Prognostic factors in stage-i (T_1N_0) breast carcinoma patients: who needs adjuvant systemic treatment?

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There is no consensus about the need of adjuvant therapy in T_1N_0 breast carcinoma patients. To select a subgroup of these patients who may benefit from adjuvant systemic therapy, prognostic factor analyses were carried out using chi-square test and Cox regression analysis in 187 patients' data in this retrospective study. Primary endpoint was distant metastasis (DM).The multivariate Cox analysis showed that age group (≤35 years vs >35 years, p=0.01; Hazard Ratio [HR], 15.4; 95% Confidence Interval [CI], 1.8-133.0), tumor size (>1 cm vs ≤1 cm, p=0.002; HR,3.5; CI:1.2-13.4) and LVI (yes vs no, p=0.002; HR,34.7; CI:3.6-326.0) were strongly associated with DM. From this analysis, a risk estimation model for DM was constructed. Whereas patients at low risk had a 96% distant metastasis-free survival, this rate for those at high risk had a 37% (p<0.00001). According to the proposed model including age, tumor size and LVI, the patients at high risk might benefit from adjuvant systemic therapy.

Key words: breast carcinoma, stage 1, prognostic factors, risk estimation, adjuvant therapy.

A group of breast carcinoma patients who have a tumor size equal or less than 2 cm (T_1), no lymph node involvement (N_0) and no distant metastasis (M_0) constitutes stage-I according to the American Joint Committee on Cancer [1]. Whereas a number of trials have focused on the adjuvant treatment of node positive patients, the optimal adjuvant management of node negative patients, especially those in stage-I, is controversial [2,3]. The introduction of mammography and a general increase in awareness among women have led to an increase in the number of stage-I breast carcinoma patients diagnosed in the recent years. Although the risk of distant metastasis for T_1N_0 patients is less than 2% at 10 years, a number of recent publications reported low rates for 10-year disease- free survival (DFS) in this stage [4,5]. The magnitude of benefit from adjuvant systemic treatment for a breast carcinoma patient depends on her risk of recurrence in the absence of this treatment [5]. Some histological factors have been described to identify a subgroup of these patients with a relatively worse prognosis who might benefit from adjuvant treatment as opposed to those with an excellent prognosis who could be spared the associated toxicity and cost [3,5]. Based on these parameters, there are some guidelines for the use of adjuvant systemic treatment, but advice of each guideline for stage-I disease differs from other [6,7,8].

The aim of our study was to assess the prognostic value of the clinicopathological parameters in stage-I patients who received no adjuvant systemic treatment that could complicate the study results, to identify a subgroup of patients who have a high risk of recurrence and therefore, those who could benefit from adjuvant systemic treatment.

Patients and methods

Clinical records and final pathology reports of consecutive breast carcinoma patients treated from 1990 to 2002 at Ankara Oncology Hospital were reviewed retrospectively. Patients received no adjuvant treatment (chemotherapy and/or tamoxifen) due to preference of patient or other reasons were selected for this study. All patients had identical surgical treatment consisting of modified radical mastectomy. Pathological lymph node classification and tumor staging were done according to the American Joint Committee on Cancer criteria [1]. Information on the p53 and the cErbB2 by immunohistochemistry was available only in a minority of patients, mostly those treated after the year 2000. Immunohistochemical score of 3+ was accepted as positive for cErbB2.

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Table 1. Patients' characteristics

	n	%
Age group		
>35 years	173	92.5
≤35 years	14	7.5
Menopausal status		
Postmenopausal	105	56.1
Premenopausal	82	43.9
Histological type		
Ductal	161	86.1
Lobular	26	13.9
Pathological tumor size		
pT_{1a}	10	5.3
pT_{1b}	32	17.1
pT_{1c}	145	77.5
Histological grade		
Grade 1-2	68	61.3
Grade 3	43	38.7
Unknown	76	–
Lymphatic vascular invasion		
No	167	89.3
Yes	20	10.7
Estrogen receptor status		
Positive	95	59.4
Negative	65	40.6
Unknown	27	–
Progestrone receptor status		
Positive	81	52.6
Negative	73	47.4
Unknown	33	–
p53 receptor status		
Positive	26	68.4
Negative	12	31.6
Unknown	149	–
cErbB2 receptor status		
Positive	13	16.5
Negative	66	83.5
Unknown	108	–

Patient selection. Patient inclusion criteria for this retrospective cohort study were as follows: Having tumor equal to or less than 2 cm and negative lymph nodes, having a modified radical mastectomy, having complete dissection of the level I, II and III axillary lymph nodes, having at least 10 lymph nodes on dissection material, no adjuvant systemic treatment, no serious concomitant diseases, age less than 70 year, no prior specific treatment.

Statistical analyses. The primary endpoint for this study was distant metastasis (DM) and distant metastasis-free survival (DM-FS). Overall survival (OS) and DM-FS estimations were established using the Kaplan-Meier method [9] and differences in survival among patient subgroups were tested with a log-rank test. Survival rates are reported with their standard errors. Chi-square test was used in univariate analysis of prognostic variables. Multivariate analysis was performed using the Cox proportional hazards model with a conditional backward stepwise elimination procedure [10], after the proportional hazards assumption was assessed by ln(-ln) survival curves. For this analysis, chunk-wise testing method, as recommended for statistical power and sensitivity, was selected [11]. A set of predictors that are logically related and equally important constitutes first chunk and backward elimination was applied. Then respectively, new factors were added to chunks and backward elimination was re-applied, whereas significant factors were kept in place in every step. The multivariate Cox model for DM was defined as "$\exp(\Sigma\beta_n v_n)$" where "v" indicates significant variable and "β" its coefficient. Probability of DM (P_{DM}) for each patient was estimated by "$P_{DM}=\exp(\Sigma\beta_n v_n)/(1+\exp(\Sigma\beta_n v_n)$". A receiver operating characteristic (ROC) analysis with the area under the ROC curve (AUC) was used for discriminating the best cut-off value of overall P_{DM}. Statistical tests were performed using the SPSS 10â statistical software package for windows (SPSS Inc, Chicago, IL).

Results

The charts of consecutive 3222 female breast carcinoma patients treated at our hospital were evaluated. A hundred and eighty-seven patients met the eligibility criteria for this study. The median age was 51 (range 25 to 70) and median tumor size was 1.5 (range 0.5 to 2.0) cm. The median number of lymph nodes in dissection materials was 18 (range 10 to 49). Patients' characteristics were given in Table 1.

Clinical outcome. The median follow-up time was 85 (range 40 to 191) months. Seven (3.7%) patients died because of cancer-related reasons in the follow-up period. 10-year OS rate was 90% (±0.04). Three (1.6%) patients had locoregional recurrence (LRR), and all LRRs were in the ipsilateral internal mammary nodes. The median time to LRR was 24 (range 22-31) months and 10-year LRR-free survival rate was 98% (±0.009). All patients with LRR had a tumor larger than 1 cm in size. Eighteen (9.6%) patients had DM. The median time to DM was 64 (range 17-109) months and 10-year DM-FS rate was 80%(±0.04). Larger tumor size was associated with a significantly more incidence of DM and a shorter DM-FS. Whereas patients with pT_{1a} had no DM, two (6.3%) of 32 pT_{1b} patients and 16 (11%) of 145 pT_{1c} patients had a DM. 10-year DM-FSs were 100% in patients with pT_{1a}, 91% (±0.02) in pT_{1b} and 81% (±0.05) in pT_{1c}, (p=0.01).

Prognostic factors. Prognostic factors related to DM in univariate analysis were shown in Table 2. This analysis demonstrated that age group, tumor size, histological grade, lymphatic vascular invasion (LVI), estrogen and progesterone receptor status, and cErbB2 status are statistically significant factors. There was no violation of the proportional hazards assumption when assessed by ln(-ln) survival curves. Prognostic factors related to DM in the multivariate Cox analysis were shown in Table 3. When the important parameters in the univariate analysis included in the multivariate analysis, tumor size, histological grade, LVI and cErbB2 status were statistically significant factors, as seen in chunk-1. When age

Table 2. The results of univariate analysis for prognostic factors related to distant metastasis*

Features	p value	Hazard ratio	95% Confidence intervals
Age group (≤35 ys. vs >35 ys.)	<0.0001	2.2	1.3-3.6
Menopausal status (pre. vs post.)	NS		
Histological type (ductal vs lobular)	NS		
pT (pT_{1c} vs pT_{1a-b})	0.01	1.3	1.2-1.4
Histological grade (gr 3 vs gr 1-2)	<0.0001	3.1	1.3-7.4
Lymphatic vascular invasion (yes vs no)	<0.0001	8.8	2.4-32.0
Estrogen receptor status (negative vs positive)	0.02	1.9	1.2-7.9
Progesterone receptor status (negative vs positive)	0.002	3.4	1.2-9.7
p53 status (positive vs negative)	NS		
cErbB2 status (positive vs negative)	<0.0001	3.6	1.7-7.5

* chi-squared test

Table 3. The results of multivariate Cox regression analysis for prognostic factors related to distant metastasis

Features	p value	β-coefficient	HR*	95% CI**
Chunk 1				
pT (pT_{1c} vs $pT1_{a-b}$)	0.009		2.3	1.2-4.5
Histological grade (gr 3 vs gr 1-2)	0.04		1.2	1.1-15.0
Lymphatic vascular invasion (yes vs no)	0.006		10.9	2.0-59.0
Estrogen receptor (neg. vs pos.)	NS			
Progesterone receptor (neg. vs pos.)	NS			
cErbB2 status	(pos. vs neg.)	0.002	7.2	2.0-26.0
Chunk 2				
Age group (≤35 ys. vs >35 ys.)	0.01	2.7	15.4	1.8-133.0
pT (pT_{1c} vs $pT1_{a-b}$)	0.002	1.3	3.5	1.2- 13.4
Histological grade (gr 3 vs gr 1-2)	NS	–		
Lymphatic vascular invasion (yes vs no)	0.002	3.6	34.7	3.6-326.0
cErbB2 status (positive vs negative)	NS	–		

* HR, hazard ratio

** 95% CI, 95% Confidence Interval

group was included into the multivariate model, age group with a 14.9 hazard ratio (HR), tumor size with a 3.7 HR and LVI with a 36.6 HR were the most important predictive factors, while histological grade and cErbB2 status no longer provided independent prognostic information (chunk 2).

Characteristics related to age groups. The subgroup of younger patients than 35 years had a higher incidence of high grade tumor [10 (83.3%) of 12 younger patients vs 33 (33.3%) of 99 older patients, (p=0.001)], lymphatic vascular invasion [11 (78.6%) of 14 younger patients vs 9 (5.2%) of 173 older patients, (p<0.0001)], negative estrogen receptor status [9 (69.2%) of 13 younger patients vs 56 (38.1%) of 147 older patients, (p=0.03)], negative progesterone receptor status [12 (92.3%) of 13 younger patients vs 61 (43.3%) of 141 older patients, (p=0.001)] and positive cErbB2 status [8 (72.7%) of 11 younger patients vs 5 (7.4%) of 68 older patients, (p<0.0001)] than the subgroup of older patients than 35 years. Although tumors more than 1 cm in size were observed even more frequently in younger patients than older patients, there was not a distributional difference of large tumors between two groups [12 (85.7%) in younger patients vs 134 (77.5%) in older patients, p=0.7].

On the other hand, patients with DM were divided into two groups as those with early DM and those with late DM according to the median time to DM (64 months), and differences in predictive factors were tested. There was a striking difference between early and late DM rates according to age groups. Whereas younger patients were associated with early DM [among 9 younger patients with DM, 8 (88.9%) patients with early DM], older patients experienced a late DM [among nine older patients with DM, 7 (77.8%) patients with late DM] (p=0.01). There was no difference in distribution of the other predictive factors between early and late DM groups.

Prognostic scheme. The parameters extracted from the final Cox model (chunk 2) were also used to construct a prognostic scheme for determining the risk of DM. Thus, the Cox model consisting of three dichotomized variables is transformed as follows: "exp[(2.7 if age≤35 years) + (1.3 if tumor > 1 cm in size) + (3.6 if tumor presents LVI)]". After estimating of probability of DM (P_{DM}) within 10 years for

each patient, patients at low risk and those at high risk were identified according to a 95% cut-off point of P_{DM} by ROC analysis ($p<0.00001$, AUC: 92%, 95% CI: 82% to 99%, sensitivity 83% and specificity 93%). Two (0.1%) of 165 low risk patients and 10 (46%) of 22 high risk patients experienced a DM at their follow-up period. Estimated 10-year DM-free survival was 96% (±0.03) for the low risk and 37%(±0.1) for high risk ($p<0.00001$).

Discussion

Adjuvant treatment can improve survival in breast carcinoma patients, and this treatment is generally offered to node positive patients [2,4,6,12]. However, the benefit of adjuvant treatment is smaller in node negative patients and must be balanced against the associated toxicities and costs [3,13]. This argument is especially valid for node negative patients with tumor less than 2 cm in size [14]. Although outcome in these patients is excellent with a DM rate of 2% or less at 10 years [4], a subgroup of these patients will suffer a recurrent disease in long-term follow-up [14]. Some recent reports indicated that 10-30% of stage-I breast carcinomas treated with locoregional therapy alone eventually recur [15,16]. In our study with a relatively long follow-up, about 10% of patients who received no adjuvant treatment had a DM.

In the literature, several prognostic factors have been described to identify T_1N_0 patients with a relatively worse prognosis who might benefit from adjuvant treatment as opposed to those with an excellent prognosis who could be spared the negative effects of this treatment. Some of these factors are tumor size, tumor grade, estrogen receptor status, progesterone receptor status, p53 status, mitotic index, young age, cErbB2 overexpression, Ki67, and lymphatic vascular invasion [5,13]. On based the different combinations of these parameters, there are some major guidelines for decission of adjuvant treatment in early breast carcinoma [3,6,7,8], but there is not a consensus between these current guidelines, when applied to stage-I [5]. Thus, we assessed the prognostic value of the clinicopathological parameters in our stage-I patients who received no adjuvant treatment such as chemotherapy and/or hormonal therapy that could complicate the results.

Our study showed that tumor size, histological grade, lymphatic vascular invasion and cErbB2 positivity were associated with DM, whereas estrogen and progesteron receptors were not, when age was not included into the multivariate model (chunk 1). Some studies in the literature pointed out the importance of tumor size for DM [3,12,13,15,17]. Ichizawa et al. [17] indicated that the DFS and OS rates for T1c patients were statistically different from T1a and T1b patients at 10 years and also at 20 years, and T1c could be defined as a high-risk category in the T1 group. In our study also, T1c patients experienced both LRR and DM more frequently and therefore DM-FS for these patients was worse than T1a and T1b patients. When a tumor attains 1 cm, tumor cell mass may reach the threshold for mutational events to produce aggressive subpopulation of cells with a high metastatic potential [12].

Joensuu et al. [14] reported that histological grade was found to be associated significantly with OS, whereas tumor size, tumor necrosis and mitotic count were not. Although histological grade is somewhat subjective parameter [5], it has been shown to correlate well with survival in numerous studies and also has been shown to be associated with a short term survival in stage-I patients [13]. However, some studies reported no prognostic effect of grade in node-negative tumors [3]. Whereas there was a positive association between DM-FS and grade, OS was not an endpoint of the presented study because of the low incidence of "events". Approximately 4% of our patiens were lost from breast carcinoma, and estimated mortality rate was 10% at 10 years. However, because of the many late deaths from breast carcinoma in patients with stage-I disease [14,18], even 15 years of follow-up may not be enough in this subgroup [14]. Fisher et al. [19] also pointed out that a follow-up time of longer than 8 years is likely to be necessary to allow for a more meaningful assessment of the outcome of patients with small tumors. On the other hand, the risk of recurrence of breast carcinoma is time dependent with two peaks as an early peak at about 18 months after surgery and a second peak at about 60 months [3]. The median follow-up time with 85 months in the presented study was enough for determining the recurrences.

The results of our study suggest that cErbB2 status and LVI might be of greater prognostic value than the ER or PR status, as even in some other studies [15,16]. ER-negative tumors were found to be associated with worse outcome in some studies in which patients did not receive systemic treatment, some studies indicated that the trend toward reduced DFS at 5-years with ER-negative tumors was lost by the 10-year follow-up [13]. The ER status is somewhat inferior to the PR status as a prognostic factor, which is plausible, because PR expression is an indicator of an intact ER pathway, and the PR requires estrogen stimulation for expression [15]. Hanrahan et al. [5] and Mirza et al. [13] stated that HR status seemed to be more valid as a predictor of benefit from adjuvant hormonal therapy than as a prognostic factor. In our study also, ER or PR status were not the independent prognosticators in multivariate analysis, whereas these parameters were important in univariate analysis.

Twenty to 30% of breast carcinomas are cErbB2 positive, whereas only 12-13% of all stage-I carcinomas were positive for cErbB2 [15]. Among our patients, approximately 17% had cErbB2 positivity. This rate might reflect the lower malignancy potential of the stage-I breast carcinomas, as indicated in another study [15]. On the other hand, although LVI was a feature of aggresive tumor biology [3,5] and was included in some consensus recommendations [6,8], this factor is not uniformly accepted in the literature [13,15]. In our study, LVI with a 37 hazard ratio was the dominant prognostic factor, as similar to other studies [3,20,21]. There were contradictory results about the prognostic significance of p53 protein [13].

In our study, p53 protein was not significant for DM in univarite analysis. This was mainly because the number of patients whose p53 protein status was determined was relatively small to detect the survival differences.

On the other hand, when the parameter age were introduced to the final multivariate model (chunk 2), tumor size and LVI, in addition to age, remained in the model, whereas grade and cErbB2 status did not. This is plausible, because the younger patients than 35 years had a higher incidence of unfavorable features such as high grade tumor, LVI, negative estrogen and progesterone receptor status and positive cErbB2 status than their counterpart. There are a considerable studies reported the importance of young age for disease-free and overall survival in the literature [22,23]. In current practice, a patient's age is often an important factor in choosing adjuvant therapy. On the other hand, the result of our study demonstrated that young patients were associated with early DM, whereas there was no difference between distributions of the other unfavorable features according to the early and late DM groups. In contrast to our study, Westenend et al. [3] indicated that grade distinguished early and late metastasis.

The current concept of adjuvant treatment is based on treating groups of patients who have similar unfavorable features, rather than individual decision. The benefit of adjuvant therapy related to the relative reduction in absolute risk of recurrence [23]. Rosner et al. [22] indicated that patients with a risk lower than 10% at 10 years were at low risk, and those with a risk over 20% were at high risk. In the presented study, a sophisticated model for determining DM risk of an individual was established by using the important prognostic factors from the multivariate Cox regression analysis. According to our knowledge, this is the first study generated a model in this cohort. In the presented study, the risks of DM were 0.1% and 46% for the low risk and the high risk patients, respectively. Estimated 10-year DM-free survival was 96% for the low risk patients and 37% for those at high risk. These patients at high risk might benefit from adjuvant systemic treatment, whereas the others might be spared toxicity and cost of adjuvant systemic treatment.

In conclusion, our study, in which patients homogeneously treated by modified radical mastectomy with complete axillary dissection and a median 18 dissected lymph nodes, demonstrated that stage-I breast carcinoma represented a heterogeneous population in terms of risk of distant metastasis and prognosis. Young age, larger tumor size and presence of lymphatic vascular invasion were the most important prognostic factors. These parameters should be taken into consideration for the recommendation of adjuvant systemic therapy in this cohort. Based on these parameters, we proposed a mathematical risk estimation model to be helpful in advising an individual patient. New trials including large numbers of patients with prolonged follow-up are necessary to validate the observations in this study and the proposed model.

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