on loco-regional recurrence or overall survival. In the multivariate analysis grading remained the only independent predictor of loco-regional recurrences. With regard to overall survival, the Cox model selected grading along with nodal status and PR status. Loco-regional recurrences after breast cancer surgery are not frequent events. They are markers of tumor aggressiveness and predictor of an increased likelihood of cancer-related death. However, loco-regional recurrence and systemic tumor progression are partially independent events, since some prognostic factors differ. ■

Key Words: breast cancer, loco-regional recurrence, predictive factors

Today, in minimally invasive surgery era, outcome of breast cancer patients after breast-conserving surgery seems better than outcome after mastectomy: actually, this effect is due to many early-stage diseases treated by conservative excision (1–4). However, while surgical procedure cannot be considered a prognostic factor for these patients, there is the need to detect reliable predictors of loco-regional recurrence, a marker of tumor aggressiveness linked to an increased risk of distant metastases and death (5–11). In fact, by identification of stronger pathologic and molecular predictors of loco-regional recurrence and more effective treatment strategies, the risk of local failure after breast surgery could decrease.

In this study, we analyzed data on 1991 women underwent surgery for breast cancer in order to determine which tumor-related factors might predispose the patient to loco-regional recurrence or death and to determine the impact of these factors on the different types of events.

PATIENTS AND METHODS

Study Population

We retrospectively analyzed the data of 1991 women hospitalized at the University of Insubria Hospital in Varese between 1 January 1998 and 30 March 2010 for a first primary nonmetastatic breast cancer and treated with surgery and neo-adjuvant/adjuvant therapy. Women were usually followed up by physical examination every 6 months and mammography with breast ultrasound (US) annually; in symptomatic cases or when clinically indicated, bone scan, chest x-ray, liver US or computed tomography scan were carried out.

Definitions of End Points

Loco-regional recurrence was defined as recurrence in the original tumor bed or in the ipsilateral axillary,

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internal mammary or supraclavicular or infraclavicular nodes with the same histopathologic features of the primary tumor. Regarding to end point of death, we considered only deaths for breast cancer.

Statistical Methods

The overall survival distribution was estimated using the Kaplan–Meier method (12). New ipsilateral breast tumor, contralateral breast tumor, distant metastases onset and other nonbreast primary tumor were considered as censoring events for loco-regional recurrence free survival and death for other causes as censoring event for overall survival. In the absence of any of these events, the observation time was censored at the last follow-up visit. The prognostic impact of several factors on cumulative overall and loco-regional recurrence free survival was evaluated by log-rank test (13). Continuous variables were categorized according to the median value. In order to consider only tumor-related factor, we excluded from analysis any patient- and treatment-related factors. Variables reaching a p value <0.1 in the univariate analysis were regressed on the cause-specific hazard, using multivariate Cox proportional hazards model (14). The stepwise (backward elimination) procedure was used. The effect of each factor was expressed as hazard ratio (HR) with 95% confidence intervals (CIs). The proportional hazard assumption was controlled using goodness of fit tests. The statistical analysis was performed with SPSS software for Windows. All reported p-values were two-sided.

RESULTS

Median age was 61.1 years (range 24–96). Median follow-up was 53 months (range 1–148), with 44.7% of patients having a follow-up >5 years. Table 1 shows the tumor-related factors of the cohort considered for analysis.

We observed 144 loco-regional recurrences and 55 cancer-related deaths as events, corresponding to a 5-year cumulative overall survival of 96.4% (Fig. 1) and a 5-year cumulative loco-regional recurrence free survival of 91.5% (Fig. 2).

Table 2 shows the univariate analysis of prognostic factors. pT, nodal status, grading, lymphangioinvasive growth, tumor diameter, ER status, PR status, and expression of Her2/neu had a prognostic value on loco-regional recurrence. At the univariate analysis of overall survival the histotype and the expression of Ki67 also were associated with outcome (but not the lymphangioinvasive growth).

In the multivariate analysis, reported in Table 3, grading remained the only independent predictor of loco-regional recurrences. With regard to overall survival, the Cox model selected grading along with

Table 1. Study Population Tumor-Related Factors Considered for Analysis

Variable	Category	No. (%)
Tumor diameter*	<15 mm	784 (50.1)
	≥15 mm	782 (49.9)
pT*	pT0–1	1356 (68.8)
	pT2	524 (26.6)
	pT3	36 (1.8)
	pT4	55 (2.8)
pN*	pN0	1385 (72.7)
	pN1	354 (18.6)
	pN2	119 (6.2)
	pN3	48 (2.5)
Histotype*	Ductal	1478 (74.4)
	Lobular	214 (10.8)
	Other	294 (14.8)
Estrogen receptors*	Negative	275 (15.0)
	Positive	1556 (85)
Progesterone receptors*	Negative	427 (23.1)
	Positive	1419 (76.9)
Grading*	G1–2	1379 (75.4)
	G3	449 (24.6)
Her2/neu*	Overexpressed	569 (36.5)
	Not expressed	989 (63.5)
Ki67*	<20%	777 (49.9)
	≥20%	779 (50.1)
p53*	Overexpressed	857 (56.6)
	Not expressed	658 (43.4)
Lymphoangioinvasive growth*	Absent	422 (76.2)
	Present	132 (23.8)

*Data not available for all patients.

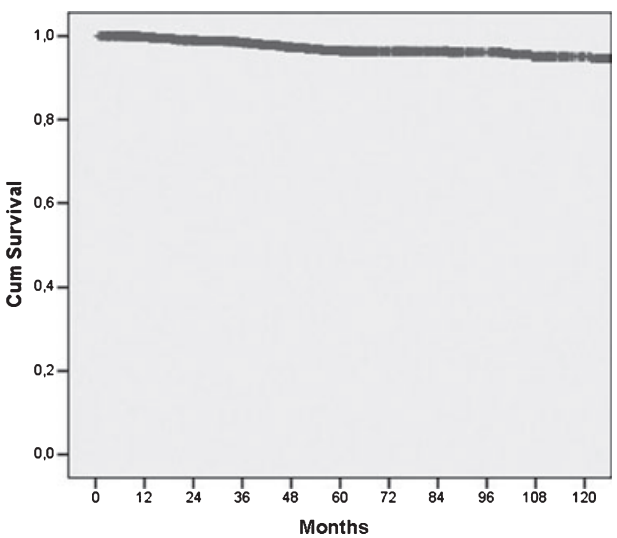

Figure 1. Cumulative overall survival for study patients.

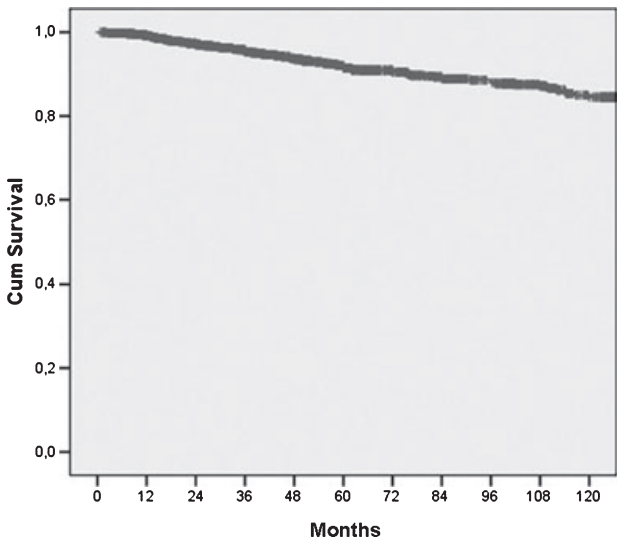

Figure 2. Cumulative loco-regional recurrence free survival for study patients.

nodal status and PR status as statistically significant independent prognostic factors.

DISCUSSION

The revolution of breast cancer treatment during the past decades has led to the progressive reduction of the surgical extent (1–4,15,16). Consequently, the quality of life has improved and women are now more motivated to follow screening programs for early diagnosis of the disease. The most relevant problem in breast-conserving surgery remains the loco-regional recurrence, which can nullify the aim of conservation for subsequent mastectomy.

In the present series, we verify the predictive factors of loco-regional recurrence and survival in a large series of patients treated by surgery. In this all-stages patients sample we observed a low incidence of loco-regional recurrences (8.5% at 5 years). This important result highlights the clear improvement of the surgical approach in local control obtained in the last few years. With this regard, the distinction between true loco-regional recurrences and new primary tumors arising in the ipsilateral breast is important, since they may have different biologic behavior and prognosis and a true recurrence might denote a persistent, radio-resistant, drug-insensitive and potentially more dangerous disease (17,18).

Even if local failure has been linked to an increased risk of distant metastases and death (5–11), in our study the 5-year cumulative rate of loco-regional recurrences was significantly higher than 5-year rate of cancer-related death (8.5% versus 3.6%). There-

Table 2. Univariate Analysis of Predictive Factors for Events

Variable	Category	5-year loco-regional recurrence free survival (%)	p-value	5-year overall survival (%)	p-value
Tumor diameter	<15 mm	96.0	<0.001	98.5	0.004
	≥15 mm	89.0		95.6	
pT	pT0–1	95.7	<0.001	99.0	<0.001
	pT2	86.3		93.9	
	pT3	75.3		85.4	
	pT4	74.9		86.9	
pN	pN0	94.5	<0.001	98.5	<0.001
	pN1	92.0		95.8	
	pN2	77.8		90.6	
	pN3	52.3		71.9	
Histotype	Ductal	91.1	0.168	95.6	0.018
	Lobular	93.4		98.4	
	Other	92.5		98.7	
Estrogen receptors	Negative	84.9	0.021	92.6	0.002
	Positive	92.4		97.2	
Progesterone receptors	Negative	85.6	0.002	92.2	<0.001
	Positive	93.2		98.0	
Grading	G1–2	94.2	<0.001	97.9	<0.001
	G3	82.4		91.1	
Her2/neu	Overexpressed	87.7	0.034	94.7	0.052
	Not expressed	93.9		97.4	
Ki67	<20%	93.9	0.057	98.0	0.016
	≥20%	90.1		95.1	
p53	Overexpressed	91.7	0.951	96.3	0.760
	Not expressed	93.3		97.0	
Lymphoangioinvasive growth	Absent	92.8	0.016	94.0	0.07
	Present	75.3		91.2	

Table 3. Multivariate Analysis of Predictive Factors for Events

Variable	Category	Loco-regional recurrence HR (95% CI)	Cancer-related death HR (95% CI)
Grading	G1–2	1	1
	G3	5.321 (1.387–20.424)	2.895 (1.187–7.063)
pN	pN0	—	1
	pN+	—	2.665 (1.141–6.226)
Progesterone receptors	Negative	—	1
	Positive	—	0.246 (0.096–0.632)

HR, hazard ratio; CI, confidence interval.

fore, loco-regional recurrence should not be considered as a failure of surgical approach (conservative or not) or responsible for systemic progression by itself: in fact, previous trials have shown that patients with a high incidence of local recurrences have the same survival rate as patients with a low local recurrence rate (1,2). Hence, loco-regional recurrence can be evaluated as a marker of tumor aggressiveness and a predictive factor for distant metastases and death (6,11,19–21), but as a condition still susceptible of cure.

By identification of loco-regional recurrence tumor-related predictors, we could identify a subset of patients, who might be curatively treated with a further therapy (surgical or not), allowing a good local control.

According to the results of univariate analysis, the loco-regional recurrence and the distant recurrence (or cancer-related death) shared some prognostic factors among the tumor characteristics, such as pT, nodal status, grading, tumor diameter, ER status, PR status, and overexpression of Her2/neu. In contrast, histotype and an expression of Ki67 were predictors of systemic progression only, specifically denoting a greater metastatic capacity.

Similarly, the multivariate models for loco-regional recurrence free survival and overall survival were different. In fact, for loco-regional recurrence free survival the Cox regression selected the grading as the only independent prognostic factor, like a more specific marker of local aggressiveness. In contrast, for overall survival the regression model selected grading along with nodal status and PR status: the nodal status as a measure of invasive potential and the PR status as a relevant feature for therapy.

Last result highlights a limitation of our study: in fact, the sample included patients underwent adjuvant (and neo-adjuvant) therapy which could favorably affected prognosis and, hence, our analysis results.

Further limitation of this study regards the duration of follow-up with the subsequent (not ever reliable) actuarial survival rates. A substantial proportion of events occurred after 5 years of follow-up, supporting the need for longer follow-up (1,6,11).

In conclusion, loco-regional recurrences after breast cancer surgery are not frequent events. They are markers of tumor aggressiveness and predictor of an increased likelihood of cancer-related death. However, loco-regional recurrence and systemic tumor progression are partially independent events, since some prognostic factors differ.

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