Evaluation of the Prognostic Stage in the 8th Edition of the American Joint Committee on Cancer in Patients with Breast Cancer and Internal Mammary Lymph Node Metastasis

JI HYEON JOO[1], SU SSAN KIM[2], BYUNG HO SON[3], SEUNG DO AHN[2], JIN HONG JUNG[2],
EUN KYUNG CHOI[2], SEI HYUN AHN[3], JONG WON LEE[3], HEE JUNG KIM[3] and BEOM SEOK KO[3]

[1]Department of Radiation Oncology, Ajou University School of Medicine, Suwon, Republic of Korea;
Departments of [2]Radiation Oncology and [3]Breast and Endocrine Surgery, Asan Medical Center,
University of Ulsan College of Medicine, Seoul, Republic of Korea

Abstract. *Background/Aim: This study evaluated the prognostic value of the 8th edition of American Joint Committee on Cancer (AJCC) cancer staging system for patients with internal mammary lymph node (IMN) metastases. Materials and Methods: Of the patients with breast cancer who were treated between 2009 and 2013, 66 were diagnosed as cN3b. We restaged the patients and analyzed the prognostic value of the prognostically staged groups. Results: With a median follow-up of 53.9 months, the 5-year overall survival rates of patients with IIIA, IIIB, and IIIC stages were 100%, 95%, and 50% (p=0.001), while the progression-free survival rates were 100%, 83%, and 50% (p=0.005). Conclusion: Despite the small number of patients, the prognostic stage provided accurate information for IMN metastasized breast cancer, which will lead to more accurate prognosis predictions and optimal treatment selection.*

After development of the American Joint Committee on Cancer (AJCC) staging system in the 1970s, the system was updated every few years, reflecting the most important factors predicting survival. The new "prognostic stage" in the 8th edition of the AJCC staging system incorporates important biological factors, such as estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER2), histological grade, and TNM stage into one system (1). This approach requires further validation,

Correspondence to: Su Ssan Kim, MD, Ph.D., Department of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-Gu, Seoul, 05505, Republic of Korea. Tel: +82 230105680, Fax: +82 230106950, e-mail: watermountain@hanmail.net

when considering the complexity of clinical use caused by a new staging system. Several validation studies from large populations of patients have demonstrated the accuracy of the new staging system (2, 3), including for patients with advanced breast cancer (4).

The tumor and patient characteristics of internal mammary lymph node (IMN)-positive breast cancer differ from locally advanced breast cancer without IMN metastasis (5). Studies have clearly shown that patients with IMN involvement have a worse prognosis that is associated with higher rates of distant disease and lower overall survival (OS) (6). Thus, the consensus discussion on the detection and treatment of IMN metastasis continues (5, 7). Therefore, we first verified the predictability of the new staging system in these patients. This retrospective study evaluated the prognostic value of the 8th edition of AJCC cancer staging system for patients with IMN metastasis.

Materials and Methods

Patients. Our Institutional Review Board approved the retrospective use of clinical data. Of the patients who were treated with neoadjuvant chemotherapy, surgery, and radiotherapy (RT) in our institution between 2009 and 2013, 114 women had suspicious IMNs either by size and morphology or by 18F-fluorodeoxyglucose (FDG) avidity. After all examinations, clinical IMN metastasis was diagnosed by a positive 18F-FDG positron emission tomography with a computed tomography (PET/CT) scan or pathological confirmation, either with (cN3b) or without (cN2b) axillary lymph node metastasis. The details of this treatment have been described previously (7). All patients received external beam RT targeting the breast or chest wall and/or regional lymphatics, including the ipsilateral axillary apex, supraclavicular fossa, and IMN compartment.

Statistics. All clinicopathological data were retrieved from the electronic medical recording system, including histological and nuclear grades, hormone receptor status, and HER2 status of the primary tumor. Locoregional recurrence included ipsilateral breast, chest wall, axillary, supraclavicular, or IMN. Distant failure was

Table I. *Patient characteristics.*

Variables	N (%) Total	N IIIA	N IIIB	N IIIC	*p*-Value
Age (median, years)	45.1±10.6	42.0	47.3	42.2	0.151
Body mass index (median)	23.2±3.4	25.8	23.1	23.0	0.554
Laterality					
Rt	26 (39)	0	15	11	0.498
Lt	40 (41)	2	23	15	
Clinical T category					
T1-2	42 (54)	1	25	16	0.393
T3	24 (36)	1	13	10	
SUV$_{max}$	3.1±2.4	3.0	3.1	3.1	0.997
Breast surgery					
BCS	29 (44)	0	16	13	0.367
MRM	37 (56)	2	22	13	
Axillary surgery					
ALND	53 (80)	1	33	19	0.218
SLNB	13 (20)	1	5	7	
Estrogen receptor					
Negative	36 (55)	0	12	24	0.000
Positive	30 (45)	2	26	2	
Progesterone receptor					
Negative	46 (70)	0	20	26	0.000
Positive	20 (30)	2	18	0	
HER2					
Negative	45 (68)	0	19	26	0.000
Positive	21 (32)	2	19	0	
Histologic grade					
2/3	29 (44)	2	22	5	0.002
3/3	37 (56)	0	16	21	
ypT-stage					
0 or 1	37 (56)	0	21	16	0.237
2 or 3	29 (44)	2	17	10	
ypN-stage					
0 or 1	47 (71)	1	27	19	0.827
2 or 3	19 (29)	1	11	7	
Adjuvant trastuzumab					
No	45 (68)	0	19	26	0.000
Yes	21 (32)	2	19	0	
Hormone therapy					
No	34 (52)	0	10	24	0.000
Yes	32 (48)	2	28	2	
RT to SCL					
No	1 (1)	0	1	0	0.688
Yes	65 (99)	2	37	26	
RT to IMN					
No	5 (8)	0	5	0	0.136
Yes	61 (92)	2	33	26	

SUVmax: Maximum standardized uptake value; BCS: breast-conserving surgery; MRM: modified radical mastectomy; ALND: axillary lymph node dissection; SLNB: sentinel lymph node biopsy; HER2: human epidermal growth factor receptor 2; RT: radiation therapy; SCL: supraclavicular lymph node; IMN: internal mammary lymph node.

defined as recurrence away from local and regional sites. Disease-free status was defined as no evidence of local failure, regional failure, distant failure, or death. Locoregional recurrence-free

survival (LRRFS), distant metastasis-free survival (DMFS), progression-free survival (PFS), and OS were calculated using the Kaplan–Meier method, and comparisons between the groups were made using the log-rank test. A multivariate analysis was performed using the Cox proportional hazards model. All analyses were two-sided, and a *p*-value <0.05 was considered significant. All statistical analyses were performed using R software (8).

Results

Patients. Seventy-four patients with breast cancer had IMN metastases and were treated with neoadjuvant chemotherapy, surgery, and adjuvant RT during the inclusion period. Of them, patients with inflammation of bilateral breast cancer (N=4) and patients with solitary IMN metastases without axillary LN metastases (N=4) were excluded. The median age of the cohort was 45 years old. Clinical T stage was T1-2 in 42 (54%) patients and T3 in 24 (36%) patients. ER, PR, and HER2 status was positive in 30 (45%), 20 (30%), and 21 (32%) cases, respectively. Adjuvant trastuzumab and hormone therapy was used in 21 (32%) and 32 (48%) patients. RT to the supraclavicular and IMN was used in 32 (48%) and 61 (92%) cases, respectively. The patient and tumor characteristics are summarized in Table I.

According to the anatomical stage, N3b patients were staged as IIIC, regardless of the T stage. These patients were separated into three stages of IIIA (N=2, 3%), IIIB (N=38, 58%), and IIIC (N=26, 39%) according to their prognostic stage. Thus, 61% had their stage reassigned and downstaged.

Survival outcomes among the prognostic stages. With a median follow up of 53.9 months (interquartile range=39-66 months), the OS, PFS, LRRFS, and DMFS rates at 5 years were 77%, 70%, 81%, and 72%, respectively (Figure 1). According to the Cox multivariate analysis, hormone receptor status and ypN-stage were independent prognostic factors for OS and DFS (Table II). Hormone receptor status, lympho-vascular space invasion, and ypN-stage were independent prognostic factors for DMFS (Table III).

The prognostic stage incorporates anatomical factors and biological factors into one system. When patients with IMN-positive breast cancer were stratified based on prognostic stage, significant differences were observed in the OS, PFS, LRRFS and DMFS rates. The 5-year OS rates of patients with IIIA, IIIB, and IIIC were 100%, 95%, and 50% (*p*=0.001), while the PFS rates were 100%, 83%, and 50% (*p*=0.005). The 5-year LRRFS rates of patients with IIIA, IIIB, and IIIC were 100%, 92%, and 63% (*p*=0.013), while the DMFS rates were 100%, 83%, and 54%, respectively (*p*=0.013). The survival graphs are shown in Figure 2. The difference between stage IIIB and IIIC was significant: OS, hazard ratio (HR) of IIIC (*vs*. IIIB)=1.997 (*p*=0.002); DFS, HR=1.441 (*p*=0.004); LRRFS, HR=5.536 (*p*=0.01); DMFS, HR=3.752 (*p*=0.006), according to the Cox-regression model.
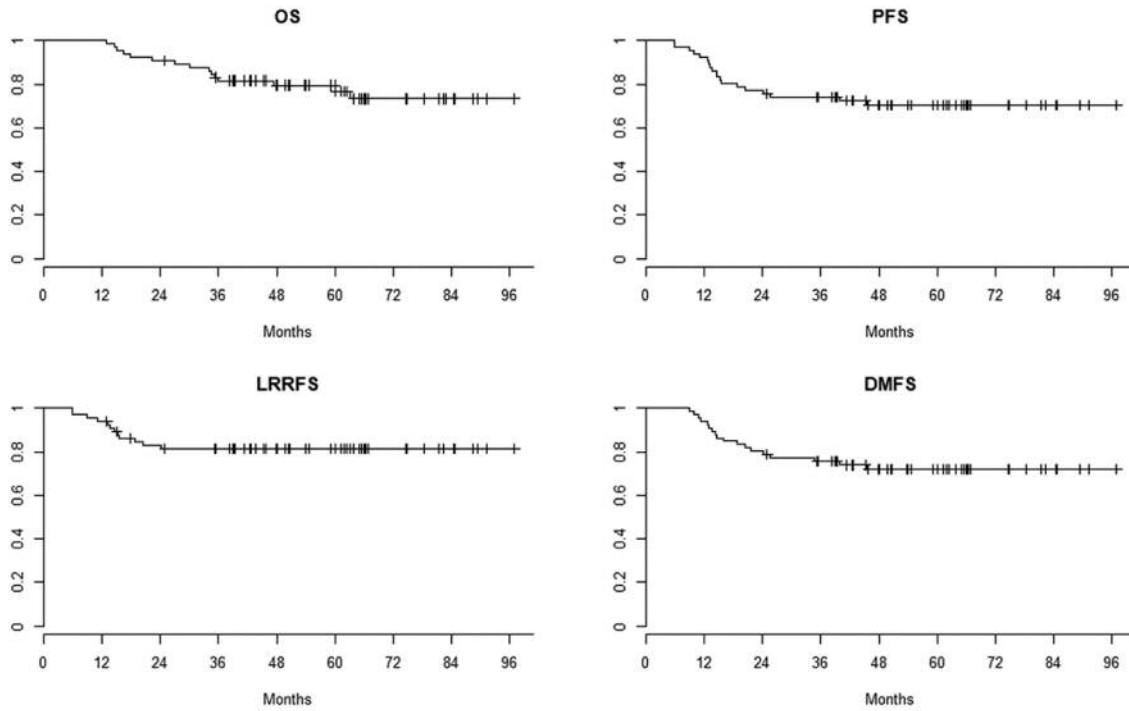
Figure 1. *Kaplan–Meier survival curves of the total patients. OS: Overall survival; PFS: progression-free survival; LRRFS: locoregional recurrence-free survival; DMFS: distant metastasis-free survival.*
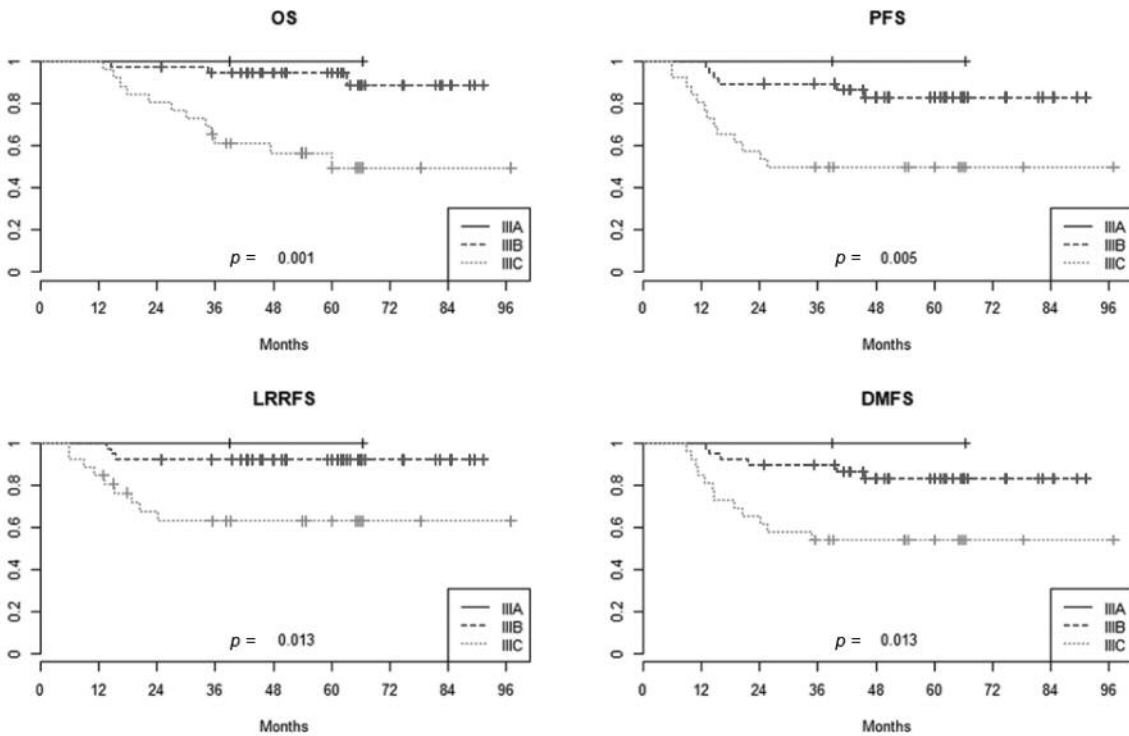

Figure 2. *Survival curves according to different stages using the 8th edition of the AJCC prognostic staging system. OS: Overall survival; PFS: progression-free survival; LRRFS: locoregional recurrence-free survival; DMFS: distant metastasis-free survival.*

Table II. *Univariate and multivariate analysis for OS, PFS.*

	OS		PFS	
	Univariate	Multivariate	Univariate	Multivariate
Lt breast	1.24 (0.45-3.43)		1.35 (0.55-3.32)	
BMI ≥23	0.61 (0.21-1.78)		0.42 (0.15-1.16)	0.42 (0.15-1.19)
cT3 (*vs.* T1-2)	0.61 (0.19-1.92)		0.6 (0.21-1.66)	
Histologic grade 3	3.54 (1-12.55)		2.68 (0.97-7.46)	
MRM	1.75 (0.6-5.11)		1.53 (0.6-3.9)	
Hormone receptor+	0.07* (0.01-0.52)	0.05* (0.01-0.40)	0.17* (0.05-0.58)	0.08* (0.02-0.28)
HER2-positive	0.5 (0.14-1.77)		0.53 (0.17-1.59)	
Ki67 ≥70	1.55 (0.56-4.28)		1.66 (0.674.08)	
LVI	1.55 (0.56-4.27)		2.63* (1.04-6.71)	5.74* (2.12-15.52)
ypN2/3 (*vs.* 0/1)	2.52 (0.91-6.96)	3.93* (1.40-11.03)	2.61* (1.06-6.44)	
Adjuvant trastuzumab	0.5 (0.14-1.77)		0.53 (0.17-1.59)	
Hormone therapy	0.13* (0.03-0.56)		0.22* (0.07-0.65)	

OS: Overall survival; PFS: progression-free survival; *Statistically significant values.

Table III. *Univariate and multivariate analysis for LRRFS, DMFS.*

	LRRFS		DMFS	
	Univariate	Multivariate	Univariate	Multivariate
Lt breast	2.15 (0.68-6.78)		1.52 (0.6-3.82)	
BMI ≥23	0.61 (0.18-2.04)		0.46 (0.16-1.29)	
cT3 (*vs.* T1-2)	0.57 (0.15-2.09)		0.66 (0.24-1.85)	
Histologic grade 3	4.57 (1-20.87)	3.05 (0.69-14.46)	2.4 (0.86-6.75)	
MRM	1.2 (0.38-3.78)		1.84 (0.69-4.91)	
Hormone receptor+	<0.01*		0.18* (0.05-0.64)	0.11* (0.03-0.38)
HER2-positive	0.66 (0.18-2.44)		0.57 (0.19-1.74)	
Ki67 ≥70	1.99 (0.63-6.28)		1.89 (0.74-4.78)	
LVI	1.01 (0.32-3.2)		2.31 (0.89-5.96)	2.93* (0.02-8.45)
ypN2/3 (*vs.* 0/1)	1.4 (0.42-4.67)		3* (1.19-7.57)	3.02* (1.08-8.42)
Adjuvant trastuzumab	0.66 (0.18-2.44)		0.57 (0.19-1.74)	
Hormone therapy	<0.01*		0.24* (0.08-0.73)	

LRRFS: Locoregional recurrence-free survival; DMFS: distant metastasis-free survival; BMI: body mass index; *Statistically significant values.

Discussion

In our study, we analyzed the clinical significance of the prognostic staging system proposed in the 8th edition of the AJCC cancer staging system for breast cancer with IMN metastases. A total of 66 patients with N3c disease were included. The prognostic stage system screened out 61% of the patients with relatively better survival outcomes from IIIC and they were grouped into IIIA or IIIB. Patients with stage IIIC were more likely to have recurrence and death in the long-term. The risk of recurrence or death was about double compared to patients in stage IIIB. The current analysis showed an improvement in the discriminatory value for the prognostic staging system compared to the anatomical staging system.

Pathological nodal staging of IMNs has changed over time. In the past, all IMN metastases were classified as pN3, because IMNs were considered of great importance in formulating the prognosis of patients (9). After the introduction of the detection technique and sentinel lymph node biopsy, IMN metastases were divided into pN1b, pN1c, pN2b, or pN3b status. IMN metastases are no longer considered to have a dismal prognosis. One of the largest retrospective reports came from Zhang *et al.* (5). Ninety-six patients who were clinically IMN metastasis-positive received neoadjuvant chemotherapy, surgery, and adjuvant radiation, including the IMN region. The actuarial 5-year locoregional control, DFS, and OS rates were 80%, 60%, and 79%, respectively (5). Another study assessed the outcomes

of patients diagnosed with cN3 disease identified by PET. Of the 12 patients with cN3b disease, LRRFS was 83%, and DFS was 67% (10). A DFS rate of 87% was reported when low-tumor burden IMN metastases were treated using a multimodal treatment, even in patients who were mostly staged as cN3b (7). Therefore, patients diagnosed as N3b are potentially curable, and it is necessary to tailor their intensive treatment. Thus, an accurate prognostic judgement is required as demonstrated by using the AJCC 8th edition.

Tumor burden and biology are considered equally in the era of personalized care. A new "prognostic stage" that included ER, PR, HER2, histological grade, and conventional TNM variables into one staging system was added to the 8th edition. As the staging system has been gradually changed and subdivided, the stages were re-evaluated differently, even though the pathological findings did not change. Weiss *et al*. analyzed more than 50,000 patients from the California Cancer Registry with stage I-IV breast cancer treated between 2005 and 2009. The prognostic stage re-staged 51.6% of the patients. The prognostic stage (C index by Harrell concordance index, 0.8426) provided more accurate stratification with respect to disease-specific survival than the anatomic stage (C index, 0.8097) (3). The prognostic stage enabled a clearer classification of survival according to disease stage subtype than that observed using the anatomic stage. In previous staging, some subgroups of patients with lower stage disease had lower survival rates than that of patients with a higher stage and better subtype disease. Thus, it has been argued that the intrinsic subtype of breast cancer has an equal or greater prognostic impact in predicting clinical outcomes (11). Lee *et al*. reported that the survival rate of patients with stage II hormone receptor (HR)(+)/HER2(–) disease is superior to that of patients with stage I HR(–)/HER(–) disease. Also, the survival rate of patients with stage III HR(+)/HER2(–) disease was better than those with stage II HR(–)/HER2(–) disease. However, the overlap of the survival curves disappeared when using the prognostic stage (2).

Conclusion

Despite the small number of patients, the prognostic stage provided accurate prognostic information for IMN metastasized breast cancer. This staging will lead to greater accuracy in the prognosis prediction and optimal treatment selection, and, therefore, better outcomes.

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