Correlation Between Scrape Cytololgy, Histopathology and Expression of Estrogen, Progesterone Receptors in Carcinoma Breast

Shalu Thomas[1], Blessy Mary Thomas[2], Prajna K.S[3]

[1]Assistant professor, Department of Pathology, Believers Church Medical College and Hospital, Thiruvalla, Kerala, India.
[2]Associate Professor, Department of Pathology, Believers Church Medical College and Hospital, Thiruvalla, Kerala, India.
[3]Assistant Professor, Department of Pathology, Kaher's JGMM Medical College, Hubballi, Karnataka , India.

Abstract

Background: The study of breast cancer has evolved from histopathological examination alone to the present scenario where further ancillary techniques including Immunohistochemistry, Fluorescence in situ hybridization and genetic studies are being incorporated. 50 cases of suspected carcinoma breast who underwent surgery at a tertiary hospital between November 2019 to November 2021 were included in the study. The specimens were cytologically examined by scrape method which was followed by histopathological examination and further by ER, PR estimation. Sensitivity of scrape cytology was 96% with a positive predictive value of 100%. 48% of patients expressed estrogen receptor, 64% expressed progesterone receptor and 50% were negative for expression of both the receptors. Histologic grading using the Modified Bloom-Richardson system showed significant association with the receptor expression. Scrape cytology is a diagnostically reliable modality according to our study, hence suggested to be a part of the pathologist's repertoire though in present times it is not in the usual practice. ER, PR status correlates well with histopathologic grading and other clinico-pathological parameters. This will guide the clinicians to make correct choice of treatment protocols which in tur helps in improved quality of life.

Corresponding Author: Dr Prajna K.S, Assistant Professor, Department of Pathology, Kaher's JGMM Medical College, Hubballi, Karnataka -580028, India.

Introduction

Breast cancer is the most common cancer among women both in developed and developing countries. It ranks as the fifth most common cause of death from cancer overall. Incidence of breast cancer in India is lower as compared to the west. In our country, it is the 2nd leading cause of cancer among women preceded by cervical cancer[1,2]**.** It has been estimated that 1 out of every 9 women will develop breast cancer during her lifetime and approximately 30% of them will die of the disease. According to the World Health Organisation(WHO), approximately 70% of breast cancers occur in women with none of the known risk factors. Only about 5% of breast cancers are inherited. The number of global cancer deaths is projected to increase by 45% from 2007-2030 (from 7.9 million to 11.5 million deaths), influenced in part by an increasing aging global population. In 1940's the risk for breast cancer was 1:22. Today it is 1:18[3]. Breast cytology is generally considered to be part of the initial assessment of breast lesions.[4]Scrape cytology is a rapid, simple and easy technique for tissue diagnosis. It would greatly affect the planning of treatment of neoplastic disease and their course, since diagnosis can be given intra operatively. This is an alternative simple procedure for frozen

section or tru-cut needle biopsy.[5] However,histopathology remains the ultimate gold standard in tissue diagnosis.[6] The assessment of steroid hormone receptors in resected breast cancer tissues is essential to decide whether endocrine therapy is indicated and to select the best treatment for each patient on the basis of receptor status.[7] With established positive correlation of ER and PR with degree of tumor differentiation, determination of ER and PR status on biopsy specimen prior to therapeutic intervention is advocated as standard practice.[8]Hence, in the present study we compare the diagnostic accuracy of scrape cytology with histopathology, as well as to determine the expression of hormone receptors (ER /PR) in carcinoma breast cases which can be used to prognosticate and treat breast cancer patients.

Materials And Methods

This was a prospective study conducted in the Department of Pathology in aa tertiary care hospital among 50 patients with suspected breast carcinoma (after undergoing preliminary investigations like Fine Needle Aspiration Cytology/ Sonomammogram), who underwent surgery (Modified Radical mastectomies, Simple mastectomies and Lumpectomies) between November 2019 to November 2021. Samples for the study were selected according to the inclusion and exclusion criteria.

Inclusion criteria

Female patients of all ages, with suspected breast carcinoma who underwent surgery.

Exclusion criteria

- Samples which had already been fixed, exclusively necrosed, calcified, degenerated or undergone ischemic changes.
- Benign and non neoplastic conditions.

Gross examination of the fresh specimen removed from the patient was done. The specimen was then cut with a sharp knife into two halves and scrapings were done from the representative area using a sharp scalpel or the end of a glass slide, depending and a thin smear was made. The slides were stained with Rapid Papanicolaou (PAP) stain, Haematoxylin and Eosin (H and E) stain and Leishman stain. The slides were examined immediately and reported. The remaining specimen was then fixed.Sections were taken from the same area from where scrapings were taken, labeled and processed. The slides were then stained with HandE stain and taken up for histopathological diagnosis by examining under microscope which was considered as the gold standard. The Modified Bloom-Richardson system of cancer grading system was used in this study. Immunohistochemistry (ER, PR) was applied to suitable tumor sections and their status was evaluated using Allred scoring system. Tumors were defined as hormone receptor positive if their total IHC score was greater than 2 and hormone receptor negative if their score was 0 or 2. Data for all the 50 patients were compiled and scrape cytology findings were correlated with histopathological diagnosis and then the expression pattern of hormone receptors (ER/PR) was evaluated in these cases. Statistical analysis were performed to compute the sensitivity, specificity, accuracy, positive and negative predictive values of scrape cytology, with histopathology as the gold standard.

Observations And Results

The present study included 50 cases of suspected carcinoma breast. The youngest patient was 30 years of age and the eldest was 74 years of age. Maximum number
of cases belonged to the age group of 41 – 50 years (42%) followed by 51 – 60 years (38%). The least number of cases were seen in the 21- 30 years (2%) and 71 – 80 years (2%) age group. In our study, majority of the patients presented with lump in the breast, seen in 36 of the cases (72%) followed by both pain and lump which was seen in 10 cases (20%).4 cases presented with lump in the breast and nipple discharge (8%). Left sided breast carcinoma was more

common, seen in 64% compared to 36% in right breast.45 patients (90%) underwent modified radical mastectomy, 4 (8%) underwent simple mastectomy and 1 (2%) underwent lumpectomy. Out of these 50 cases on which scrape cytology examination was done, 30 cases(60%)were diagnosed as Invasive carcinoma breast of no special type (Figure 1). This was followed by 10 cases (20%) of Invasive lobular Carcinoma, 2 cases (4%) each of Carcinoma with medullary features, Mucinous and Invasive Lobular Carcinoma –Probably Pleomorphic variant. There was 1 case (2%) of Tubular carcinoma and 1 case (2%) of Carcinoma –Probably of the Medullary type. Two cases were not showing definite features of malignancy and were diagnosed as Atypical Ductal Hyperplasia and Fibrocystic Disease of breast with Atypia.

On subsequent microscopic examination,the predominant histologic subtype was Invasive carcinoma breast of no special type which was seen in 31 (62%) cases (Figure 2). This was followed by 5 cases(10 %) each of Invasive lobular and Pleomorphic variant of Invasive lobular carcinoma. There were 3 cases (6%) each of Carcinoma with medullary features and Mixed Invasive carcinoma of no special type and lobular Carcinoma. Also there were 2 cases (4%) of Mucinous Carcinoma and 1 case (2 %) of Tubular Carcinoma. The following histopathologic findings were also observed across these 50 cases. 22 (44%) of the cases had necrosis, 21(42%) had desmoplasia, 3 (6%) had calcification, 12(24%) had vascular invasion, 14(28%) had lymphatic invasion and 5(10%) had perineural invasion.Out of the 50 cases, majority belonged to grade 2 i.e., 28 (56%) followed by 12 (24%) cases of grade 1 and 10 cases (20%) of grade 3.
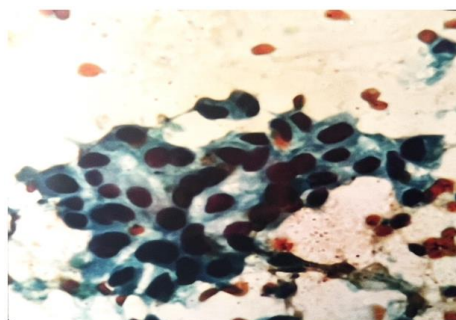

Figure 1: Photomicrograph of scrape smear: Invasive carcinoma breast of no special type showing loosely cohesive clusters of malignant ductal epithelial cells exhibiting moderate degree of atypia. (Papanicolaou stain, 40x)
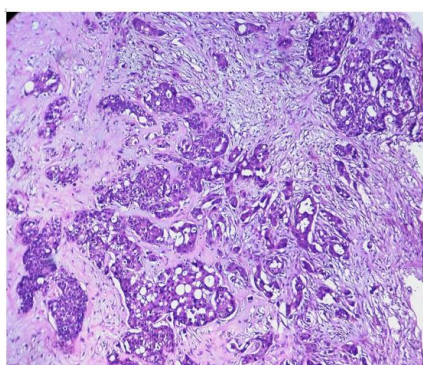

Figure 2: Photomicrograph of Invasive carcinoma breast of no special type, showing infiltrating tumor cells in cords and glandular pattern (H&E, 20x)

Of the entire 50 cases, 48 showed concordancy between scrape cytology and histopathology diagnosis. 29 cases were diagnosed as Invasive carcinoma breast of no special type (IC NST) both on Scrape cytology as well as Histopathology. 8 cases were diagnosed as Invasive Lobular Carcinoma (ILC) on scrape cytology with 2 diagnosed as probably the pleomorphic variant. Of these 5 cases were diagnosed as Invasive Lobular Carcinoma and 5 as Pleomorphic variant of Invasive Lobular Carcinoma. 2 cases were diagnosed as Carcinoma with medullary features

and 1 case as probably Carcinoma with medullary features on Scrape cytology examination. All three cases were diagnosed as Carcinoma with medullary features on Histopathology. 2 cases were diagnosed as ILC and 1 case as IC NST on scrape cytology and all three were diagnosed as having features of Mixed Invasive carcinoma breast of no special type and Invasive lobular carcinoma on histopathology. 2 cases were diagnosed as Mucinous Carcinoma and 1 as Tubular Carcinoma on Scrape cytology. All these were concordant with the histopathology diagnosis as well.

A case diagnosed as Atypical Ductal Hyperplasia on Scrape Cytology was later diagnosed to be IC NST on Histopathology. Another case reported as Fibrocystic Disease with Atypia was also diagnosed to be IC NST on Histopathology. Thus these two cases showed discordancy between Scrape Cytology diagnosis and Histopathology diagnosis.(Table 1)

TABLE 1: RELATIONSHIP BETWEEN SCRAPE CYTOLOGY AND HISTOPATHOLOGY DIAGNOSIS

SCRAPE CYTOLOGY (No of Cases)	HISTOPATHOLOGY (No of Cases)	CONCORDANT/ DISCORDANT
Invasive carcinoma breast of no special type (29)	Invasive carcinoma breast of no special type (29)	CONCORDANT
Invasive lobular Carcinoma (8) Invasive lobular Carcinoma – probably pleomorphic variant(2)	Invasive lobular Carcinoma (5) Invasive Lobular Carcinoma – pleomorphic variant(5)	CONCORDANT
Carcinoma with medullary features(2) Carcinoma breast- Probably Medullary type(1)	Carcinoma with medullary features(3)	CONCORDANT
Invasive carcinoma breast of no special type (1) Invasive Lobular Carcinoma (2)	Mixed Invasive carcinoma breast of no special type and Invasive lobular carcinoma (3)	CONCORDANT
Mucinous Carcinoma(2)	Mucinous Carcinoma(2)	CONCORDANT
Tubular Carcinoma(1)	Tubular Carcinoma(1)	CONCORDANT
Atypical Ductal Hyperplasia(1)	Invasive carcinoma breast of no special type(1)	DISCORDANT
Fibrocystic Disease with Atypia (1)	Invasive carcinoma breast of no special type (1)	DISCORDANT

Scrape cytology showed a sensitivity of 96 % with a confidence interval of 86.29% to 99.51% and a positive predictive value of 100%. As there were no true negatives in our study, specificity and negative predictive values are not applicable. (Table 2)

TABLE 2: RELATIONSHIP BETWEEN SCRAPE CYTOLOGY AND HISTOPATHOLOGY DIAGNOSIS

SCRAPE CYTOLOGY	HISTOPATHOLOGY		TOTAL
	POSITIVE FOR MALIGNANCY	NEGATIVE FOR MALIGNANCY	
POSITIVE FOR MALIGNANCY	48 TP	0 FP	48

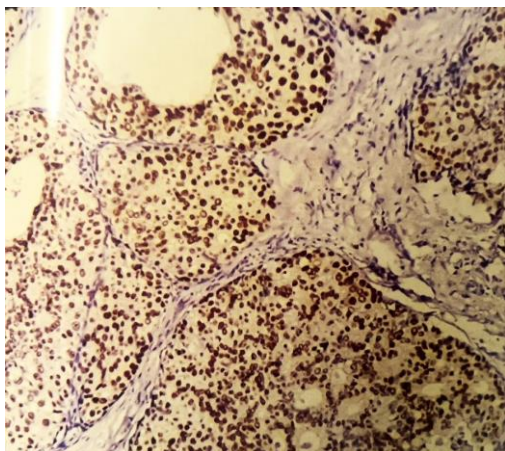| NEGATIVE FOR MALIGNANCY	2 FN	0 TN	2
TOTAL	50	0	50

Figure 3: Photomicrograph showing ER positivity with a score of 7/8. (10x)
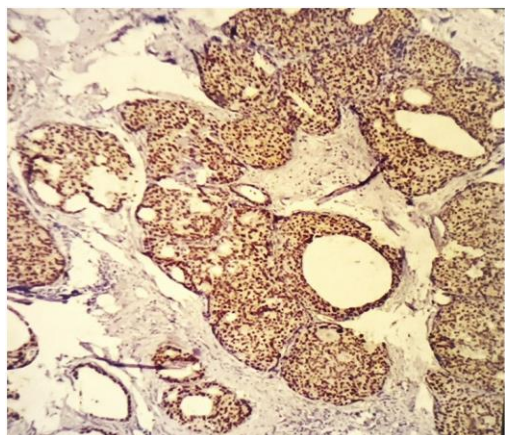

Figure 4: Photomicrograph showing PR positivity with a score of 7/8

Out of the 50 cases, 22 (44%) were ER+/PR+, 2 (4%) were ER+/PR-, 1 (2%) was ER-/PR+ and the remaining 25 (50%)were ER-/PR- (Figure 3 and 4).All the cases of Pleomorphic variant of ILC and Carcinoma with medullary featurtes belonged to ER-/PR- group whereas all ILC, Mucinous and Tubular Carcinoma belonged to ER+/PR+ group. Tubule formation showed significant association with ER/PR status (p value -0.007) with better tubule formation in ER +/PR+ group compared to other groups, with all the tumors forming >75 % tubule formation belonging to the ER+/PR + group. Severe nuclear pleomorphism was seen in ER-/PR- group compared to moderate degree of nuclear pleomorphism seen in ER+/PR+ group. Mitotic rate also showed significant association with ER/PR status (p value -0.029) with 2 cases having more than 10 mitosis/10HPF and 21 cases with 6-10 mitosis/10HPF belonging to ER-/PR- group. Histologic grade also showed a significant association with ER/PR status (p<0.001) with majority of the Grade 2 and Grade 3 tumors being ER-/PR-. (Table 3).

TABLE 3: RELATIONSHIP OF PATHOLOGIC VARIABLES WITH ER/PR STATUS

VARIABLES	ER+/PR+	ER+/PR-	ER-/PR-	ER-/PR+	p VALUE
DIAGNOSIS					
INVASIVE CARCINOMA OF	13	2	16	0	0.097

BREAST – NO SPECIFIC TYPE					
INVASIVE LOBULAR CARCINOMA	5	0	0	0	
MEDULLARY CARCINOMA	0	0	3	0	
MIXED INVASIVE NON SPECIFIC TYPE AND LOBULAR CARCINOMA	1	0	2	0	
PLEOMORPHIC INVASIVE LOBULAR CARCINOMA	0	0	4	1	
MUCINOUS CARCINOMA	2	0	0	0	
TUBULAR CARCINOMA	1	0	0	0	
TUBULE FORMATION					
>75% OF TUMOUR	3	0	0	0	0.007*
10 – 75% OF TUMOUR	19	2	15	0	
<10% OF TUMOUR	0	0	10	1	
NUCLEAR PLEOMORPHISM					
MINIMAL VARIATION IN SIZE AND SHAPE OF NUCLEI	4	0	0	0	0.053
MODERATE VARIATION IN SIZE AND SHAPE OF NUCLEI	14	2	12	0	
SEVERE VARIATION IN SIZE AND SHAPE OF NUCLEI	4	0	13	1	
MITOTIC SCORE/ 10 HPF					
0-5	9	2	2	0	0.029*
6-10	13	0	21	1	
>10	0	0	2	0	
HISTOLOGIC GRADE					
GRADE I	11	1	0	0	<0.001*
GRADE II	11	1	16	0	

GRADE III	0	0	9	1	

Discussion

In the present study 50 specimens received of suspected Carcinoma breast were evaluated by scrape cytology examination followed by light microscopy to determine the histologic type and other histologic features exhibited by them. Subsequently IHC was done to find out the ER, PR status of the tumor. Breast cancer being the most common cancer among women in India and in many regions of the world, constant research on prognostic and predictive markers of breast carcinoma are going on, ER and PR being mandatory markers among them. So we took tup this study to evaluate these important prognostic markers in different types of carcinoma breast as well.

Age of patients in the present study varied from 30 to 74 years with maximum number of cases(42%) belonging to the 41- 50 age group. The mean age of the patients was found to be 52 years. Another study by Rao C showed maximum number of patients in the 41-50 age group(46.8%),similar to our study which showed 42%[9].This age distribution is significantly younger than what is currently seen in Western countries[10]. Leong et al also noticed in his study that in Asia, breast cancer incidence peaks among women in forties while in Western countries, it peaks in sixties[11]. This could be attributed to multiple factors like environmental factors, socioeconomic status, inadequate implementation of screening programmes and lack of appropriate care.

In our study majority of the patients presented with left sided carcinoma breast, 32 cases (64%) which was similar to study done by Tiwari et al [1] who reported 68.6 % cases in left breast and by Moses Ambroise et al [12]who reported 59.2% cases in left breast.

Scrapings of the cut surface prior to fixation facilitates the harvesting of cells, hence scrape cytology could be preferred over touch preparation / imprint cytology as the former technique would yield much more material than the latter. In scrape preparations, cut surface of the specimen is scraped with the edge of the glass slide. Relevant clinical data and gross morphological features are valuable information for evaluating the cytological smears[14]. In our study we correlated the diagnosis on scrape cytology with the gold standard which was histopathological diagnosis. 48 cases showed a concordant diagnosis on both scrapings and histopathology with two showing discordant results. One case was diagnosed as Atypical Ductal Hyperplasia on Scrape Cytology in view of cell rich smears of cohesive sheets and aggregates of ductal epithelial cells exhibiting variable cytological atypia along with absence of necrosis and presence of few clusters of myoepithelial cells. Lumpectomy was done and the case was later diagnosed to be IC NST on Histopathology, Grade I and positive ER but Negative PR status on Immunohistochemistry. Another case was reported as Fibrocystic Disease with Atypia on Scrape cytology in view of ductal epithelial cells and single bare nuclei along with few cyst macrophages and apocrine metaplastic cells. Focal areas also displayed disorganized atypical epithelial cell clusters having greater degree of nuclear enlargement and macronucleoli, hence diagnosed as above. Simple mastectomy was done for this patient after correlating with clinical features and radiological findings. This case was diagnosed as Grade 1 IC NST on histopathology with an associated area showing features of Fibrocystic change. Thus two cases showed discordancy between the cytological and histopathological diagnosis in our study thus giving a sensitivity of 96 %, confidence interval of 86.29% to 99.51% and a positive predictive value of 100%. As there were no true negatives in our study, specificity and negative predictive values are not applicable. In the study done by Akhtar ZM et al [4], 40 cases of breast lesions including benign and malignant were studied. When they used atypical cases as negative both touch and scrape imprints gave sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 100%. In their study none of the malignancies were scored as benign on scrape cytology. This result was well supported by the study

conducted by Venti S[15] and co-workers who recommended scrape preparations over touch imprint cytology to get better cellularity. Cellular atypia is seen in some cases of fibrocystic change. These atypical findings are also described by Veneti et al and Jacobs et al[16]. Bipolar cells are helpful in differentiating these lesions from malignancies. Jacobs et al[16] and Anlauf et al [17] also recommended clinical correlation and complementary diagnostic procedures to avoid false diagnosis.

Pathak TB [8] et al studied 136 cases of Carcinoma breast in which the morphologic categories were infiltrating ductal carcinoma, not otherwise specified (131 cases, 96%) followed by carcinoma with medullary features (2 cases, 1.4%). Mucinous carcinoma, infiltrating lobular carcinoma and infiltrating papillary carcinoma constituted 1 case(0.7%) each. In his study Page et al[13] observed 70% cases of IC NST and 10% cases of ILC.5% cases were Medullary carcinoma,2 % Mucinous carcinoma, 3 % Tubular, 2% Mixed Carcinomas and others were 8%. In our study which comprised a total of 50 cases, the predominant histologic subtype was Invasive carcinoma breast of no special type, seen in 31 (62%) cases followed by 5 cases(10 %) each of Invasive lobular and Pleomorphic variant of Invasive lobular carcinoma. There were 3 cases (6%)each of Carcinoma with medullary features and Mixed Invasive Carcinoma of No Special Type and Lobular Carcinoma. Also there were 2 cases (4%) of Mucinous Carcinoma and 1 case (2 %) of Tubular Carcinoma. This was, hence, in concordance with other studies.

In the study done by Tiwari et al [1] out of 70 cases, 60% cases belonged to grade II, 22.9% grade III and 17.1% to grade I. Out of 136 cases of Carcinoma breast studied by Pathak TB et al[8] majority of them, 80 cases (58.8) belonged to grade II, followed by 29 cases (21.3 %) belonging to grade III and 27 cases (19.9%) belonging to grade I. Our study showed similar findings with majority of the patients belonging to grade II, 28 cases (56%), followed by grade I with 12 cases (24%) and grade III with 10 cases (20%).

22 out of 50 patients (44%)in our study belonged to the ER+/PR+ group whereas 25 patients (50%) belonged to ER-/PR- group. 2 (4%) cases belonged to ER+/PR- group while 1 (2%) showed ER-/PR+ status. In published literature, approximately 50% of tumors are ER+ PR+, 25% ER- PR-, 20% ER+ PR- and 5 % ER - PR+ [18]. This was similar to the results obtained in our study. In contrast to the higher rates reported in the Western literature, only 32.6% of the tumors were ER positive and 46.1% were PR positive in the study done by Desai et al[19]. Tumors were separated into four categories: ER+PR+ (25%), ER+PR- (7.4%), ER-PR+ (21.1%) and ER-PR- (46.5%). Redkar et al[20] have also reported a higher incidence of steroid receptor non–reactivity in breast cancer patients in India. This can be partially explained by the younger age of our patients and higher grade of tumors in our practice. Breast cancer patients seen by us are a decade younger as compared to those seen in the West. Young patients have high levels of circulating estrogens and a correspondingly low expression of steroid receptors which is reflected in their tumors.

In our study we had 1 case (2%) of ER -/PR + tumor. The biological and clinical significance of the ER-/PR+ breast cancer subtype is even more controversial, with some reports claiming it represents a distinct, clinically useful biologic entity [21,22] with others postulating that ER-/PR+ classification is primarily a technical artifact [23,24] and too rare to be of clinical use [25]. In large published series the percentage of ER-/PR+ cases has been in the range of zero to four percent[25].

Study by Shet T et al [26]showed a significant correlation between hormone receptor expression and the histologic subtype of breast carcinoma wherein ILC, mucinous carcinoma and variants of papillary carcinoma expressed hormone receptors at a significantly higher level than IC, NST. Rao C et al[9] in his study also found higher expression of ER, PR in lobular than ductal carcinomas. Tumors which were predominantly ER and PR negative were the higher grades of infiltrating duct carcinoma, medullary carcinoma and the cases of poorly differentiated, pure comedo DCIS in the study by Desai et al [19]. Similarly in our study all cases of ILC, Mucinous

carcinoma and Tubular carcinoma showed ER and PR positivity whereas all cases of medullary Carcinoma, 4 cases of Pleomorphic Lobular type and 2 Mixed carcinomas showed ER and PR negativity. 1 case of Pleomorphic Lobular carcinoma was ER +/PR-. Majority of the cases of Invasive breast carcinoma of no special type (16 cases) were ER-/PR -, whereas 13 were positive.2 cases were ER+/PR-. However there was no significant association between receptor expression and histologic subtype (p value – 0.097) in the present study.

Our study showed a significant inverse correlation between the histologic grade and expression of ER/PR (p value- <0.001). Of the individual variables both tubule formation and mitotic count showed significant association again(p values -0.007 and 0.029 respectively).Out of 12 Grade I tumors, 11 (91.66 %)were ER/PR+ and 1 (8.33 %) was ER+/PR-. 9 out of 10 Grade 3 tumors (90%) were ER-/PR- and 1 (10%) was ER-/PR+. 16 of the Grade 2 tumors (57%) were ER-/PR- and 11 (39.2%) were ER+/PR+, 1 (3.5%) was ER+/PR-. Individually again ER and PR expression showed significant association with the histologic grade. Similarly in their study Shet T et al [26] found a significant correlation of receptor expression with the tumor grade. The entire Grade I tumors, 93% of Grade II tumors and 39.5 % of Grade III tumors expressed hormone receptors. Similarly in their study Shet T et al [26] found a significant correlation of receptor expression with the tumor grade. The entire Grade I tumors, 93% of Grade II tumors and 39.5 % of Grade III tumors expressed hormone receptors.

Stierer M et al[27] correlated individual characteristics like tubule formation, nuclear plemorphism and mitotic rate with steroid receptor status. They concluded that there was no correlation between tubule formation and ER content while nuclear pleomorphism and rate of mitosis showed significant correlation.

Thus our results are in agreement with the reports of earlier studies which have shown that higher grade tumors are more common in receptor negative patients. This relationship between receptor content and histologic grade was enhanced by considering estrogen and progesterone receptor simultaneously.

Conclusion

In the recent years there has been outstanding advances in breast cancer diagnosis and management leading to earlier detection of disease and the development of more effective treatment. This has resulted in improved quality of life with a significant decline in breast cancer deaths for those women living with the disease. Prognosis and management of breast cancer are influenced by classic variables such as histologic type and grade, tumor size, lymph node status and status of hormone receptors- ER and PR. A good correlation was obtained between scrape cytology and histopathology diagnosis in our study, hence scrape cytology could be preferred over touch preparation / imprint cytology. ER and PR status correlates well with histopathologic grading. Higher grade is associated with ER/PR negativity. Hence, immunohistochemical assessment of ER and PR status should be incorporated as a routine investigation. This along with histopathological grading will guide the clinicians to make correct choice of treatment protocols and helps in improved quality of life.

References

1. Tiwari S, Malik R, Trichal V K, Nigam R K, Rai A, Balani Set al. Breast cancer: Correlation of Molecular Classification with Clinicohistopathology. Sch. J.App. Med. Sci.2015; 3(2G):1018-1026.
2. Devi KU; Current status of gynaecological cancer care in India. J Gynecol Oncol., 2009; 20(2): 65- 66.
3. Bob Riter. History of Breast Cancer Advocacy. Personal Reflections. Cancer Resource Centre.2010: 5-8.

4. Akhtar ZM, Qureshi SA, Aziz N, Niazi S, Qureshi SS, Bukhari MH. Evaluation of Accuracy of Intra Operative Imprint Cytology for Detection of Breast Lesions.Annals of KEMU.2010;16(1)48-54.

5. Mehar R, Panchonia A, Kulkarni CV. Role of Scrape Cytopathology in Early Diagnosis of Neoplastic Lesions and its Histopathological Correlation. International Journal of Medical Science and Public Health.2014; 3(4):489-492.

6. Gal AA. The Centennial Anniversary of the Frozen Section Technique at the Mayo Clinic. Arch Pathol Lab Med 2005 December; 129 (12): 1532-5.

7. Kurosumi M.Significance of immunohistochemical assessment of steroid hormone receptor status for breast cancer patients.Breast Cancer.2003;10(2):97-104.

8. Pathak TB, Bashyal R, Pun CB,Shrestha S, Bastola S,Neupane S et al. Estrogen and progesterone receptor expression in breast carcinoma. J Pathol Nepal.2011;1:100-103.

9. Rao C, Shetty J, Kishan Prasad HL.Morphological profile and receptor status in breast carcinoma: An institutional study. J Cancer Res Ther.2013; 9: 44-49.

10. Saleh F, Abdeen S.Pathobiological features of breast tumors in the state of Kuwait : A Comprehensive analysis.J Carcinog. 2007; 6;12.

11. Leong SPL, Shen Z, Liu T, Agarwal G, Tajima T, Paik N, et al. Is breast cancer the same disease in Asian and Western countries?. World J Surg. 2010; 34: 2308–2324.

12. Ambroise M, Ghosh M, Mallikarjuna VS, Kurian A. Immunohistochemical profile of breast cancer patients at a tertiary care hospital in South India. Asia Pacific Journal of Cancer Prevention.2011;12(3): 625-629.

13. Page DL, Anderson TJ. Diagnostic histopathology of the breast. Edinburgh: Churchill Livingstone, 1987.

14. Mahore SD, Bothale K A, Joshi A, Wilkinson A, Patrikar A, Gowardhan V et al.Scrape cytology in rapid intraoperative diagnosis of tumors.IOSR Journal of Dental and Medical Sciences.2015;14(3):65-72.

15. Ventis S, Mouzaka LI, Toufeni H, Xemtides J, Anas-tasiadis P. Imprint cytology, a rapid, reliable method of diagnosing breast malignancy. Acta Cytol 1996; 40: 649-52.

16. Jacobs TW, Silverman IF, Schroeder B, Raza S, Baum JK, Schnitt SJ. Accuracy of touch imprint cytology of image directed breast core needle biopsies. Acta Cytol 1999; 43: 169-74.

17. Anlauf M, Nicklaus S, Rode G, Jackel C, Neumann K, Kalbfleisch H et al. Clinical experience with percuta-neus large- core needle biopsies of the breast and evaluation of cytopathological and histopathological results. Zentralbl Gynakol 2003; 125: 353-61.

18. Barnes D M, Millis R R. Oestrogen receptors: the history, the relevance and the methods of evaluation. In Progress in Patholog Hormone receptor status of breast cancer in India 269 Vol. 2, Kirkham N. Lemoine N (eds). London: Churchill Livingston 1995.

19. Desai SB, Moonim MT, Gill AK, Punia RS,Naresh KN, Chinoy RF.Hormone receptor statusof breast cancer in India: A study of 798 tumours.Breast.2000 ;9: 267-70.

20. Redkar A A, Kabre S S, Mittra I. Estrogen and progesterone receptors measurement in breast cancer with enzyme-immunoassay and correlation with other prognostic factors. Ind J Med Res 1992;96: 1–8.

21. Hefti M M, Hu R, Knoblauch N W, Collins L C, Kains B H, Tamimi R M et al. Estrogen receptor negative/progesterone receptor positive breast cancer is not a reproducible subtype. Breast Cancer Research 2013, 15:R68e.

22. Rakha EA, El-Sayed ME, Green AR, Paish EC, Powe DG, Gee J, Nicholson RI, Lee AH, Robertson JF, Ellis IO: Biologic and clinical characteristics of breast cancer with single hormone receptor positive phenotype. J Clin Oncol 2007, 25:4772–4778.

23. Rhodes A, Jasani B: The oestrogen receptor-negative/progesterone receptor-positive breast tumour: a biological entity or a technical artefact? J Clin Pathol 2009, 62:95–96.

24. De Maeyer L, Van Limbergen E, De Nys K, Moerman P, Pochet N, Hendrickx W, Wildiers H, Paridaens R, Smeets A, Christiaens MR, Vergote I, Leunen K, Amant F, Neven P: Does estrogen receptor negative/progesterone receptor positive breast carcinoma exist? J Clin Oncol 2008, 26:335–336. author reply 336–338.

25. Nadji M, Gomez-Fernandez C, Ganjei-Azar P, Morales AR: Immunohistochemistry of estrogen and progesterone receptors reconsidered: experience with 5,993 breast cancers. Am J Clin Pathol 2005, 123:21–27.

26. Shet T, Agrawal A, Nadkarni M, Palkar M,Havaldar R, Parmar V et al. Hormone receptors over the last 8 years in a cancer referral center in India: what was and what is?.Indian J Pathol Microbiol. 2009;52(2):171–174.

27. Stierer M, Rosen H, Webes R, Hanak H, Spona J and Tuchler H. Immunohistochemical and biochemical measurement of estrogen and progesterone receptors in primary breast cancer. Correlation of histopathology and prognostic factors. Annals of surgery 1993;218(1):13-21.