International Journal of Clinical and Diagnostic Pathology

ISSN (P): 2617-7226
ISSN (E): 2617-7234
www.patholjournal.com
2020; 3(1): 323-327
Received: 02-11-2019
Accepted: 29-11-2019

Dr. Neema Ankur Rana
Assistant Professor, Department of Pathology, SSG Hospital and Medical College, Baroda, Gujarat, India

Dr. Hiral Samir Shah
Tutor, Above Samir Hospital, Lakdipul, Dandiabazar, Baroda, Gujarat, India

Dr. Meena Rajiv Daveshwar
Associate Professor, Department of Pathology, SSG Hospital and Medical College, Baroda, Gujarat, India

Dr. Rinkal Patel
Resident Doctor, Department of Pathology, SSG Hospital and Medical College, Baroda, Gujarat, India

Dr. Jinal Shah
Resident Doctor, Department of Pathology, SSG Hospital and Medical College, Baroda, Gujarat, India

Dr. Kishna Vasoya
Resident Doctor, Department of Pathology, SSG Hospital and Medical College, Baroda, Gujarat, India

Dr. Brijesha A Patel
Resident Doctor, Department of Pathology, SSG Hospital and Medical College, Baroda, Gujarat, India

Corresponding Author:
Dr. Hiral Samir Shah
Tutor, Above Samir Hospital, Lakdikapul, Dandia Bazar, Baroda, Gujarat, India

Histopathological subtypes of breast cancer and its correlation with various prognostic factors

Dr. Neema Ankur Rana, Dr. Hiral Samir Shah, Dr. Meena Rajiv Daveshwar, Dr. Rinkal Patel, Dr. Jinal Shah, Dr. Kishna Vasoya and Dr. Brijesha A Patel

DOI: https://doi.org/10.33545/pathol.2020.v3.i1e.194

Abstract
The role of the pathologist in the evaluation of breast cancer now transcends that of determining the correct morphologic diagnosis, including the grading and staging of the cancer. Lumpectomy or modified radical mastectomy is the most commonly used tools for disease management. The objective of this study is to identify the clinical, macroscopic and microscopic examination of breast cancer which evaluates details like age, laterality, tumor size, stage, grade, lympho-vascular invasion and lymph node status. The study comprised a total of 212 breast cancer patients of which 209 were females. The mean age was 51.16 years. Majority of female patients were within age group 41 to 50 years. Left breast was more commonly involved than right breast. Invasive ductal carcinoma was the most common observed histological type of breast carcinoma. Grade II tumors were most frequent followed by Grade III and Grade I. Maximum 125 cases (59%) were 2-5 cm size. Mean size was 4.8 cm. There was increased incidence of Lymphovascular invasion as grade increased. Maximum number of lymphnode involvement was seen in grade II followed by grade III cases. Present study provides significance of various prognostic factors in breast cancer.

Keywords: Breast cancer subtype, histopathology, infiltrating ductal carcinoma, lymphovascular invasion

Introduction
Carcinoma of breast has become the major public health problem among females in developing as well as developed countries. Breast cancer is the most common malignant neoplasm in the world and still accounts for a number of unfavorable outcomes that make it the second leading cause of cancer death in women [1]. The tumor histological grade is one of the most important pathological features. The Nottingham classification system, which is a modification of the Scarff-Bloom-Richardson (SBR) [2, 3]. One, is the most commonly used classification system to determine histological grade in breast cancer [4]. In 1991, its prognostic value was demonstrated for the first time [2], and since then several studies have validated it, which has made it a recommended classification system worldwide [5, 6].
The histopathological factors of breast tumors like tumor size, lymph node status, histological type, histological grade, presence or absence of hormone receptors and age of patients play crucial role on chemotherapy and radiation therapy. The objective of this study is to identify the clinical, macroscopic and microscopic features of MRM specimens.

Materials and Methods
This retrospective was carried out at Department of Pathology, S.S.G. Hospital and Medical College, Baroda. Details of clinical, macroscopic and microscopic examination had been done which provided the data regarding age, gender, tumor size, histological type, stage, grade, lymph node status and lymphovascular invasion. Data were collected and analysed.
A total number of 212 cases that underwent modified radical mastectomy (MRM) received between May 2014 to September 2018 were included in present study. MRM specimens with no residual tumor, patients having previous history of radiotherapy, neo-adjuvant therapy and trucut biopsy were excluded from the study. The clinical details like age, sex, laterality, duration of tumor, skin and nipple areola changes were assessed.

Macroscopic examination provided information regarding size of specimen and tumor, tumor location and lymphnode examination in mastectomy specimens. Histological type, grade, lymphovascular invasion (LVI), and lymph node involvement were evaluated by microscopic examination of Hematoxylin and Eosin Stained tissue sections. Tumor grading was done according to the Nottingham modification of the Scarff Bloom and Richardson's (SBR) grading system [2, 3].

Results

The study comprised a total of 212 breast cancer patients of which 209 (98.6%) were females and 3 (1.5%) were males. The age of the female patients ranged from 20 to 85 years with the mean age of 51.16 years. Majority of female patients were within age group 41 to 50 years. The age for male breast cancer patients was between 59 and 84 years with the mean age of 70.67 years (Table 1).

Out of 212 MRM cases, 112 cases involved left breast whereas, 100 cases involved right breast and no any bilateral breast involvement was observed. In present study, invasive ductal carcinoma (Figure 1) was the most commonly observed histological type of breast cancer with 192 cases among which 3 cases showed changes of predominant ductal carcinoma in situ. (Table 2). Metaplastic(5 cases)(Figure 2) and mucinous (5 cases) (Figure 3) carcinoma were the second most observed type followed by lobular (4 cases), medullary (2 cases), micropapillary (1 case), secretary (1 case)(Figure 4), cribriform (1 case)(Figure 5) and basal type (1 case).

In the present study 12 cases (6.28%) were of Grade I, 96 cases (50.26%) were of Grade II and 83 cases (43.46%) were of Grade III (Table 3). Thus, Grade II tumors were most frequent comprising 50.26% followed by Grade III (43.46%) and Grade I (6.28%). In the present study, maximum 125 cases (59%) were of T2 stage (2-5 cm) followed by 46 cases (21.7%) of T3 stage (5-8cm). There were 25 cases (11.8%) of T1 stage (<2 cm) and 16 cases (7.5%) of T4 stage (>8 cm) tumors. Mean size was 4.8 cm.

LVI and lymphnode involvement by neoplastic breast cancer cells were correlated with histologic grade and type. There is positive correlation between LVI and histologic grade as there is increased incidence of LVI as grade increases. Maximum number of lymphnode involvement was seen in grade II followed by grade III cases.

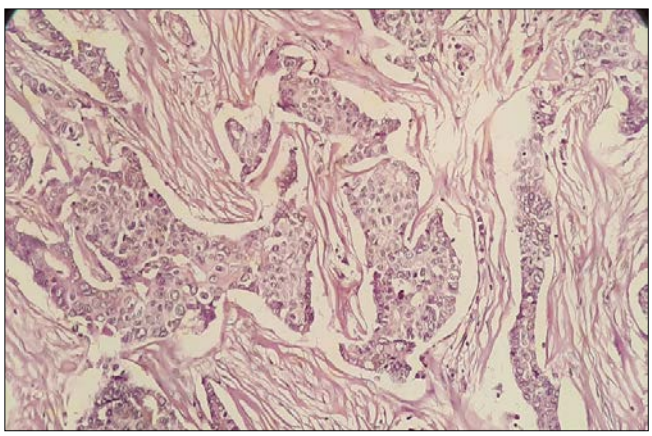

Fig 1: Infiltrating duct carcinoma shows tubule formation, pleomorphism and atypical mitosis (H&E, 200X)

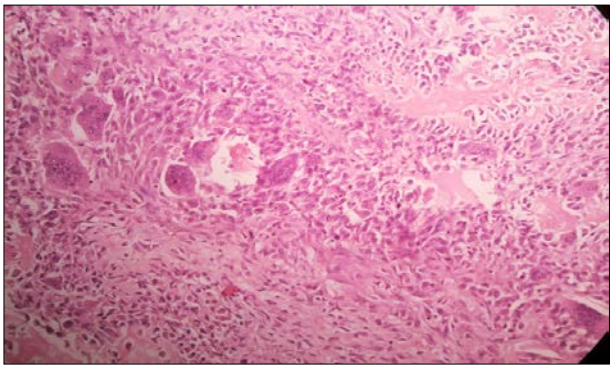

Fig 2: Metaplastic carcinoma of breast shows osteoclastic giant cells (H&E, 100X)

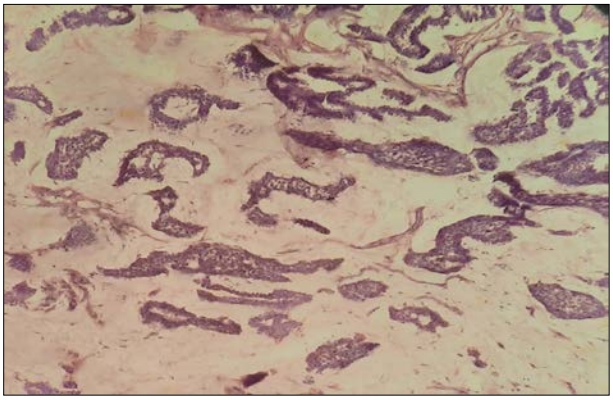

Fig 3: Mucinous carcinoma of breast shows tumor cells floating in mucin pools (H&E.100X)

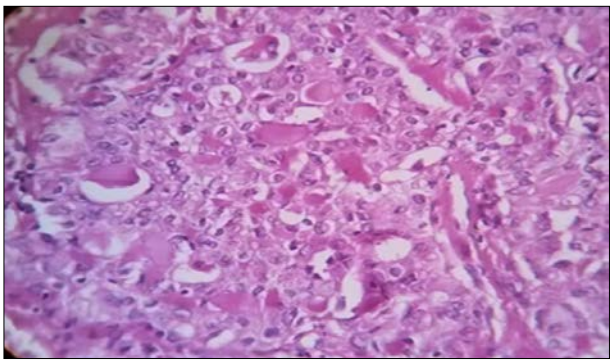

Figure 4: Secretary carcinoma of breast shows tumor cells with vacuolated and foamy cytoplasm and abundant intracellular and extracellular eosinophilic secretions. (H&E, 400X)

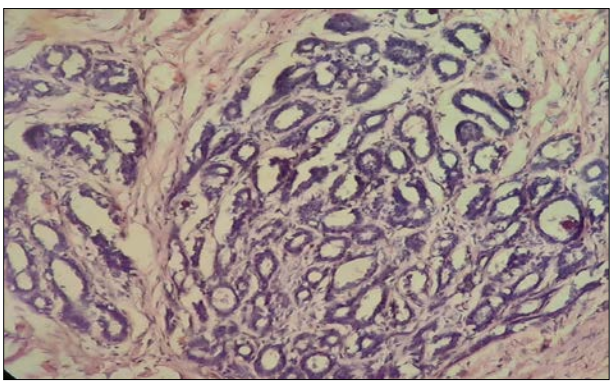

Fig 5: Angulated epithelial nests with lumen formation arranged in sieve like pattern surrounded by fibrosclerotic stroma. (H&E stain, 400X).

Table 1: Age and sex distribution of breast cancer patients

Age(years)	Female	Male	Total cases (%)
20-30 years	8	0	8
31-40 years	33	0	33
41-50 years	74	1	75
51-60 years	51	1	52
61-70 years	34	1	35
71-80 years	7	0	7
81-90 years	2	0	2
Total	209	03	212

Table 2: Incidence of various histologic types of breast neoplasm

Sr. No.	Histologic type	Female	Male	Number of cases (%)
1	Invasive Ductal carcinoma (IDC)	186	03	189(89.1%)
2.	IDC with DCIS*	03	0	03(1.41%)
3.	Metaplastic	05	0	05(2.35%)
4.	Mucinous	05	0	05(2.35%)
5.	Invasive lobular carcinoma	04	0	04(1.88%)
6.	Carcinoma with medullary features	02	0	02(0.94%)
7.	Secretary	01	0	01(0.47%)
8.	Micropapillary	01	0	01(0.47%)
9.	Basal type	01	0	01(0.47%)
10.	Cribriform	01	0	01(0.47%)
	Total	209	03	

*DCIS Ductal carcinoma in situ

Table 3: Distribution of number of cases in relation to Nottingham grade

Degree of differentiation	Nottingham grade	Number of cases
Well differentiated	I (3-5)	12(6.28%)
Moderately differentiated	II (6-7)	96(50.26%)
Poorly differentiated	III (8-9)	83(43.46%)

Table 4: Lymphovascular invasion and lymphnode involvement in relation to histologic grade and type.

	Lymphovascular invasion		Lymphnode involvement		
IDC	Present	Absent	Present	Absent	Not received
Grade 1	1	11	8	3	1
Grade 2	42	54	64	29	3
Grade 3	44	39	50	23	10
IDC+DCIS	1	2	1	2	0
Metaplastic	2	3	3	2	0
Mucinous	2	3	1	4	0
Lobular carcinoma	0	4	2	1	1
Carcinoma with medullary features	1	1	0	2	0
Secretary	0	1	0	1	0
Micropapillary	1	0	1	0	0
Basal type	0	1	0	0	1
Cribriform	0	1	1	0	0
Total cases (%)	94 (44.3%)	118 (55.7%)	131 (61.8%)	67 (31.6%)	14 (6.6%)
Grand total	212		212		

Discussion

In men the most common cancer was lung cancer. In females, cervix cancer and breast cancer were the most common incident and fatal forms of cancer. Majority of Indian breast cancer patients self detect their disease when it is a palpable lump or when it has progressed to involve local skin and/or chest wall or has resulted in distant metastasis. Illiteracy, lack of awareness about the disease, inadequate diagnostic facilities in peripheral areas and financial constrains may be some of the reasons for delayed diagnosis of the disease. As a result, Indian breast cancer patients present with advanced disease stage and have numerous poor prognostic factors like large tumor, lymphnode metastasis and high pathological grade etc [7].

Breast cancer is a biologically heterogeneous disease and patients with the same diagnostic and clinical prognostic profiles can have markedly different clinical outcomes. Breast cancer survival is linked to early detection, timely appropriate treatment and genetic predisposition. Prognosis and management of breast cancer are influenced by many clinical, pathologic and molecular features. The clinicopathological parameters include age, histopathologic type, grade of tumor, size of tumor, lymph node metastasis and lymphovascular invasion.

Acharya *et al.* Observed the most common age group to be diagnosed with breast cancer was 41 to 55 years [8]. Study

conducted by Afsharfard *et al.* concluded that the mean age of disease diagnosis was 49.35 years [9]. The incidence of male breast cancer is very rare but we found 3 cases accounting 1.4% of total cases. The result was in accordance with a study conducted by Rai *et al.* who found 0.5% incidence of male breast cancer [10].

Sofi *et al.* Reported 52% cases of breast carcinoma in left breast [11]. Mushood G. Nabi *et al.* Also showed more common involvement of left breast (53.9%) than right breast (46%) which correlates with the findings of present study [12].

According to the AJCC TNM staging criteria, T is classified on basis of tumor size. T1 (Less than 2 cm), T2 (2.0 to 5.0 cm), T3 (more than 5 cm), and T4 (tumor growing to chest wall or skin). Majority of studies observed highest frequency of tumors with T2 stage. Majority of the cases (59%) had tumor size of 2 to 5cm. Studies by Suvarchala SB *et al.*, [13] Pallavi Shrigondekar *et al.* [14] and Sofi *et al.* [11] recorded majority of patients presenting with tumor size of 2 to 5 cm. Siddiqui *et al.* [15] also studied morphologic parameters of breast carcinoma, and observed 47.72% cases of T2 stage that correlates with the results of present study which concluded 59% cases of T2 stage.

In present study, Infiltrating Ductal carcinoma (IDC) was the predominant histopathological subtype with IDC NOS (not otherwise specified) in 189 (89.1%) cases. Infiltrating Duct carcinoma NOS was also the predominant histopathology in studies by Aziz un Nisa *et al.* [16] (85.8%), Sofi *et al.* [11] (80.30%), Pallavi Shrigondekar *et al.* [14] (93.2%), Suvarchala SB *et al.* [13] (93.7%) and Bhagat Vasudha M *et al.* [17] (94.8%). Kakarala *et al.* [18] reported that Asian Indian/Pakistani women had more number of invasive ductal carcinoma and less number of invasive lobular carcinoma as compared to Caucasians.

In male patients, we observed that invasive ductal carcinoma was the most common type of breast cancer as among 212 cases, all three male patients were of invasive ductal carcinoma. A study performed at PGIMER by Rai *et al.* [10] reported male breast cancer is a rare disease representing 1% of all breast cancers and less than 1% of all cancers in men. They concluded that infiltrating ductal carcinoma was most common type of breast cancer in male and invasive papillary was second most common.

Histological grading are based on Nottingham modification of the Scarff Bloom and Richardson's grading system. The extent of tubule formation, nuclear size and pleomorphism, and mitotic rate are the parameters measured. Each of the three elements was assigned with a score 1 to 3 and the final grade was identified from the sum of each individual scores. Depending on the degree of differentiation, well differentiated (grade I) scores 3 to 5, moderately differentiated (grade II) scores 6 to 7 and poorly differentiated (grade III) scores 8 to 9 [19].

In the present study, majority of tumors were moderately differentiated grade II accounting 96 (50.26%) of total cases followed by 83 (43.46%) tumors with poorly differentiated grade III and 12 (6.28%) tumors with well differentiated grade I. Studies by Suvarchala S B *et al.* [13], Sofi *et al.* [11], Bhagat Vasudha M *et al.* [17], Acharya *et al.* [8] and Pathak TB *et al.* [20] also recorded Grade II as the predominant Grade with 42.1%, 52.1%, 43.1%, 47.40% and 59% cases respectively. Mushood G. Nabi *et al.* [12] Observed that majority 65(46.7%) cases had modified SBR grade II tumor followed by 61(43.8%) cases with grade III tumors and 13 (9.3%) cases with Grade I tumor which is in accordance with of findings of present study.

LVI is a significant predictor of poor prognosis in patients with primary invasive breast cancer as involvement of peritumoral blood and lymphatic vessels is necessary for metastasis to occur. A study by Song *et al.* [21] reported that 55% MRM cases had LVI which is comparable to present result i.e. 94 cases (44.3%). Young Jae Ryu *et al.* compared LVI and pathological complete response as prognostic marker following neoadjuvant chemotherapy and concluded that LVI in breast cancer specimen obtained after neoadjuvant chemotherapy was a significant independent and better prognostic factor than pathologic complete response.

Lynphnode involvement by neoplastic cells of breast cancer is an important prognostic factor as disease free lymphnodes display better prognosis, both for overall and for disease free survival. Hammond *et al.* [23] and Fitzgibbons *et al.* [24] considered high histologic grade as the first-choice morphological feature to predict prognosis in cases of breast cancer. Leong *et al.* [25] evidenced high histologic grade as a good predictor of prognosis. However, they fstated that low-grade tumors might also present unfavorable outcomes, with axillary metastasis in cases with a long survival time.

Conclusion

In present study majority of patients were of 41 to 50 years of age with mean age of 51.16 year. Invasive ductal carcinoma (NST) was the most common histological type of breast cancer for both gender. Majority of patients were diagnosed with tumor size 2-5 cm (T2) and histologic Grade II tumors. LVI is more common in higher grade tumors. LVI and lymphnode involvement are important prognostic factors.

Acknowledgement: None

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