Research Article

Histopathological Grading and Staging of Invasive Ductal Carcinoma in Modified Radical Mastectomy Specimens

Qurat ul Ain Javaid[1], Farrukh Kamal[2], Munazza Iqbal[3], Rahat Sarfaraz[4], Asmaa Qureshy[5], Rabia Basharat[6]

[1,2,3,5,6]Department of Pathology, Fatima Jinnah Medical University, Lahore; [4]Department of Pathology, King Edward Medical University, Lahore

Abstract

Background: Breast carcinoma is the most common malignancy in females associated with high mortality rate.

Objective: The purpose of present study was to describe the histological grade and histopathological stage of invasive ductal carcinoma of breast among female patients and to determine the association of tumor size and histological grade with nodal metastasis.

Methods: This is an analytical cross sectional study, conducted in the Department of Pathology Fatima Jinnah Medical University Lahore, Pakistan from September, 2019 till February, 2020. Female patients of all age groups who were diagnosed with invasive ductal carcinoma and underwent modified radical mastectomy were included in the study. Tissue processed and Hematoxylin and Eosin staining was performed. All the sections were examined under the light microscope by myself and two other consultant pathologists independently. Histological grading of invasive ductal carcinoma was done by following Modified Scarff Bloom Richardson grading system and histopathological staging was done according to CAP protocols.

Results: Total of 60 female patients diagnosed with invasive ductal carcinoma were included in the present study. Mean age of the patient calculated was 48.17± 13.12 years with age range from 26 to 90 years. Size of the tumor ranged from 1cm to 10cm. On microscopy, histological grade III was the most frequent grade (36, 60%). Out of total 60 cases n=43(71.6%) were diagnosed with regional lymph node metastasis and T2N1Mx(17,38.3%) was the most frequent stage of the tumor. Statistically no significant association of tumor size and histological grade was observed with regional lymph node metastasis ($p > 0.05$).

Conclusion: Most of the cases of invasive ductal carcinoma in this study were diagnosed with high histological grade (Grade III) and presented with regional lymph node metastasis. Most frequent tumor stage observed was pT2N1Mx. Statistically no significant association of tumor size and histological grade was observed with lymph node metastasis.

Corresponding Author | Dr. Qurat ul Ain Javaid, Department of Pathology, Fatima Jinnah Medical University Lahore.
Email: drqurat.q@gmail.com

Key words: Invasive ductal carcinoma, Modified radical mastectomy, Histological grade, Histopathological stage.

Introduction:

Breast carcinoma is one of the most common malignancy seen in women worldwide and is considered to be the most common cause of high mortality[1]. In developed countries like USA, approximately 268,600 new cases of breast cancer were diagnosed among US women in 2019 and about 41,760 women died from this disease[2,3]. It is being predicted that by the year of 2021 the incidence of breast carcinoma will be 85 per 100,000 women[1].

According to 2018 WHO data the incidence of breast carcinoma among Asian countries like India was 27 % which is the highest among all other types of carcinomas. The overall mortality with breast carcinoma is 13.4% which is also highest[4,5]. In Pakistan with reference to WHO data of 2018 about 92,639 women were diagnosed with different types of malignancies and among those proportion of breast carcinoma was 36.8% which

is the highest[6]. The incidence and mortality of females diagnosed with breast carcinoma is highest in Asian countries like India and Pakistan[7].

Just like other carcinomas arise from different organs of the body the development of breast carcinoma is also having diverse complex multiple genetic and environmental factors. Major risk factors include increase age, strong family history, hormone replacement therapy, early menarche and late menopause. Regardless of ethnic and racial origin all females are at equal risk of developing breast carcinoma[8].

Histological breast parenchyma is composed of multiple ducts and lobules. About 80% of the breast carcinomas arise from the ducts and nearly 10-15% arises from the lobules. There are many other histological subtypes of breast carcinomas but these are very rare and less than 10% of such rare types are diagnosed per year[9].

Among all the histological types of breast carcinomas diagnosed so far, invasive ductal carcinoma (IDC) is the most common type. Patients diagnosed with invasive ductal carcinoma usually present with the higher lymphatic invasion and ultimate poor prognosis as compare to other types[9].

There are many clinicopathological factors that are related to the prognosis of breast cancer patient. These factors include old age, Hormone receptor status, type of gene mutation, size of the tumor, presence or absence of lymphovascular invasion and tumor necrosis. Tumor size estimation and lymphnode metastasis provides prognostic information. However, lymphnode metastasis is one of the most important independent prognostic parameter[9,10].

Nottingham modification of Scarff Bloom Ritchardson grading system is the most common and strongest applicable system recommended by WHO to grade the invasive ductal carcinoma in to three different histological grades (Grade I, II and III). This grading system is based on the total score obtained from different histological features including: tubule formation, degree of nuclear pleomorphism and mitotic count[10].

Objective:

The objective of present study is to observe the most common histological grade and the histopathological stage of invasive ductal carcinoma of breast among female patients in modified radical mastectomy specimen and to determine the association of tumor size and histological grade with nodal metastasis.

Methods:

This is an analytical cross sectional study, conducted in the department of Pathology Fatima Jinnah Medical University Lahore, Pakistan from September, 2019 till February, 2020. A sample size of 60 was calculated by using Cochran formula by taking margin of error (e) 0.05, an estimated proportion of population (p) 0.5, population of 60, and Z score from the Z table at 95% confidence interval which was 1.96. Non-probability convenient sampling technique was adopted to collect the data. Female patients of all age groups who were diagnosed with invasive ductal carcinoma and underwent modified radical mastectomy were included in the study. Patients with prior chemotherapy or radiotherapy and those who diagnosed with other histological types of breast carcinoma were excluded from the study. All modified radical mastectomy specimens received in histopathology section were kept in 10% formalin solution for fixation. Representative sections were taken according to CAP protocols and all sections were processed accordingly[11]. Hematoxylin and Eosin staining was performed and all sections were examined under the light microscope with two consultants independently to reduce observer bias. In case of disagreements, further extensive tumor sampling and deeper cuts of the sections were carried out and observed by third consultant pathologist independently. Histological grading of the invasive ductal carcinoma was done by following Modified Scarff Bloom Richardson grading which includes standards for tubule formation, mitotic count and nuclear pleomorphism. Each of these features is scored from 1-3 and then score is added to given a final total score ranging from 3-9. The final total score is used to determine the grade i.e Grade I (3-5), Grade II (6-7), Grade III (8-9)[22]. Histopathological staging (pTNM, T=Tumor size, N= Nodal metastasis, M= Distant metastasis) was observed according to the cancer protocols of college of American Pathologists. T1 includes tumor size ≤2cm, T2 >2cm but ≤ 5cm, T3 tumor is >5cm and T4 is tumor of any size with direct extension to the chest wall and/or to the skin ulceration

or skin nodule. In lymph node metastasis N0 is no regional lymphnode metastasis, N1= 1-3, N2= 4-9 and N3= 10 or more lymph nodes metastasis[11].

Collected data were entered and analyzed in SPPS version 21. Mean and standard deviation was calculated for the quantitative variable i.e age and tumor dimensions. Frequencies and percentages were determined for qualitative variables i.e gender, stage and grade of the tumor. Chi-square test was used to determine association of tumor size and histological grade with lymph node status. A value of $p < 0.05$ was considered statistically significant.

Results:

Total 60 patients were included in present study. Mean age of the patient calculated was 48.17± 13.12 years and age ranged from 26 to 90 years. Most common side of tumor origin was from left breast (43, 71.6%). Tumor in right breast was seen in 17 (28.3%) patients. Tumor size in our study ranged from 1cm to 10cm in greater dimensions with mean tumor size 4.1cm.

Histological grading of all the cases of invasive ductal carcinoma was done according to Modified Scarff Bloom Richardson grading system. Most common histological grade observed in present study was high grade, Grade III (36, 60%, Figure 2), whereas grade II tumor was seen in 24(40%, Figure 1) cases. No case was

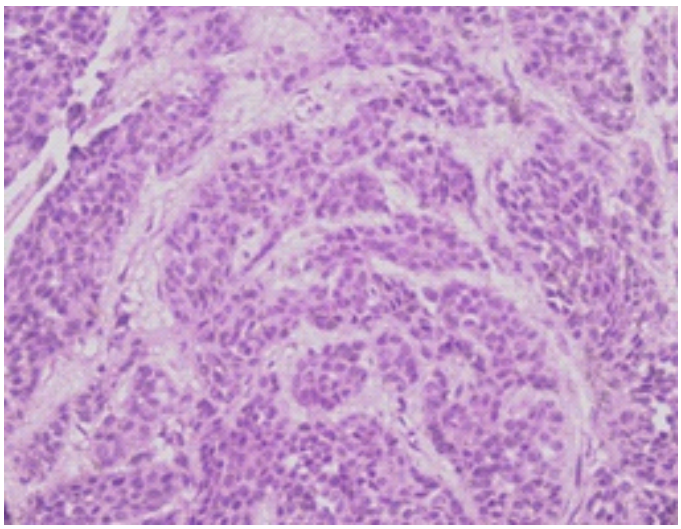

Figure 1: *Invasive ductal carcinoma grade II*

diagnosed with histological Grade I in this study.

Out of total 60 cases, n=43 (71.6%) showed regional lymph node metastasis. Out of 60 cases, 27 (45%) cases

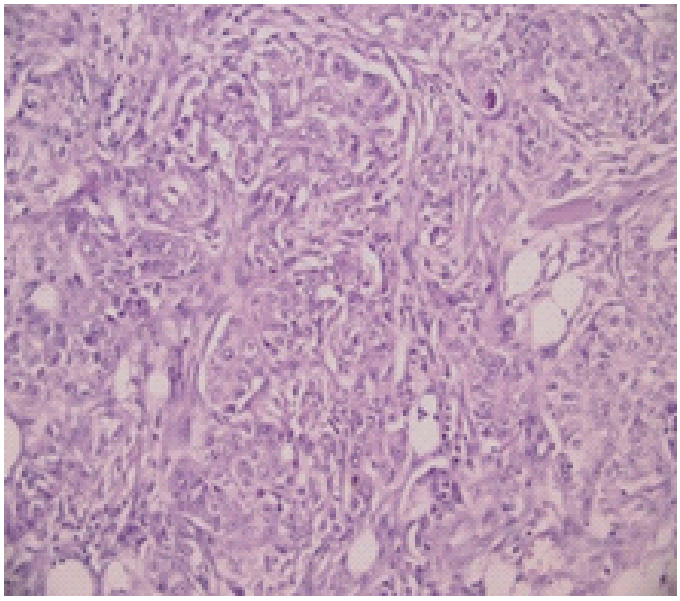

Figure 2: *Invasive ductal carcinoma grade III.*

showed nodal metastasis in 1-3 (N1) axillary lymph nodes and 5 (8.3%) cases had nodal metastasis in 10 or more than 10 lymph nodes (N3). Table 1 and 2.

Status of nodal Metastasis was observed with histologcal grade of the tumor. Out of n=36 (60%) cases of grade III morphology, 14(38.9%) showed nodal metastasis in 1-3 lymph nodes (N1) and 11 (30.6%) showed no regional lymph node metastasis. In grade II tumors 13(54.2%) showed nodal metastasis in 1-3 regional lymph nodes (N1) and 6 (25%) were negative for nodal metastasis(N0). Chi-Square test was applied to determine the relationship of tumor grade with nodal metastasis which turned out non-significant (p= 0.224) (Table 1).

Table 1: *Tumor Grade and Nodal metastasis (n=60)*

Tumor Grade	Nodal Metastasis					
	N0	N1	N2	N3	Total	P value
Grade II	6 25.0%	13 54.2%	5 20.8%	0 0.0%	24 100.0%	0.224
Grade III	11 30.6%	14 38.9%	6 16.7%	5 13.9%	36 100.0%	
Total	17 28.3%	27 45.0%	11 18.3%	5 8.3%	60 100.0%	

Histopathological staging (pTNM) was done according to the CAP protocol. Out of total 60 cases of invasive ductal carcinoma, 42 (70%) had tumor size between 2 to 5cm (T2) and 9 (15%) cases had tumor size more than 5cm (T3) and only 3 (4%) cases had tumor size between

1 to 2cm (T1) in greater dimension. When cross tabulation between tumor size and nodal metastasis was done by using Chi-Square test, turned out non-significant (p= 0.85) (Table 2).

Table 2: *Tumor Size and Nodal Metastasis (n=60)*

Tumor size	Nodal Metastasis					
	N0	N1	N2	N3	Total	P value
T1	1	2	0	0	3	0.852
	33.3%	66.7%	0.0%	0.0%	100.0%	
T2	11	17	10	4	42	
	26.2%	40.5%	23.8%	9.5%	100.0%	
T3	3	5	0	1	9	
	33.3%	55.6%	0.0%	11.1%	100.0%	
T4	2	3	1	0	6	
	33.3	50.0%	16.7%	0.0%	100.0%	
Total	17	27	11	5	60	
	28.3%	45.0%	18.3%	8.3%	100.0%	

Most frequent tumor stage observed in present study was pT2N1Mx (17, 38.3%) followed by pT2N2Mx (10; 16.6%) (Table 3).

Table 3: *Frequency of Tumor Stage (n=60)*

Stage	Frequency	Percentage
pT1N0Mx	1	1.7
pT1N1Mx	2	3.33
pT1N2Mx	0	0.00
pT1N3Mx	0	0.00
pT2N0Mx	11	18.3
pT2N1Mx	17	38.3
pT2N2Mx	10	16.6
pT2N3Mx	4	6.66
pT3N0Mx	3	5
pT3N1Mx	5	8.3
pT3N2Mx	0	0.00
pT3N3Mx	1	1.7
pT4N0Mx	2	3.3
pT4N1Mx	3	5
pT4N2Mx	1	1.7
pT4N3Mx	0	0.00
Total	60	100.0

Discussion:

Breast carcinoma is the most common diagnosed malignancy in females and the most frequent primary cause of increased mortality worldwide.[1] Previously breast carcinoma is reported in elderly females, but now different studies from western countries and from Pakistan have reported increased in incidence of breast carcinoma in younger females as well because of the shift of mean age (50 to 45.7 years)[13,14,21]. In present study mean age of the patient was also 48.7 years which is identical to the previous studies carried out in India and Pakistan[13,15]. According to US database breast cancer in Asian women who are under 40 years of age is more aggressive and advanced in similar age group of US women[16].

Left breast side was the most common (71%) side of carcinoma in our study. Raisa bano et alreported most common side of breast carcinoma from right side which is not only in contrast to our study but also to other local studies[8]. Recent studies that are carried out in Pakistan and neighboring countries reported most common side of breast carcinoma from left side that are the same to our study[13,17,21].

Studies show that the size of tumor is associated with the metastasis of breast carcinoma which is not only in regional lymph nodes but also at other sites of the body which results in the poor outcome of the patient[18]. In present study most of the cases had tumor size between 2 to 5cm (T2) followed by 15 % T3, 10% T4 and only 5% T1. Our study findings are similar to the results of previous studies done in India and Pakistan[9,19].

Metastasis to axillary lymph nodes was seen in 71.6% of cases out of which 45% had metastasis in 1-3 lymphnodes (N1) followed by N0 (28%), N2 (18%) and N3 (8%). Most frequent tumor stage observed was pT2N1Mx. Our findings are similar to the findings of another studies carried out in Pakistan and other countries of this region[10,17,19].

According to the literature, in western countries majority (64%) of patients who diagnosed with breast carcinoma have disease limited to the breast at the time of presentation but in our country Pakistan, patients with breast carcinoma present at already locally advanced stage (regional lymph node metastasis) and even with distant metastasis[21].

Presentation at locally advanced stage in our country Pakistan is may be due to a combination of factors such as poor health education, social stigma, faith in substitute therapy and the economic burden of recent

medical treatment. These all factors explain the low levels of involvement in screening and early diagnosis programs of breast carcinoma.

In present study majority of the patients were diagnosed with histological grade III (60%) and few cases were diagnosed with grade II (40%) and no case was diagnosed with grade I histology. Our study findings are in contrast with the findings of other Pakistani studies carried out in 2016 and 2017 who reported most common histological grade, grade II (45% of 90 cases and 90 % of 140 cases)[13,19]. However, a study carried out in India in 2016 and in Pakistan 2019 also reported histological grade III the most common grade observed in invasive ductal carcinoma cases.[9,20]EmanGusbi et al also observed majority cases of grade III invasive ductal carcinoma in their study that is also in support of our study results[22].

In present study the relationship of tumor size and histological grade with regional nodal metastasis was also determined which was found statistically non-significant ($p > 0.05$). Number of studies have suggested statistically non-significant association of tumor size and histological grade with nodal and distant metastasis[23,24].

Invasive ductal carcinoma diagnosed with high grade histology and early lymph node metastasis are associated with the poor prognosis of patient.[17] Metastasis to lymph nodes is itself an independent prognostic factor. Considering this high grade of tumor and presentation at already locally advanced stage, emphasizes on awareness programs, early screening and diagnosis of breast carcinoma in our population is needed. Accurate long term breast cancer risk assessment for women who will attend routine screening could help to reduce the disease burden along with intervention associated harms.

Our present study include limited number of cases collected from single center. Therefore, the authors suggest a study comprising on maximum number of cases collected from different hospitals to ascertain detailed and in- depth knowledge of the spectrum of histological grade, tumor stage their relationship with nodal metastasis.

Conclusion:

Most of the cases of invasive ductal carcinoma in this study were diagnosed with high histological grade (grade III) and at locally advanced stage (Lymph node metastasis) at the time of presentation. Most frequent tumor stage observed was pT2N1Mx. Statistically no association of tumor size and histological grade was found with regional lymph node metastasis.

Ethical Approval: Given

Conflict of Interest: The authors declare no conflict of interest.

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