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Retrospective evaluation of operated stage I breast cancer patients

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ABSTRACT

As there is no national screening programme in our country, information about stage I breast carcinoma is limited. In this study, 131 stage I breast cancer patients followed between April 1989 and March 2001 at our department, were retrospectively evaluated. Median age was 49 (range: 26-77). Painless breast mass was the most common symptom (75%). Tumor size was larger than 1 cm in 66% of the patients. Seven percent of the patients had no adjuvant therapy, 43% had adjuvant tamoxifen and 50% had adjuvant chemotherapy ± tamoxifen. CMF combination (± tamoxifen) was the most common (71%) adjuvant chemotherapy regimen. Median follow-up period was 43 (range: 5^{+}-148^{+}) months. During the follow-up period, 1 patient had local recurrence and distant metastases, 3 had distant metastasis, and 5 patients (3.8%) had metachronous breast carcinoma. Two patients died with distant metastasis. Median disease free survival and median overall survival were not reached. Five-year disease free survival was 97% and, 5-year overall survival was 98.5%. Follow-up period was short and long-term follow-up is necessary for better analysis. [Turk J Cancer 2003;33(1):40-50]

KEY WORDS:

Breast cancer, stage I, prognosis, survival

INTRODUCTION

Breast carcinoma is the most common neoplasm in women and constitutes the second leading cause of cancer deaths (1). As the screening programs are more widespread, and the education increases, the diagnosis of early breast carcinoma is increasing. About half of the patients with newly diagnosed breast carcinoma do not have axillary lymph node (ALN) involvement (2). Recurrence of breast carcinoma is seen in about 30% of operated ALN negative patients (3,4).

Adjuvant systemic therapy is the standard option of ALN positive breast carcinoma. High-risk subgroups that need adjuvant therapy should be described in ALN negative patients (5). In the routine daily practice; age, the size of the tumor, grade, estrogen (ER) and/or progesterone receptor (PR) status are the main parameters to determine these subgroups.

Since there is no national screening program in our country, information about stage I breast carcinoma is limited. In this study, 131 stage I breast carcinoma patients were evaluated retrospectively.

MATERIALS AND METHODS

In this study, 131 stage I breast cancer patients followed between April 1989 and March 2001 were evaluated, retrospectively. The tumor size was recalculated by reevaluation of the biopsy and surgical pathology reports. Staging was done according to tumor size, lymph

node involvement, and metastasis (TNM) classification of American Joint on Cancer Committee (6). Greatest tumor dimention 2 cm and ALN negative patients were included into the study. Greatest tumor dimention undetermined in the biopsy or surgical pathology reports (Tx), carcinoma-in situ (Tis), Paget's disease, microinvasive tumors (invasive component 1 mm) (T1mic), ALN unknown (Nx) cases were discarded from the study. The number of dissected ALN was not regarded as inclusion or exclusion criteriae.

Hormone receptors were studied with immunohistochemical staining methods. Locoregional recurrence was described as recurrence of breast cancer in the primary region (breast, chest wall, incision scar or skin flap) or the local lymphatics (axillary, internal mammary, ipsilateral supraclavicular). The recurrences other than these sites were described as distant recurrences. Disease free survival (DFS) was described as the time from the diagnosis till local recurrence or distant metastasis or last control. Overall survival (OS) was described as the time between the diagnosis till death or last control (6).

Statistical analysis was done with the computer using SPSS 6.0 for Windows. Survival analysis was done with the Kaplan-Meier method.

RESULTS

The distribution of the patients according to the years of diagnosis was shown in figure 1. Twenty-six of 131 patients (19.8%) was admitted at 2000. Seven patients admitted in the first 3 months of 2001 were also included.

Median age was 49 (range: 26-77). Sixty-four patients (49%) were premenopausal, 63 (48%) were postmenopausal, and 4 (3%) perimenopausal. Twenty-four (18.3%) patients were diagnosed with screening mammography, 107 (81.7%) were with the clinical symptoms. Painless breast mass was the most common symptom (74.8%). Twenty of 24 patients (83.3%) diagnosed with screening mammography were postmenopausal, 2 were premenopausal, and 2 were perimenopausal. Clinical characteristics of the patients are shown in table 1.

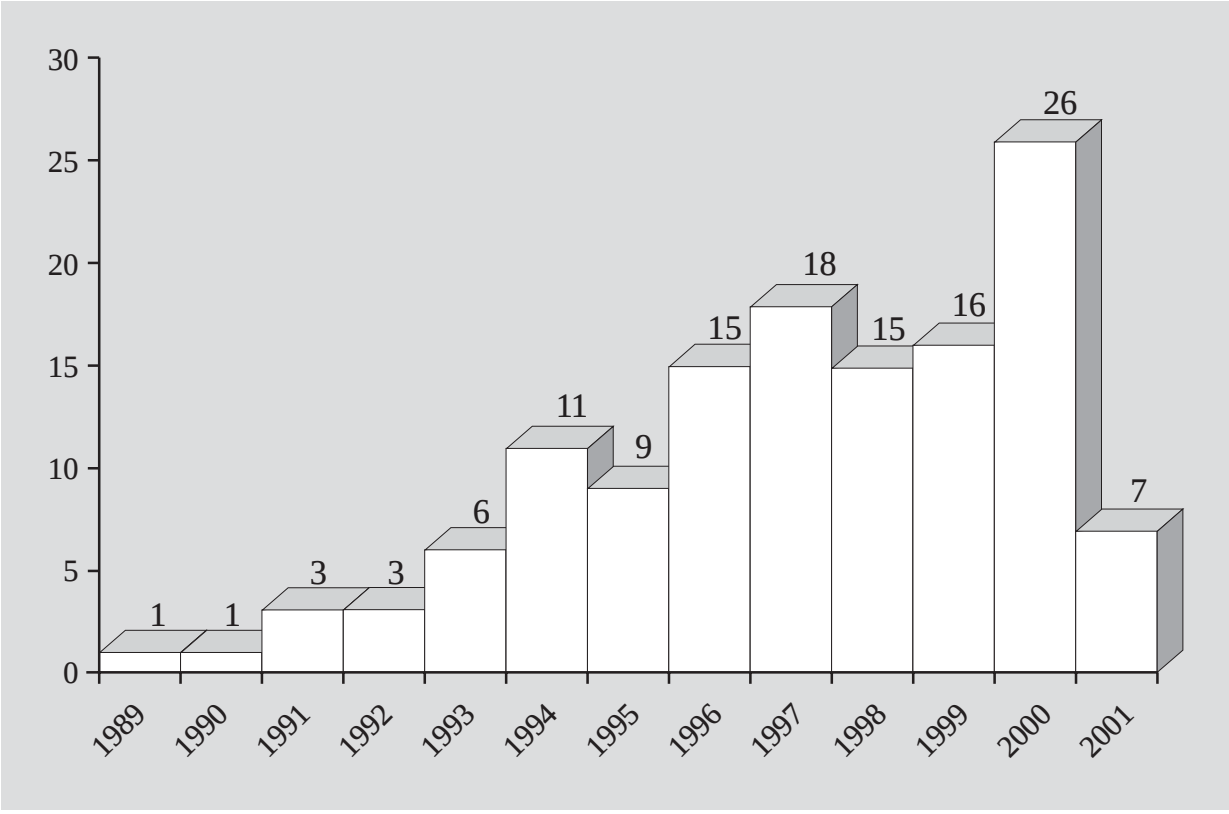

Fig1. Distribution of operated stage 1 breast cancer patients according to their year of admission

Table 1
Clinical characteristics of operated stage I breast carcinoma patients

Clinical Characteristics	N	(%)
Total	131	100
Age	49 (range:26-77)	
Menopausal Status		
Premenopausal patients	64	49
Postmenopausal patients	63	48
Perimenopausal patients	4	3
Reason of Admission		
Screening mammography	24	18.3
Clinical symptoms	107	81.7
Breast mass	98	74.8
Breast mass + pain	4	3.1
Breast mass + discharge	1	0.8
Pain in the breast	3	2.3
Discharge + pain	1	0.8

Tumor size was T1a in 7 patients (5.3%), T1b in 37 patients (28.2%), and T1c in 87 patients (66.4%). Infiltrative ductal carcinoma was the most common histological subtype and found to be in 89 patients (67.9%). Ten patients (7.6%) had medullary carcinoma, 6 patients (4.6%) had mucinous carcinoma, 3 patients (2.3%) had tubular carcinoma, 3 patients (2.3%) had infiltrative lobular carcinoma, and 20 patients (15.3%) had other histopathologies (infiltrative carcinoma, clear cell carcinoma, cribriform carcinoma).

Grade was pathologically reported in 69 patients (52.6%). Twenty-five patients (19.1%) had grade 1, 32 patients (24.4%) had grade 2, 12 patients (9.2%) had grade 3 tumor. Lymphovascular invasion (LVI) was reported in 39 patients, and 13 patients (9.9%) was found to be positive. Besides the invasive component, 32 patients (24.4%) had concomittant carcinoma in-situ component.

Estrogen receptor (ER) was studied in 83 patients (63%). ER was positive in 48 patients (36.6% of total group, and 58% of stained group). Progesterone receptor (PR) was studied in 73 patients (56%) and positive in 40 patients (30.5% of total group, and 55% of stained group). Both receptors were stained in 70 patients (53.4%). C-erbB2 was stained in only 5 patients, and found to be negative in 3 patients. Tumor characteristics of the patients are shown in table 2.

The type of the operation was breast conserving surgery (BCS) in 26 patients (19.9%) and mastectomy in 105 (80.1%) patients. Median number of dissected axillary lymph nodes was 20 (range:1-52). None of the dissected ALN had macroscopic or microscopic tumor involvement. Only 11 patients (8.4%) had less than 10 ALN dissection. Treatment characteristics of the patients and the distribution of treatment according to the tumor size was shown in table 3 and 4, respectively.

Table 2
Tumor characteristics of the patients

Tumor Characteristics	N	(%)
Total	131	100
Tumor Size		
T1a	7	5.3
T1b	37	28.2
T1c	87	66.4
Histological Subtype		
Infiltrative ductal carcinoma	89	67.9
Infiltrative lobular carcinoma	3	2.3
Medullary carcinoma	10	7.6
Mucinous carcinoma	6	4.6
Tubular carcinoma	3	2.3
Others	20	15.3
Grade		
Grade I	25	19.0
Grade II	32	24.4
Grade III	12	9.2
Unknown	62	47.4
Lymphovascular Invasion		
Positive	13	10.0
Negative	26	19.8
Unknown	92	70.2
ER*		
Positive	48	36.6
Negative	35	26.8
Unknown	48	36.6
PR*		
Positive	40	30.5
Negative	33	25.2
Unknown	58	44.3

**Percentages are accounted in the whole group. ER positivity was 58%, and PR positivity was 55% in the studied (stained) group*

Nine patients (6.9%) were followed without adjuvant medication, postoperatively. Fifty-six patients (42.8%) were treated with tamoxifen, 48 (36.6%) with chemotherapy, and 18 (13.7%) with tamoxifen + chemotherapy. CMF regimen was the most commonly used chemotherapy regimen (47/66; 71.2%) (Table 3).

Twenty-eight patients had received local adjuvant radiotherapy. Indications of radiotherapy after mastectomy was multicentric tumour, lymphovascular invasion, and unsatisfactory ALN dissection (Table 3).

Fifteen stage I patients were in minimal/low risk and 35 were in the high-risk group according to St. Gallen 2001 (5). Thirteen (86.7%) of low-risk patients (stage I, grade I, age 35, ER and/or PR positive) had tamoxifen, 2 (13.3%) had CMF chemotherapy + tamoxifen therapy. The tumor sizes of chemotherapy patients were T1b and T1c.

Table 3
Treatment characteristics of the patients

Treatment Method	N	(%)
Total	131	100
Type of Surgery		
Modified radical mastectomy	90	68.7
Radical mastectomy	11	8.4
Simple mastectomy	4	3.1
Breast conserving surgery	26	19.9
Radiotherapy		
Radiotherapy positive	28	21.4
After breast conserving surgery	3	10.7
Postmastectomy	25	89.3
Radiotherapy negative	103	78.6
Postoperative Treatment		
No medication	9	6.9
Tamoxifen	56	42.8
Chemotherapy alone	48	36.6
CMF	39	29.7
CAF	7	5.3
AC	1	0.8
CEF+Taxol	1	0.8
Chemoterapy + tamoxifen	18	13.7
CMF + tamoxifen	8	6.1
CAF + tamoxifen	6	4.5
AC + tamoxifen	3	2.3
CEF + tamoxifen	1	0.8

CMF: cyclophosphamide, methotrexate, fluorouracil; CAF: cyclophosphamide, adriamycine, fluorouracil; AC: adriamycine, fluorouracil; CEF: cyclophosphamide, epirubicin, fluorouracil

Table 4
The distribution of treatment of the patients according to tumor size

	T1a	T1b	T1c
No Medication	3 (43%)	4 (11%)	2 (2%)
Tamoxifen	4 (57%)	19 (51%)	33 (38%)
Chemotherapy	-	10 (27%)	38 (44%)
Chemotherapy+ tamoxifen	-	4 (11%)	14 (16%)

Median follow-up of all patients was 43 (range: 5^{+}-148^{+}) months. Five patients (3.8%) had metachronous breast cancer in a median duration of 64 months (range: 27-86 months). Histological subtype was infiltrative ductal carcinoma in 4 patients, and infiltrative lobular carcinoma in 1 patient.

In the follow-up period, 4 patients (3%) had progressive disease (Table 5). Median period of disease progression was 19 months (range: 13-81 months). One patient (0.8%) had local recurrence, 4 (3%) had distant metastasis. Local recurrence occurred 12 months after lumpectomy and local radiotherapy for breast carcinoma, and this patient also had distant metastasis. All patients with distant metastasis had bone involvement. Two patients had only bone involvement, 1 had bone + contralateral supraclavicular lymph node, 1 had bone + liver + lung involvement. One of the metastatic patients also had metachronous breast carcinoma after 81 months of primary breast carcinoma (Table 5, patient 1). Two of the patients with distant metastasis of bone and visceral organ or contralateral supraclavicular lymph node died. Since only 4 patients progressed, factors affecting DFS were not analysed. Median DFS and OS were not reached. Mean DFS was 45.2 months (range: 5^{+}-123^{+}). Mean OS was 43 (range: 5^{+}-148^{+}) months. Since only two patients died, factors that have effect on OS were not analysed. Five-year DFS was 97% and 5-year OS was 98.5%.

Table 5
Clinical and pathological characteristics of progressive, operated, stage I breast carcinoma patients

	1 (AD)*	2 (CU)	3 (KY)	4 (HU)
Age	66	58	44	35
Diagnosis by	Clinically	Clinically	Clinically	Clinically
Menopause	Post	Post	Pre	Pre
Tumor Size	T1a	T1b	T1c	T1c
Surgery	MRM	MRM	MRM	Lumpectomy
Dissected ALNs	10	14	34	24
Pathology	Inf Ca	Inf Ductal	Inf Lobular	Inf Ductal
Grade	NA	NA	NA	2
LVI	NA	NA	NA	-
ER	NA	NA	NA	-
PR	NA	NA	NA	Weak positive
Treatment	None	CMF+Tam	CMF	CAF+tam
DFS	81	44	19	15
OS	148^{+}	89	32	18^{+}
Progression Site	Bone	Bone + contralateral SLN	Bone + liver + lung	Bone (+local recurrrence)
Result	Alive	Dead	Dead	Alive

Post: postmenopausal, Pre: premenopausal, MRM: modified radical mastectomy, ALN: axillary lymph node, Inf: infiltrative carcinoma, LVI: lymphovascular invasion, NA: not assessed, tam: tamoxifen, SLN: supraclavicular lymph node
**: This progressive patient also had metachronous breast carcinoma*

DISCUSSION

As the screening programs are more widespread, and the education increases, the diagnosis of early breast carcinoma is increasing in the developed countries. In USA, 50% of newly diagnosed breast carcinoma patients have no ALN involvement (7). The prevalence of stage I breast carcinoma patients was found to be 19.3% (289/1495) in one retrospective study (8). Patients included in the NSABP studies were retrospectively evaluated, and 12.2% (1259/10.302) was found to be 1cm (9). In Turkey, the incidence of stage I breast carcinoma patients is not known and there are limited number of studies. The ratio of stage I breast carcinoma was found to change between 2.9% to 16.5% in 3 studies made in our department (10-12).

In our country, there is no national mammographic screening program except screening mammography advised for perimenopausal or postmenopausal women planned to take hormonal replacement therapy in the gynecology clinics. In the study of Lee et al. (13) the prognosis of breast carcinoma patients with tumor size <1 cm, diagnosed by screening mammography was found to be better than diagnosed by clinical findings and palpation. In our study, only 24 of 131 patients (18.3%) were diagnosed with screening mammography (Table 1). Twenty of 24 patients (83.3%) diagnosed with screening mammography was postmenopausal, and they were planned to take hormonal replacement therapy. The number of stage I breast carcinoma patients admitted was found to be increasing year by year (Figure 1) which may be the result of increasing the use of mammography and education.

The effect of surgical method on survival was studied in many randomised trials (14). In a metaanalysis, 10-year OS was found to be equivalent between BCS + radiotherapy and mastectomy in early breast carcinoma patients (15). In our study, only 19.9% of patients had BCS. There was only one patient with local recurrence, and she had BCS. Since no significant survival difference between the patients who undergoes radical surgery and BCS + radiotherapy, BCS is an appropriate alternative therapy to radical surgery, and the number of BCS operations in early stage breast carcinoma are needed to increase, in our country.

ALN status is an important predictor of survival and guides the selection of patients for adjuvant treatment, but the effect of number of dissected ALN on DFS and OS is controversial. Camp et al. (16) found that OS is lower when 20 ALN were dissected, in a multivariate analysis. Moorman et al. (17) found that the number of dissected ALN has no effect on OS. In our study, median number of dissected ALN was 20. The optimal treatment of axilla in the management of patients with early-stage breast carcinoma is controversial. Sentinal lymph node mapping and biopsy is an emerging alternative to ALN dissection in determining the lymph node status of patients with early-stage breast carcinoma but needs experience (5). Sentinal lymph node biopsy was not applied to any of our patients. It is a good alternative to axillary dissection, and experience should increase in early stages breast carcinoma.

Adjuvant radiotherapy is standard after BCS, but debatable after mastectomy in early breast cancer. When the cases with high risk of local recurrence (ALN 4 positive, and T3 or stage III) are excluded, radiotherapy is not routinely recommended for multicentricity, lymphovascular invasion, insufficient number of dissected ALNs, and tumors in the inner quadrant or centrally located (5,18).

In the past, only surgical approach without any adjuvant treatment, was thought to be satisfactory for ALN negative early breast carcinoma patients. But on follow-up, about 30% of these patients recurred after 10 years of surgical resection. Joensuu et al. (8) evaluated the reports of 265 stage I breast carcinoma patients retrospectively, and 14% (37/265) of patients died in a median 17 year follow-up, and if other causes other than breast cancer was discarded, 10 and 20 year survival was 93% and 81%, respectively.

Adjuvant cytotoxic polychemotherapy was offered to be the standard recommendation of breast carcinoma treatment if the tumor size 1 cm regardless of the lymph node, menopausal, and hormonal receptor status, according to NIH consensus (19). Also, inclusion of anthracyclines in adjuvant chemotherapy regimens produce a small but statistically significant improvement in survival

over non-anthracycline containing regimens (20). In our study, 66 patients (50.4%) had chemotherapy (± tamoxifen). None of the 7 patients with tumor size of T1a was offered chemotherapy. Fourteen of 37 T1b (37.8%), and 52 of 87 T1c (59.7%) patients had chemotherapy (± tamoxifen) (Table 4). CMF was the most commonly used regimen (47 patients, 71.2%) (Table 3). The treatment decisions according to the tumor size is comparable with the literature.

Median follow-up period of our study was short (43 months) and median DFS and OS were not reached. Recurrence rate was 3% (4/131), and death rate was 1.5% (2/131). Long-term follow-up will result in better analysis in larger series of patients.

We could not evaluate the factors that have effect on DFS and OS of operated stage I breast carcinoma patients because of the short follow-up period and the small number of the patients. Despite many prognostic and predictive factors described, age, menopausal status, tumor size, grade, lymphovascular invasion, and hormonal status were the most accepted ones.

Age is an independent prognostic factor in most studies (20). In patients with ALN negative and <35 years old, 10 year recurrence risk is higher (3). Risk of dying is also higher in breast carcinoma patients <35 years old (21). It seems that more aggressive tumor development process occurs in younger ages. Age <35 years was accepted as one of the high risk factors in St. Gallen 2001 meeting (5). In our study, none of our patients <35 years old recurred, but median age was 49, and only 12 patients (9.1%) were <35 years old (Table 1).

Since menopausal status correlates with age and hormonal status, its acceptance as an independent prognostic factor is controversial. In St. Gallen 2001 meeting, menopausal status in ALN negative patients is not stratified into different risk group but in the endocrine responsive high risk premenopausal subgroup, adjuvant treatment including ovarian ablation or GnRH analogue was noticed (5).

As the tumor size increases, it gains metastatic potential, and the risk of ALN involvement increases (7). Clinical and pathological tumor size was found to be an independent prognostic factor in most studies and also important in risk stratification in ALN negative patients (7,22). Rosen et al. (23) evaluated 767 ALN negative breast carcinoma patients retrospectively, and 20 year DFS was 88% in 1 cm. tumors, 72% in tumors between 1.1-3.0 cm, and 59% in tumors between 3.1-5.0 cm. Rosner and Lane (3) concluded that the most powerful independent predictive factor was tumor size, then comes grade and age in ALN negative patients. Joensuu et al. (8) reported 10 and 20 year OS of 94% and 92% in patients with 1 cm, and 93% and 75% in >1 cm invasive breast carcinoma patients. In our study, 2 of 87 T1c (2.3%), 1 of 37 T1b (2.7%), and 1 of 7 T1a (14.3%) patients progressed (Table 5). Since the total number of patients is limited, recurrence rate is low (4/131, 3%), and follow-up period is short, effect of primary tumor size on DFS could not be demonstrated. As the tumor size decreases, recurrence occurs later, as a result; longer follow-up period is needed in early stage breast carcinoma patients (9).

Although histological and nuclear grade are independent prognostic factors on recurrence and survival in ALN negative and stage I patients, its subjectivity among pathologists limits its use (2,8,24,25). LVI also correlates with recurrence and death (26). In our study, grade was reported in 52.6% (69/131), and LVI was reported in 29.8% (39/131) of patients in the pathology reports (Table 2).

The prognostic importance of ER and/or PR positivity in ALN negative breast carcinoma patients is controversial. As the ER expression in tumor increases, the response to hormonal treatment increases, in other words ER positivity has predictive role, and to determine the prognostic importance of receptor positivity, patients not taking adjuvant hormonal treatment should be evaluated. In the NSABP B-06 trial, ALN negative 1157 patients without adjuvant treatment postoperatively was followed for 5 years, and ER positivity makes 8% and 10% difference in DFS and OS, respectively, and PR positivity makes 8% difference in OS (25). ER positivity has prognostic and predictive value for hormonal treatment in breast carcinoma patients with tumor size 1

cm (9). In our study, ER was stained in 83 of 131 (63%) patients, and PR was stained in 55% (73/131) of the patients (Table 2).

Primary breast carcinoma risk in the contralateral breast increases in the breast carcinoma patients (0.3%-0.6% per year) (27). In our study, 5 patients (3.8%) had metachronous breast carcinoma in a median period of 64 months (range: 27-86 months). Bilaterality risk is higher in infiltrative lobular carcinoma than other histologies. Only 1 of 5 (20%) metachronous breast carcinoma patients had infiltrative lobular carcinoma in the metachronous breast cancer histology.

Five-year recurrence risk of ALN negative patients is about 20%. In 20 years of follow-up 20% recurrence in stage I, and 12% in tumors <1 cm seen (26,28). In our study, 4 patients (3%) progressed in a median duration of follow-up of 43 months. Median DFS of progressive patients was 19 months (range:13-81 months). One patient (0.8%) had local, 4 had (3%) distant recurrence (Table 5). Breast carcinoma can metastasize to any organ via neighbourhood, lymphatics, and blood. In the autopsy series, the most common sites of metastasis is reported to be bone, lung, and the liver (6). All of our patients with distant metastasis had bone involvement. Sites of distant metastasis are only bone in 2 patients, bone + supraclavicular lymph node in 1 patient, and bone + liver + lung in 1 patient. Survival of patients with visceral organ metastasis is worse than with bone or soft tissue involvement. Two out of 4 progressive patients died, and one of them had visceral organ involvement. In patients with tumors <1 cm and ALN negative, <2% disease related death is seen in 5 year follow-up (7). In our study group, mortality rate was 1.5% (2/131) in a median follow-up of 43 months. Unfortunately, most of the prognostic factors including grade, LVI, ER, and PR was not reported in the pathology reports of progressive patients.

Although survival is long in stage I breast carcinoma patients, disease related recurrences and even death occurs. Age, menopausal status, tumor size, grade, receptor status, and LVI are still keeping their importance as the most important predictive factors in determining the treatment plan in stage I breast carcinoma (5,19,29). Standardisation of pathology reports concerning the information of these factors needed to reach an accurate treatment plan. Besides these, new markers as proliferation markers (Ki67, Thymidin Labeling Index, etc.), angiogenesis markers (VEGF, etc.), and molecular studies (p53, cerbB2, etc.) can help identification of bad prognostic subgroup, and subclassification. During the last few years, the urokinase system of plasminogen activation was found to have prognostic and predictive significance. The proteolytic enzyme urokinase-type plasminogen activator (uPA) plays an important role in degrading extracellular matrix, which is an important step in cancer invasion and metastasis. Plasminogen activator inhibitor 1 (PAI-1), is a specific inhibitor of uPA, and important in the formation of tumor stroma. Both uPA and PAI-1 correlate significantly with disease recurrence and death in breast cancer (30). UPA and PAI-1 measurement may be useful in determining the prognosis of intermediate risk group of early stage breast cancer (5).

In the latest studies, a new method, namely microarray technology, has been reported. This technology has allowed us the analysis of thousands of genes (expression and copy numbers of genes) and gene products, simultaneously. Microarray based expression profiles can detect tumor cells in peripheral blood samples, predict chemotherapy responses in fine-needle aspiration samples in neoadjuvant chemotherapy, and predict DFS and OS from profiles in breast cancer surgical specimens (31). In the nearest future, microarray based gene expression profiling is expected to lead subclassification of breast carcinoma and predict the clinical outcome of early stage patients.

Since there is no screening mammography, patients with invasive breast carcinoma usually diagnosed late, and in advanced stages in our country. Since early diagnosis of breast carcinoma leads to a decrease in the disease related death, national screening programmes should be initiated for women >40 years of age in the nearest future.

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