Original Study

The Effect of Total Size of Lesions in Multifocal/Multicentric Breast Cancer on Survival

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Abstract

Multifocal/multicentric (MF/MC) breast cancer was identified about 10% of all breast cancer. Approximately 4000 breast cancer patients were evaluated and it was found that the MF/MC breast cancer was better T stage classified and more predictive according to T_{sum} which is the sum of the longest diameters of the lesions. This is more prominent in MF/MC patients with low disease burden.

Background: In this study, we aimed to assess the prognostic performance of determining the T stage according to the total size of lesions compared with the size of the largest lesion in the breast in patients with multifocal/multicentric (MF/MC) breast cancer. **Patients and Methods:** The charts of the patients with MF/MC breast cancer who were diagnosed between 2003 and 2014 were reviewed. The T stage of MF/MC tumors was determined according to the largest lesion size (T_{max}) as well as the sum of the longest diameters of the lesions (T_{sum}) in the breast. **Results:** Multifocal/multicentric tumors were identified in 323 of 3890 patients (8.3%) with breast cancer. Ten-year rates of overall survival (OS; 75% and 74%; $P = .965$) and disease-free survival (DFS; 66% and 61%; $P = .817$) were similar in patients with unifocal and MF/MC tumors, respectively. When the T stage was determined by summing the sizes of the lesions, the T stage of 67 (20.7%) and 63 (19.5%) patients advanced from T1 to T2 and from T2 to T3, respectively. Thus, the T stage increased in 130 patients (40.2%) according to American Joint Committee on Cancer. Discriminatory ability of T_{sum} was better than T_{max} in terms of OS and DFS, as shown with higher Royston D and Harrel C statistics and Schemper V values. **Conclusion:** The new T classification proposed in this report stands out as a better predictive classification particularly in patients with low disease burden.

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Introduction

Multifocal (MF) and multicentric (MC) are descriptors to define the presence of more than 1 focus of tumor in the same breast, within the same quadrant (MF) or within different quadrants (MC). The incidence of MF/MC breast cancer ranges from 4% to 50%.[1,2] The effect of MC and MF breast cancer on survival is not well characterized. In some studies, multifocality itself does not appear to be a contributing factor for worse outcome.[3] The American Joint Committee on Cancer (AJCC) staging guidelines recommend the greatest dimension of the tumor to be used to stage the disease for MF/MC tumors, and when multiple tumors are present, this is denoted by suffixing the T stage with "m" (for example, T2m). This has no effect on overall staging category.[4] However, the largest unidimensional measurement might not be representative of the total breast tumor burden in patients with MF/MC disease.[5] In this study, we investigated and compared the prognostic value of determining the T stage according to summation of diameters of the lesions or according to the size of the largest lesion alone in patients with MF/MC breast cancer.

Patients and Methods

In this retrospective single-center study, we analyzed data from 3890 patients with breast cancer at the department of medical oncology at Hacettepe University between 2003 and 2014. We assessed patient and tumor characteristics including age, menopausal status, TNM stage, histologic subtype, Grade, lymphatic and vascular invasion, hormone receptor (HR) and c-erb-B2 expression, and all therapies. Tumor classification as unifocal, MF, or MC was determined according to pathology reports. Tumors were classified

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Table 1 Patient Characteristics

	Unifocal (n = 3567)	MF/MC (n = 323)	P
Mean Age, Years	49.7	46.8	<.001
Premenopausal, %	47.8%	61.3%	<.001
BMI, kg/m^2	27.6	26.6	.002
Histology, %			.014
Ductal	70.6	68.2	
Lobular (pure or mixed)	16.2	21.8	
Other	9.4	6.5	
Grade			.567
1	12.5	10.8	
2	45.0	44.1	
3	42.5	45.1	
LVI, %	25.9	33	.006
T Stage			.565
T1	33.2	34.8	
T2	47.7	49.7	
T3	14.4	12.4	
T4	4.7	3.1	
Nodal Status (LN Positivity), %	56.2	64.4	.005
Stage			.082
I	23.6	18.4	
II	42.8	42.1	
III	24.9	39.9	
IV	8.8	9.7	
HR$^+$, %	79.3	84.3	.034
HER2$^+$, %	19.7	24.4	.045
BCS, %	34%	22.3%	< .001
Chemotherapy, %	72.4	78.7	.016
Radiotherapy, %	71.5	71.3	.952

Abbreviations: BCS = breast conserving surgery; BMI = body mass index; HR = hormone receptor; LN = lymph node; LVI = lymphovascular invasion; MC = multicentric; MF = multifocal.

as MF if multiple invasive lesions were found in the same quadrant of the breast or MC when multiple lesions were found in more than 1 quadrant of the same breast.[6] Tumor size was obtained from pathology reports. In patients with MF/MC tumors, T stage was determined using 2 methods; the diameter of the largest tumor focus, T_{max}, and the summation of the largest diameters of each tumor focus present in the pathology sample, T_{sum}. We separately compared the prognostic value of the AJCC stages on the basis of T_{max} ($Stage_{max}$) and T_{sum} ($Stage_{sum}$). The effect of both T categories (T_{max}, T_{sum}) on disease-free survival (DFS) and overall survival (OS) estimates was evaluated. All patients were treated according to local protocols and followed-up every 3 months for 2 years, every 6 months for 3 years, and then annually. This study was approved by the institutional ethical committee.

Statistical Analysis

Statistical analyses were performed using SPSS for Windows, version 20.0 (IBM Corp, Armonk, NY), STATA (StataCorp, College Station, TX) and R (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were reported as median (interquartile range). Survival rates were calculated using the Kaplan–Meier method and differences between groups were assessed using the log rank test. The 95% confidence interval was calculated for all hazard ratios in Cox regression analysis. A 2-tailed $P < .05$ was considered statistically significant.

Monotonicity of gradients for the staging systems was examined by comparing the event rates across different stages as well as by testing the trend as stage progresses using the corresponding versions of the log rank test. Patients with better prognostic stage are expected to have smaller event rates compared with those with poorest prognostic stage.

The discriminatory ability assessments were measured using the following tests :

1. Likelihood ratio and Akaike Information Criterion (AIC): the AIC value within the Cox proportional hazard regression model was calculated for each system to measure its discriminatory ability.[7] A smaller AIC value or a higher likelihood ratio (LR) χ^2 indicates a better model.
2. The Harrell C statistics were calculated to evaluate the performance of the 2 systems in predicting the outcomes and were compared to estimate the increase in predictive value.[8] The result of the Harrell C index indicates "no discrimination" if equal to 0.5 and changes toward the direction of "perfect discrimination" as approaches 1.
3. Royston D statistics is a measure of prognostic separation in survival data and estimates separation between independent survival distributions.[9] Higher D statistics show better discriminatory capacity.
4. The proportion of the variation of survival explained by each factor was measured using the Schemper V statistics.[10] A higher V value corresponds to a higher explained variability and is indicative of a better prognostic score.

Figure 1 Overall Survival of the Patients With Unifocal Tumors versus Multifocal/Multicentric Tumors (Log Rank Test, $P = .97$)