Original Article

Comparison of 7th and 8th American Joint Committee on Cancer Tumor-Node-Metastasis Staging in Infiltrating Ductal Carcinoma of the Breast: A Retrospective Study

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Abstract

Context: The American Joint Committee on Cancer (AJCC) staging system is a very important prognostic factor for treating patients with carcinoma breast. There has been a recent change in the staging of breast cancer, from the 7th edition to 8th edition AJCC. Hence, the present study aimed to analyze the stage migration from 7th to 8th edition AJCC staging in infiltrating ductal carcinoma (IDC) and comparison of each staging system with the Nottingham prognostic index (NPI) prognostic scoring system. **Aims:** The aim is to evaluate the stage migration between the 7th and 8th edition AJCC in IDC of the breast and compare both staging systems with the NPI prognostic scoring system. **Settings and Design:** In this retrospective study, we collected the clinical and pathological data from 56 IDC cases from January 2019 to June 2021 presenting at our institute. We restaged all the cases as per the prognostic staging system (8th AJCC) and calculated the survival status with NPI as long-term (5-year survival status) follow-up of the cases was not possible. **Statistics:** Categorical data were represented in the form of frequencies and proportions. Chi-square test or Fischer's exact test (for 2 × 2 tables only) was used as a test of significance for qualitative data. Continuous data were represented as mean and standard deviation. *P* value was calculated. **Results:** In this study, majority of the cases were in grade 1 and in Stage II. Among 16 cases in Stage II A, 7 (43.8%) showed down staging and 3 (18.8%) showed up staging, while 12 (70.6%)/17 cases in Stage II B showed down staging. When compared with NPI both 6th and 7th AJCC showed statistical significance. **Conclusion:** Stage migration (upstaging and down staging) was seen in the 8th edition AJCC when compared to the 7th edition AJCC. Both the staging system correlated with the NPI prognostic index. However, long-term follow-up of these patients must be done to look into the efficacy of the 8th AJCC staging system before changing the treatment protocol.

Keywords: *Anatomic staging system, infiltrating ductal carcinoma, prognostic staging system*

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Introduction

Breast cancer is a heterogeneous disease which differs in their clinical behavior and response to treatment and outcome. The prognosis of breast cancer depends on many factors such as histological grade, molecular type, size of the tumor, lymphnode status, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 status (Her2 neu).[1] To provide the appropriate treatment for these patients, it is essential to understand the tumor staging which also helps in determining the prognosis and survival of these patients.[2]

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The American Joint Committee on Cancer (AJCC) first published the widely used cancer staging system (tumor-node-metastasis [TNM] staging-tumor, node, and metastasis) in 1977. From January 1, 2010, oncologists worldwide have been using AJCC 7th edition for the patient care. Parameters included in the 7th edition such as large tumor size, lymph node involvement, and metastasis was directly proportional to the poor prognosis.[3,4]

However, it is well established that factors such as tumor grade, biomarkers (ER, PR, Her2 neu, and Ki67) are also known to influence the therapeutic regimen in breast carcinoma patients. To provide a more accurate and personalized treatment approach a panel of AJCC experts revised the traditional guidelines to include the biomarkers, giving rise to the 8th edition of AJCC.[4,5] Only few studies have been done to look into the validation of the 8th edition AJCC breast cancer prognostic staging system. Earlier they have used the "will rogers phenomenon" in cases of breast, lung, prostate and other carcinoma patients to define the effect of stage migration and the stage-specific survival. Will Rogers phenomenon describes the effect of stage migration in cancer patients where the stage-specific survival improved compared to previous studies. In the original study patients with cancers were reclassified into different prognostic groups by considering the subtle disease manifestations or diagnostic modalities and were shown to have improved survival.[6,7]

Hence, the present study aimed to evaluate the stage migration between the 7th and 8th edition AJCC in infiltrating ductal carcinoma (IDC) of the breast and to compare the 7th and 8th AJCC system with the Nottingham prognostic index (NPI) prognostic scoring system.

Subjects and Methods

This retrospective study included all invasive ductal carcinoma (NOS) cases. Since it was retrospective study sample size was not calculated and total of 6120 specimens received from January 2019 to June 2021. Among that 158 were breast carcinoma which comprises tru-cut biopsy, lumpectomy, and mastectomy specimens. All mastectomy specimens received in a rural tertiary teaching hospital attached to a medical college. Only 56 IDC cases were included which satisfies our inclusion and exclusion criteria [Figure 1]. After obtaining the institutional ethical clearance and de-identifying the patients their demographic details, tumor size, grade, lymph node status, paraffin blocks, histopathology slides, and immunohistochemical slides were retrieved from the archives of the Department of Pathology. Consent was waived off since this was a retrospective study and patients were de-identified before the start of the study. The study was conducted according to ethical guidelines established by the Declaration of Helsinki and other guidelines like Good Clinical Practice Guidelines and those established by the ICMR. No funding was received for our study.

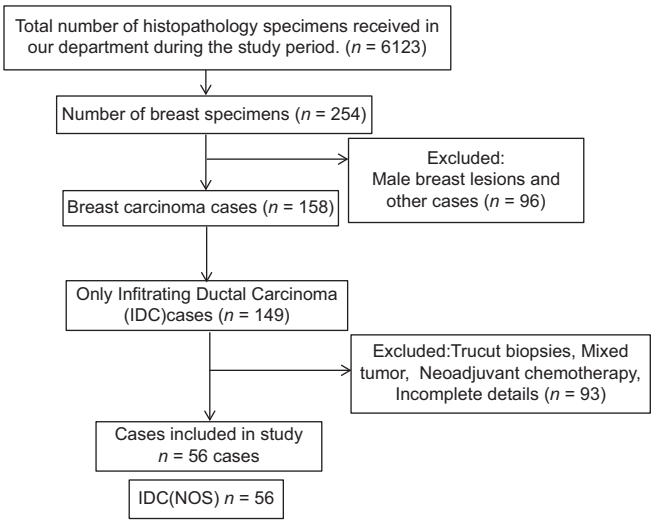

Figure 1: Derivation at number of cases included in our study

All the IDC cases diagnosed during our study period have been included. Incomplete clinicopathological data and patients who received neoadjuvant chemotherapy/ radiotherapy before modified radical mastectomy were excluded from our study.

Study methodology

All the hematoxylin and eosin slides were rescreened by two authors to confirm the histological type, tumor grade, presence and absence of nodal metastasis, and lymphovascular invasion. Immunohistochemistry slides of ER, PR, Her2, and Ki67 were also screened. Any discrepancies were resolved by the 3rd author. Immunohistochemistry was done using the principle of the peroxidase-anti peroxidase method using appropriate positive and negative control.

With the above data, all cases were staged according to the 7th and 8th AJCC staging systems. All the cases were evaluated and stage migration from 7th to 8th edition AJCC breast cancer in IDC of breast was analyzed. In view of the short duration of the study follow-up data were not available for all the cases. Since the NPI score is an established prognostic tool to determine the survival status of breast carcinoma cases, we compared both the 7th and 8th staging systems with the NPI score to determine the same.

Tumor grading was done as per the Modified Scarff-Bloom-Richardson Histologic Grading.[8] Patient survival status was determined using NPI and was

calculated using the standard formula.[9] ER and PR were interpreted as per the Allred score and Her 2 neu were scored as per the 2018 ASCO guidelines.[10,11] Ki67 was scored using the standard guidelines.[12]

Statistical analysis

Data were entered in Microsoft Excel data sheet and were analyzed using SPSS 22 version software (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). Categorical data were represented in the form of frequencies and proportions. The Chi-square test or Fischer's exact test (for 2 × 2 tables only) was used as test of significance for qualitative data. Continuous data were represented as mean and standard deviation.

For the statistical significance, *P* value (probability that the result is true) was calculated for comparison between the 7th AJCC and 8th AJCC with NPI and a score of < 0.05 was considered statistically significant after assuming all the rules of statistical tests.

Statistical software

MS Excel, SPSS version 22 (IBM SPSS Statistics, Somers NY, USA) was used to analyze data.

Results

We had collected all the IDC cases during the study period.

Among 149 IDC NOS cases, 56 cases from Stage I to Stage III were included in this study. The clinicopathological data of this study group are given in Table 1. Most of the patients were in 51–60 years with a median age of 52 years. Among the 56 cases, majority of them were in grade I that is 26 (46.4%) and 21 cases (37.5%) belong to moderate NPI scoring.

Most of the cases belong to molecular subtype such as luminal A 23 (41.1%), followed by triple-negative breast cancer (TNBC) 15 (26.8%). Table 2 represents the biomarkers.

When we sub classify all the cases among 56 cases 23 (41.1%) were of luminal A type, 7 (12.5%) were of luminal B type and 11 (19.6%) were of Her2 + type and 15 (26.8%) were in TNBC type.

The patients were staged according to the 7th TNM Stage and majority of the cases were in II B and II A. Among 56 cases, 17 (30.4%) cases found to be in Stage II B and 16 (28.6%) cases were in II A. Moreover, the remaining cases were 4 (7.1%) in I A, 11 (19.6%) in III A, 3 (5.4%) in III B, and 5 (8.9%) in III C.

When we applied the 8th TNM staging system to 56 patients, 15 cases (26.8%) found to be in IA, 10 cases (17.9%) were in I B, nine cases were in II A (16.1%), nine cases were in II B (16.1%), seven cases were in III A (12.5%), two cases were in III B (3.6%), four cases were in III C (7.1%).

Furthermore, we evaluated the stage migration of individual cases and grouped them into upstaging, downstaging, and no changes. The distribution of participants with respect to the 7th and 8th AJCC system is given in detail in Table 3.

As per 7th AJCC majority of the cases belong to Stage II 33 (59%) and on the contrary in the 8th AJCC system preponderance observed in Stage I with 25 (44.7%) cases. When we analyzed stage migration we found that in our study group 28 (50%) cases were downstaged and 5 (8.9%) cases were upstaged and 23 cases showed no change in staging.

NPI was found to be statistically associated with both 7th and 8th TNM staging systems.

Table 1: Clinico pathological characteristics

Characteristics	Number of cases, *n* (%)
Age (years)	
31–40	11 (19.6)
41–50	13 (23.2)
51–60	18 (32.1)
61–70	6 (10.7)
>70	8 (4.3)
Tumor grade	
Grade 1	26 (46.4)
Grade 2	20 (35.7)
Grade 3	10 (17.9)
NPI scoring	
Excellent	9 (16.1)
Good	13 (23.2)
Moderate	21 (37.5)
Poor	13 (23.2)

NPI: Nottingham prognostic index

Table 2: Distribution of biomarkers (*n*=56)

	n (%)
ER	
Positive	29 (51.8)
Negative	27 (48.2)
PR	
Positive	28 (50.0)
Negative	28 (50.0)
Her2neu	
Positive	24 (42.9)
Negative	32 (57.1)
Ki67 (%)	
<10	9 (16.1)
10–25	29 (51.8)
>25	18 (32.1)

ER: Estrogen receptor, PR: Progesterone receptor, Her2neu: Human epidermal growth factor receptor 2

Table 3: Stage migration in 8th American Joint Committee on Cancer

7th AJCC	8th AJCC (%)			
	Stage	Upstage	Downstage	No change
IA (4)	IA			4 (100)
IIA (16)	IA: 5 (31.3)	3 (18.8)	7 (43.8)	6 (37.5)
	IB: 2 (12.5)			
	IIA: 6 (37.5)			
	IIB: 2 (12.5)			
	IIIA: 1 (6.3)			
IIB (17)	IA: 6 (35.3)	-	12 (70.6)	5 (29.4)
	IB: 4 (23.5)			
	IIA: 2 (11.8)			
	IIB: 5 (29.4)			
IIIA (11)	IB: 4 (36.4)	1 (9.1)	6 (54.6)	4 (36.4)
	IIA: 1 (9.1)			
	IIB: 1 (9.1)			
	IIIA: 4 (36.4)			
	IIIB: 1 (9.1)			
IIIB (3)	IIIA: 1 (33.3)	1 (33.3)	1 (33.3)	1 (33.3)
	IIIB: 1 (33.3)			
	IIIC: 1 (33.3)			
IIIC (5)	IIB: 1 (20)	-	2 (40)	3 (60)
	IIIA: 1 (20)			
	IIIC: 3 (60)			
Total		5	28	23

AJCC: American Joint Committee on Cancer

Discussion

The prognostic outcome depends on several factors such as age, size, grade, hormonal and lymphnode status, histologic type, familial, and staging of the disease. The previous edition of AJCC was based on the anatomic information about tumor hence to improve the prognostic utility, the biomarkers such as ER, PR, and Her 2 neu has been included in the 8th AJCC staging system for breast carcinoma.[13-15]

Epidemological studies found that the incidence of breast carcinoma was more in women around perimenopausal period. In our study population, the median age of diagnosis was 52 years (ranges from 31 to 73 years) which is similar to the study which showed a median age of 54 years.[14]

Histologic grading remains an important prognostic factor, especially in breast carcinoma regardless of lymph node status and size of the tumor.[16] Comparison of histological grades in other studies shows < 20% of cases were in grade 1, while the present study showed 46.4% in grade 1 which was in concordance with the Indian study, in which 57.9% were in grade 1.[17,18] As compared to studies done in other countries grade 1 cases were more in our population. This may be because of the variation in the tumor pathogenesis biology in our population.[18,19]

Breast carcinomas are heterogeneous tumors with distinct hormonal expressions and characteristics. The gene expression patterns reflect the tumor phenotype, disease prognosis, and systemic treatment planning. Based on the gene expression profile with the immunohistochemical panel of ER, PR, Her2neu, Ki67 index tumors are classified into four groups such as luminal A (ER+, PR+/-, Her 2 neu-, Ki67 < 14%), luminal B (ER+, PR+/-, Her 2 neu+/-, Ki67 > 14%), Her2 + (ER-, PR-, Her2neu +, Ki67 > 14%), triple negative (ER-, PR-, Her2neu-, Ki67 > 14%).[18] In the present study, majority of the cases 23 (41.1%) were in luminal A type which is in concordance with other studies which showed 65.6% and 60.0%.[5,17] Biological behavior of the tumor decides the molecular subtype. Luminal A tumors have a better prognosis as compared to other variants.[20,21]

Studies done to compare the anatomic staging with the prognostic staging has showed conflicting results.[5,17,18] The previous study done shows that in the case of TNBC despite receiving chemotherapy, exhibits moderate-to-high nuclear pleomorphism and results in a worse prognosis.[22]

In our study, 15 (26.8%) triple-negative cases were observed among that only 6.7% (1/15) showed down staging with a better prognosis and the remaining had no significant change. The study involving two cohorts of the Chinese population including TNBC cases showed upstaging in 46.1% and 62.4%. However, they did not find better prognostic value with 8th AJCC as compared to the traditional anatomic staging system of both disease-free survival and overall survival (OS) status.[23] Data analysis of similar studies in TNBC found that majority of the cases had upgraded.[24-26]

When we look into the other molecular subtypes of IDC, the study done by Jang *et al*. in the Korean population shows that among 714, 71 (9.9%) were upstaged and 254 (35.6%) were downstaged and 389 (54.5%) shows no change. Another study done by Wong *et al*. in Singapore shows that 363 (5.8%) were upstaged, 2558 (40.7%) were downstaged and 3366 (53.5%) shows no change. The comparable result seen in a study done by Aldrees *et al*. in the Canadian population shows 797 (16.1%) were upstaged, 1346 (27.2%) were down staged and 2799 (56.7%) shows no change.[5,17,18] Recently, study done by Nittala *et al*. showed 45.0% upstaging in Caucasian and 69.7% in African–American population. Also found downstaging of 16.5% and

14.4% in both populations, respectively. They concluded that there was significant variability found between the races while analyzing the stage migration, hence attention need while interpreting of data.[27]

To know the therapeutic outcome and survival status follow-up of the patient must be done and disease-free survival should be documented. However, 5 years of follow-up of the patients could not be done due to the design of the study. Many studies have shown that 5 years disease-free survival correlated well with the 8th AJCC staging system as compared to the 7th AJCC system.

NPI is known to correlate with disease-free survival of the patient. Many studies have proved the same.[27,28] Prognosis was analyzed by the disease-free survival status (DSS) and overall survival (OS) status by Jang *et al*. and He *et al*.[17,23]

Results of our study comparing the NPI index with both 7th and 8th staging systems showed a good correlation.

Conclusion

The newly proposed 8th edition AJCC system has incorporated biomarkers to stratify the patients of IDC of the breast. Stage migration was seen between both systems in 33 (59%) of patients. Since both the staging system correlated well with NPI more studies has to be done to look into the efficacy/outcome of present treatment protocols after upstaging/downstaging the patients as per 8th edition AJCC.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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