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Prognostic importance of the outcomes of updating staging system in patients with stage II breast cancer

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Abstract

Breast cancer is the most common cancer in women. Staging plays an important role in treatment planning. In the staging system published by AJCC in 2002, micrometastasis, the total number of metastatic lymph nodes, internal mammarian and supraclavicular lymph node metastases, and level III (apical) lymph node metastases were incorporated to the staging system. These modifications are likely to cause upstaging and changes in treatment plans, precisely in patients previously considered as stage II. This study aimed to investigate the outcomes of update in staging system in terms of mortality and morbidity. The records of 150 patients who underwent surgery for stage II breast cancer were retrospectively reviewed. The patients who were accepted as stage II according to the previous staging systems and planned to be treated accordingly were re-evaluated according to the newly updated staging system. Patients with and without stage change were compared in terms of mortality, local and systemic recurrence, and disease-free survival. We found that 41 (27.3%) of the patients who were accepted as stage II according to the previous staging systems had been upstaged in the new staging system. The relationship between stage migration and tumor diameter was statistically significant. Thirty-one patients (20.7%) had recurrence during follow-up. We found that most of the patients with recurrence (77.4%) had stage migration. There was a statistically significant relationship between apical lymph node involvement and recurrence. Updates in staging system of breast cancer cause stage migration in a significant proportion of patients with stage II breast cancer and are likely to lead to a change in treatment plans in some patients. Stage migration also has an impact on prognosis. In fact, recurrence is more common in patients with stage migration.

Keywords: Breast cancer, cancer staging, stage migration, TNM, AJCC

Introduction

Cancer is one of the leading causes of death worldwide. The number of cancer cases and deaths is expected to increase rapidly as a result of population growth, prolonged life expectancy, and a lifestyle that increases the risk of cancer formation [1]. Breast cancer is the most common cancer in women all over the world. One in eight women will experience breast cancer throughout her life. Although the incidence increased over the years, the mortality rate decreased as a result of early detection and effective treatment. However, in underdeveloped countries, the mortality rate is still increasing [2, 3]. Approximately 1.67 million new cancer cases diagnosed in 2012 accounted for 25% of all cancers among women. Breast cancer is the fifth most common cause of cancer death [4]. It is considered a public health problem because of this high risk. Genetic predisposition and spontaneous mutations are also known to play a role in the development of breast cancer that is associated with multiple risk factors such as age, a family history, an exposure to estrogen effect, a history of hormonal therapy, a history of benign breast disease, diet, and environmental factors [1]. Early diagnosis and treatment are of great importance.

Proper staging of breast cancer is crucial for the physician to guide the treatment and evaluate the effectiveness of treatment options. The staging system used today is the TNM staging system. It classifies malignant tumors based on tumor size (T), the presence of lymph node metastasis (N), and the presence of distant metastasis (M). The worldwide accepted and used system for staging breast cancer is the American Joint Committee on Cancer (AJCC) classification. The AJCCS (American Joint Committee for Cancer Staging) classification, first defined in 1959 and continuously modified according to new developments, is considered as an important indicator that determines the success of the treatment, the probability of survival and recurrence. In addition, the use of a reliable staging system helps to compare the prognosis of patients and the efficacy of treatments among

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different institutions and countries. The results of research on breast cancer required significant changes in the staging system [5] after the fifth edition of the AJCC Cancer Staging Manual in 1997. The TNM classification aims to assist clinicians in planning treatment, determining prognosis, evaluating treatment results, and facilitating information exchange [6].

We retrospectively evaluated the records of patients treated at Hacettepe University Medical Faculty Hospitals and diagnosed with stage II breast cancer according to the fifth AJCC classification. Our study aimed to investigate whether modifications in the AJCC classification made in 2002 may cause stage changes in these patients and this stage change, if any, affects disease-free survival and mortality.

Materials and Methods

Of the patients who underwent surgery for stage II breast cancer in Hacettepe University, Faculty of Medicine, Department of General Surgery and were followed up for at least five years between January 1982 and December 2000, 150 patients' records were available and analyzed retrospectively. The data in the study were obtained from the preoperative evaluation and postoperative follow-up records in the patient files as well as the information in the surgery and pathology reports.

We evaluated the risk factors that may be associated with breast cancer and the criteria that are used in staging and may impact prognosis in patients who were considered stage II according to previous staging systems and planned to be treated accordingly. The localization of metastatic lymph nodes is based on the definition of lymph nodes grouped as apical, axillary vein, and central region lymph nodes in pathology reports. We evaluated the lymph nodes that are referred to as apical lymph nodes as level III lymph nodes (Figure 1).

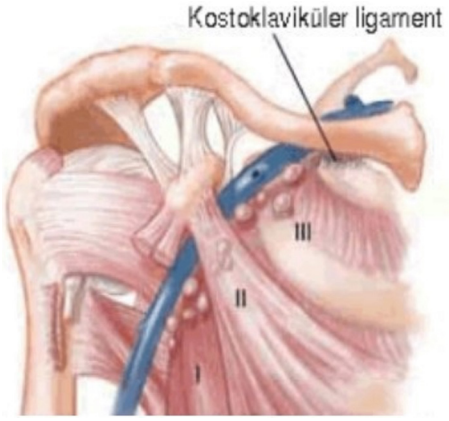

Figure 1. The localization of axillary lymph nodes was evaluated according to the description in the pathology reports (apical, axillary vein, and central lymph nodes)

We determined the patients' stages both according to the previous and the new editions of the TNM classification, compared the prognostic factors and surgical and non-surgical treatments of the patients who migrated to stage III in the modified system with those who remained in the same stage. We planned to investigate whether there was a difference between the groups in terms of mortality, local and systemic recurrence, and disease-free survival.

The patients included in the study were operated by the same surgical teams and treated by the same medical oncologist. In this way, differences and variables in treatment approaches could be ignored and changes in the staging system could be considered as the most important variable.

Statistical analysis was performed using the STATA 8.0 (StataCorp LP, Texas, USA) statistical package. For statistical evaluation, a percentage distribution was used and the chi-square test was applied on the tables 2x2 (degree of independence 1) and 3x2 (degree of independence 2) between the groups. P-value was found from the Chi-square distribution tables. In chi-square assessment, the alpha significance level was taken as 0.05 (safety interval 95%). Factors that may be associated with breast cancer risk and recurrence were also evaluated by a multiple logistic regression analysis (safety interval 95%).

TNM Classification

The staging system used today is the TNM staging system that classifies malignant tumors according to tumor size (T), the presence of lymph node metastasis (N), and the presence of distant metastasis (M). It is based on the classification prepared by the Union Internationale Contre le Cancer in 1959 and subsequently by the American Joint Committee for Cancer Staging and End-Results Reporting. It has been modified in the light of current information over time.

Results

The study included 150 patients with stage II breast cancer according to the previous staging system and with follow-up for at least five years. Their mean age was 56.45 years (range, 34-78 years) and 52.7% of them were in the premenopausal period. Ten of the patients were operated before 1994 and 140 (93.3%) were operated between 1994-2000. The mean follow-up of the patients ranged from five to 21 years, with an average of eight years. Twenty-five (16.7%) patients had a history of hormone replacement therapy. There were no patients with nipple inversion or skin edema. The tumor was located in the upper outer quadrants in 64% of the patients (Figure 2). In 52% of the patients, the tumor diameter was between 20-30 mm with a mean tumor diameter of 29.9 mm. Histopathological examination revealed that the tumor was infiltrative ductal carcinoma in 139 (92.7%) patients and the lobular (nine patients, 6%) and ductal + lobular (two patients, 1.3%) types were very rare. Estrogen receptors were evaluated in 99 patients and found strongly positive in 72 (72.7%) of them. Progesterone receptors were positive in 55 (65.47%) out of 84 patients.

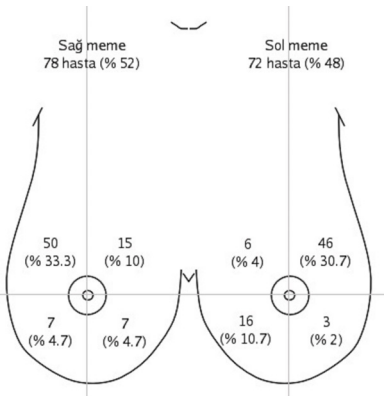

Figure 2. The distribution of breast masses

Applied Treatments and Their Activities

When the surgical interventions were evaluated, we found that most of the patients underwent a modified radical mastectomy. 38.7% of the patients had no metastatic lymph nodes in the axilla. These patients were included in stage II because the tumor was between 20-50 mm in diameter and accepted as T2. There was no statistically significant relationship between the surgical technique and the frequency of finding metastatic lymph nodes (chi-square = 3.404, p≥0.20, CI 95%). The number of total and metastatic lymph nodes were also higher in patients who underwent a radical mastectomy, in parallel to the frequency of axilla involvement. While 92.7% of the patients received chemotherapy protocols, radiotherapy and tamoxifen treatment was applied in a smaller number of patients.

Frequency of Stage Migration and Affecting Factors

We compared the demographic and clinical characteristics of patients with and without stage migration and found no difference between the groups in terms of the use of hormone replacement therapy and the histological type of tumor. When the patients who were stage II according to the previous staging system were re-evaluated according to the new staging system, 41 (27.3%) of them had an increase in stage (stage III). In our study, there were no patients who underwent internal mammary artery (IMA) lymph node sampling, immunohistochemical (IHC) analysis or polymerase chain reaction (PCR) testing, and who had supraclavicular lymph node metastasis or axillary lymph node micrometastasis. Therefore, the factors causing stage migration were level III (apical) lymph node involvement and the total number of metastatic lymph nodes (Table 1). Some of the patients had both reasons. Thirty-two patients had four or more metastatic lymph nodes in total. They were evaluated as N2 or N3, and even with this parameter alone, they skipped the stage. Twenty-nine patients had stage migration because of stage III (apical) lymph node involvement. What is remarkable is that 15 of these patients could skip the stage even because of a single level III metastatic lymph node. When the patients were evaluated according to the previous and new systems, the patients who were accepted as N1 according to the previous system but classified as N2 and N3 in the new system migrated to a higher stage. This stage migration was higher in T2 tumors (78%) (Table 2). The relationship between stage migration and tumor diameter was statistically significant (Table 3) (chi-square = 16.462, p = 0.001, CI = 95%). When the subgroups were grouped with different limit values and compared with each other (Table 4), we noticed this relationship was significant only in the grouping where the 20-mm tumor diameter was the limit value which showed parallelism with the T1-T2 separation in the current staging system.

Table 1. Causes and frequency of stage migration.

	Number	Percentage
Level III (apical) lymph node involvement	29	70.7
Total number of metastatic lymph nodes	32	78
Both	22	53.6

Table 2. Distribution of stage migration according to T and N classification.

Previous Staging	New Staging	Number	Percentage	Relationship Between Tumor Size and Stage Migration
T1N1	T1N1	12	8	
T1N1	T1N2	5	3.3	% 22
T1N1	T1N3	3	2	
T2N0	T2N0	57	38	
T2N1	T2N1	41	27.3	
T2N1	T2N2	17	11.3	% 78
T2N1	T2N3	15	10	
Total		**150**		

Table 3. The relationship between tumor diameter and stage migration

	In All Patients	Those with Stage Migration	Percentage of Those with Stage Migration
10-20 mm	24	9	% 37.4
20-30 mm	79	22	% 27.8
30-40 mm	36	7	%19.4
40-50 mm	11	3	%27.3
Total	**150**	**41**	**% 27.3**

Table 4. The relationship betwen tumor diameter and different limit values

Limit Value	Chi-square	p
20 mm	9.902	<0.01
30 mm	1.426	<1
40 mm	1.097	<1

Prognostic Importance of Stage Migration

Because none of the patients underwent internal mammarian lymph node sampling and patients with supraclavicular lymph node involvement were treated as stage IV, the only possibility that may change the treatment plan in patients with stage change was the presence of three or less metastatic lymph nodes in the axilla with at least one of them localized in the apex axilla. In this study, we found seven patients who skipped the stage (<4 metastatic lymph nodes with at least one localized in the apex axilla). The mean follow-up of these seven patients was 7.2 years, six of them underwent MRM and one had RM, and all of them received chemotherapy. During follow-up, four of these seven patients developed recurrence. There was no mortality among the patients included in the study. Thirty-one patients (20.7%) had recurrence during follow-up. We found that most of the patients with recurrence (77.4%) had stage migration (chi-square = 65.731, p ≤ 0.001, CI = 95%). In terms of local and systemic recurrence, we found that 84% of 25 patients with systemic recurrence and three of six patients with local recurrence had stage migration. Therefore, local and systemic recurrence were significantly higher in patients with stage migration compared to patients without (Table 5). All patients with stage migration received chemotherapy. However, radiotherapy was not required in four patients (9.7%) and tamoxifen was not required in 14 patients (34.2%). Although there was a relationship between tumor diameter and stage migration, we could not find a statistically significant relationship between tumor diameter and recurrence frequency (Table 6). We found a statistically significant relationship between apical lymph node involvement and recurrence (chi-square = 37.586, p ≤ 0.001, CI = 95%) (Table 7).

Table 5. Relationship between stage migration and recurrence

Limit Value	All Patients		Patients with Stage Migration		Percentage of Patients With Stage Migration Among Recurrence Patients
	Number	Percentage	Number	Percentage	
Local recurrence	6	4	3	7.3	50
Sistemic recurrence	25	16.7	21	51.2	84
Total	31	20.7	24	16	77.4

Table 6. Relationship between tumor diameter and recurrence (chi-square = 1.602, p≤1, CI = 95%)

	Patient Number	Patients With Recurrence	Percentage
10-20 mm	24	3	12.5
20-30 mm	79	19	24
30-40 mm	36	7	19.4
40-50 mm	11	2	1.8
Total	150	31	20.7

Table 7. Relationship between apical (level III) lymph node involvement and recurrence

	All Patients	Patients With Recurrence	Percentage
Apical Lymph Node involvement positive	29	18	62.1
Apical Lymph Node involvement negative	121	13	10.7
Total	150	31	20.7

The Relation of Variables that Can Affect the Course of Disease and Recurrence

We performed a multiple logistic regression analysis to investigate the extent to which the variables that are associated with tumor and treatment approaches and may affect the course of the disease impact recurrence. At the end of the analysis, we found the presence of three or more metastatic axillary lymph nodes and level III (apical) lymph node involvement to be the factors related to recurrence (Table 8). These findings are consistent with those of previous studies and the results of the chi-square tests mentioned above.

Table 8. Relationship between the variables that may affect the course of the disease and recurrence

	Odds Ratio	P value
Age	0.9426	0.207
Menapausal Condition	1.3569	0.729
History of Hormone Replacement Therapy	0.4066	0.602
Tumor Diameter	1.041	0.191
Total number of metastatic lymph node	1.029	0.664
More than three metastatic lymph nodes	6.310	0.032
Metastatic lymph node in the apex axilla	4.916	0.018
Surgery type	1.3420	0.593
Radiotherapy	1.3181	0.691
Chemotherapy	0.3648	0.407
Hormone Therapy	0.5941	0.391

Discussion

Breast cancer is an important cause of mortality and morbidity among women. Early diagnosis and proper planning of surgical and non-surgical treatments are highly important in reducing this morbidity and mortality. In addition to morbidity related to the disease, avoidable side effects related to treatment should also be prevented. This planning is based on a correct pathological staging of the disease. Significant advances in the diagnosis and management of breast cancer since the publication of the fifth edition of the AJCC Cancer Staging have required important changes to the staging system [5].

There were significant modifications in the staging system published by AJCC in 2002 compared to the previous one. In general, the definition of micrometastasis was added to the staging. In terms of lymph node metastasis, the total number of metastatic lymph nodes, internal mammarian and supraclavicular lymph node metastases, and level III (apical) lymph node metastases were added to the staging in detail [7, 8]. It has been shown that these changes lead to an increase in the stages of patients considered to be stage II in the previous systems [6, 9-10]. It is possible that stage elevation will change the treatment plans. We aimed to investigate whether stage migration due to the modifications actually had an impact on prognosis and whether mortality and disease-related morbidity increased in patients with stage migration.

We re-evaluated the patients who were accepted as stage II according to the previous staging system: we found that 41 (27.3%) of the patients' stages increased (stage III). This ratio is similar to that of previous studies [9, 11]. Adjuvant therapy is required for the treatment of local or systemic microscopic foci that may be left behind after curative surgical treatment in breast cancer. Adjuvant systemic therapy is used if axillary lymph node metastasis is present, tumor size is greater than 2 cm and high-grade, and estrogen receptor is negative. The protocol content and dosage given in the treatment is important. When at least 85% of the planned dose is given, the 20-year disease-free survival rate is 49% and survival is 52%. There is a decrease in rates in those treated at lower doses. In addition, combinations of more than one medication may provide more benefit in axillary metastatic lymph nodes 1-3 [12].

There was no mortality among the patients included in the study. Thirty-one patients (20.7%) had recurrence during follow-up. As for the relationship between stage migration and recurrence, patients with stage migration had more local recurrence and distant metastasis than those without stage migration. In 32 (48%) of the patients, the total number of metastatic lymph nodes

was four and above, which was considered to be N2 or N3, and even with this parameter alone, patients skipped the stage. Our clinical experience and the results of multicenter and large-scale studies indicate that the number of positive lymph nodes affects prognosis regardless of tumor size [13]. However, in the previous classifications of AJCC staging, there is no consideration regarding the number of positive lymph nodes. In the sixth edition, axillary lymph node involvement was classified as 1 to 3, 4 to 9, and 10 and more positive lymph nodes. It is known that prognosis is very bad especially in the last group. At least ten lymph nodes should be sampled to minimize errors in axilla staging. The increase in the number of metastatic lymph nodes increases the risk of death from the disease [14].

In addition to the number of lymph nodes, an important prognostic finding was the involvement of level III lymph nodes (apical lymph nodes) [9, 11]. The number of patients who skipped the stage due to apical lymph node involvement was 29 (43.5%). Other important findings among the results of the study are as follows: the presence of level III (apical) lymph node metastasis shifted the stage to an upper stage in 15 patients (36.6% of the stage skippers) even with a single metastatic lymph node and change the treatment plan. Also, recurrence is significantly more common in patients with level III (apical) lymph node metastasis. In the multiple logistic regression analysis, we found that more than three axillary metastatic lymph nodes and a level III (apical) lymph node involvement are factors related to recurrence. This demonstrates the prognostic significance of level III (apical) lymph node involvement, similar to previous studies [11, 15, 16]. Therefore, the surgery for breast cancer, especially in patients with negative parameters, should ensure to remove these lymph nodes. In addition, the surgical material removed by the surgeon should be identified, if possible, for the correct detection of level III (apical) lymph nodes by a pathologist. If not possible, the specimen's orientation by a pathologist should be ensured by marking the apex axilla and lateral margin.

Patients who were accepted as N1 according to the previous system but classified as N2 and N3 in the new system moved to an upper stage. This stage migration was higher in T2 tumors (78%). Therefore, it may be necessary to classify the tumor diameter as a parameter that may directly affect the stage migration in staging systems to be developed in the future. Smaller tumors are less likely to cause axillary lymph node metastasis. Therefore, it was concluded that it may unnecessarily increase morbidity to perform complete axillary dissection in these patients and that limited axillary dissection can be performed to avoid it. Silverstein et al. evaluated the relationship between tumor diameter and the presence of axillary lymph node metastasis in 1220 patients with breast cancer. They found that the incidence of axillary lymph node metastasis increased from 3.5% in tumors of less than 5 mm to 17% in tumors of 5-10 mm in diameter. They found that tumor diameter was an important prognostic factor for disease-free and overall survival [17, 18].

Previous classifications of the AJCC staging system included no explanation for the magnitude of lymph node metastasis. Therefore, there is no distinction between the effect of a single tumor cell identified in the lymph node and a 5-mm-diameter metastasis on the treatment plan. The new staging system treats tumor foci of less than 0.2 mm in the lymph node as isolated metastatic cells. A metastasis must be between 0.2 mm and 2 mm to be counted as micrometastasis. However, the clinical significance of the presence of metastatic foci especially of less than 0.2 mm is not clear [19].

The treatment plan may change in patients with stage change according to the new staging system. This change requirement may occur if:

1. Although axillary is negative, radiotherapy may be required in patients with internal mammarian lymph node metastasis.

2. Although there are fewer than four metastatic lymph nodes in the axilla, radiotherapy may be required in patients when at least one of these metastatic lymph nodes is located in the apical region (level III).

3. Patients previously considered stage IV because of the presence of supraclavicular lymph node metastasis may be considered to be stage III according to the new system and aggressive treatment with surgical and non-surgical methods may be required. However, because our study involved only stage II patients, this possibility is not expected in this group.

All patients with stage migration received chemotherapy. However, radiotherapy was not required in four patients (9.7%) and tamoxifen in 14 patients (34.2%). Two of the five patients who did not receive radiotherapy and developed recurrence were those who skipped the stage. Considering that, it can be predicted that a treatment planned according to the new staging system may prevent such recurrences.

Conclusion

Modifications in the staging of breast cancer in 2002 cause stage migration in a significant proportion of patients with stage II breast cancer and may change the treatment plan in some of them. Stage migration also has an impact on prognosis. In fact, recurrence is more common in patients with stage migration.

Factors causing stage migration are four and more metastatic lymph nodes and the presence of level III (apical) lymph nodes in our study group.

Stage migration is more common in patients with T2 tumors. However, we could not find a significant relationship between tumor diameter and recurrence frequency. Level III (apical) lymph node involvement is closely associated with recurrence. Even a single lymph node involvement at this level may cause stage migration in a significant proportion of patients. For these reasons, a complete sampling of level III (apical) lymph nodes is required.

Conflict of interests
The authors declare that they have no conflict of interest

Financial Disclosure
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Ethical approval
The study protocol has approved from local ethic committee.

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