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Management of phyllodes tumour of breast: 5 year experience at Madina Teaching Hospital, Faisalabad.

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ABSTRACT… Objectives: To determine the oncological outcome of different types of phyllodes tumour (PT) and to analyze the impact of radiotherapy on outcome. **Study Design:** Experimental study. **Setting:** Madina Teaching Hospital, Faisalabad, Pakistan. **Period:** April 2015 to April 2020. **Material & Methods:** Female patients diagnosed as phyllodes tumour of breast were included and classified into benign, borderline and malignant PT according to WHO criteria. Borderline and malignant PT were further divided into 2 groups; Group A (Surgery alone) and Group B (Surgery + Radiotherapy). Oncological outcome based on local recurrence, distant metastasis and overall survival rate among different types of phyllodes tumour and those patients who received or not received radiotherapy was assessed. **Results:** In 5 years, 29 patients of phyllodes tumour were studied. 15 (51.7%) patients had benign, 8 (27.6%) malignant and 6 (20.7%) borderline tumour. Mean age of our patients was 39.5 years (range: 25-55 years). The disease free survival rate was 82.8% (100% for benign, 83.4% for borderline and 50% for malignant PT). Malignant histotype and tumour size >6cm were significantly associated with recurrence ($p<0.05$). In Group A, 4 patients developed local recurrence and 2 of them developed distant metastasis; while in group B only 1 patients developed local recurrence ($p=0.2$, OR=0.147). Overall survival rate was 93.1%. It was 100% for radiotherapy group compared to 88% for non irradiated patients. **Conclusion:** Malignant phyllodes tumour and large tumour size is associated with worse prognosis. Post operative radiotherapy is associated with improved local recurrence, distant metastasis and overall survival.

Key words: Local Recurrence, Metastasis, Phyllodes Tumour, Post operative Radiotherapy.

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INTRODUCTION

Phyllodes tumours (PT) of the breast are large and rapidly growing fibroepithelial tumours of the breast that account for less than 1 % of all the breast tumours. These tumours remain as poorly understood tumours of the breast as randomized controlled trials are lacking to establish a standard management protocol due to their rarity.[1,2] These tumours usually occur in females in the third and fourth decades.[3]

PT shows a diverse biologic behaviour. In their least aggressive form, they behave similarly to benign fibroadenoma, although, they grow rapidly and show a propensity for local recurrence. Presence of epithelial component differentiates it from stromal sarcomas.[4] Virchow (1867) characterized this tumor as of limited malignant potential but capable of metastasizing. Involvement of Axillary lymph nodes is rare, but blood borne spread is seen into lungs, pleura, bone, and liver.[5] These tumours are classified into benign, borderline and malignant subtypes by The World Health Organization (WHO), based on the frequency of mitosis, margins invasion, stromal overgrowth, degree of atypia of stromal cell and appearance of margins.[6]

The main treatment option of phyllodes tumor remains surgery. Breast conservation is preferred whenever possible. Management Guidelines of National Comprehensive Cancer Network (NCCN) for the phyllodes tumors recommend wide tumour excision with a margin of ≥1cm.[7] However, even taking a wide surgical margin, local recurrence rate remains high and is reported

to be as high as 21–36% for borderline and malignant tumors. Furthermore, a more malignant phenotype has been seen in recurrent phyllodes tumors and a metastasis in up to 25% of patients have been estimated in such cases.[1] Mastectomy is indicated if tumour is large and wide margins cannot be achieved by breast conservation.[2] As the axillary lymph nodes are rarely involved in PT, routine axillary lymph node dissection is not recommended.[7,8] After surgery, because of the strong potential of tumor recurrence, patients have been treated with adjuvant radiotherapy. Research has shown variable results of impact of radiotherapy on disease recurrence.[1,9,10]

Currently, the impact of adjuvant radiotherapy on a patient's overall survival or disease free survival outcome for phyllodes tumours remains controversial.[9] In this article we evaluated the oncological outcome in different types of phyllodes tumour and prognostic impact of adjuvant radiotherapy over a 5-year period.

MATERIAL & METHODS

An experimental study was conducted from March 2015 to March 2020. Female patients with phyllodes tumour of breast were included in the study. Patients with metastatic tumour and those with severe systemic diseases were excluded from the study. This was a non probability purposive sampling. Female patients with suspected phyllodes tumour were evaluated in Breast Clinic of Madina Teaching Hospital and were subjected to triple assessment. Most of the patients were diagnosed phyllodes tumour on core needle biopsy as the role of FNAC to diagnose phyllodes tumor remains controversial and an overall accuracy of around 63% is seen with FNAC. Core needle biopsy gives extra architectural information provided by histology and its sensitivity is reported to be around 99%.[11] Some of our patients with diagnostic confusion underwent incisional biopsy. Those with malignant phyllodes underwent metastatic workup. Decision for breast conservation surgery or mastectomy was based on size of tumour and tumour to breast size ratio. Breast conservation surgery was done by wide local excision taking > 1cm gross tumour free margin. In patients with large tumour to breast ratio or those with a huge mass involving >70% of breast volume, mastectomy was performed. Axillary lymph nodes dissection was not performed in either method. Cases with close margin on histopathology (< 1 mm) were supposed to undergo a revision surgery.

Cases of benign phyllodes tumour (15 patients) underwent surgical treatment only, however those with borderline and malignant phyllodes tumour (14 patients) were divided into 2 equal groups with 7 patients in each group; Group A (Surgery alone) and Group B (Surgery + Radiotherapy). Following wound healing, half of the patients were referred to regional oncology centre for radiotherapy. External beam radiotherapy (EBRT) was given to the patients in a dose of 50 Gray.

Follow up was done every 3 months in first year, 6 monthly in second year and annually thereafter. At each follow up visit, clinical assessment and ultrasonography was performed to detect local recurrence or distant metastasis. For recurrent malignant cases, mastectomy was performed. However, in recurrent borderline case, wide local excision was performed, followed by radiotherapy. Metastases was managed in accordance with principles of soft tissue sarcoma.

The outcome parameters included the local recurrence rate, distant metastasis (DM), disease free and overall survival rates. Local recurrence rate refers to the proportion of the patients who develop local recurrence after surgery. Overall survival rate refers to proportion of patients who survive from date of surgery till the end of study.

This study was approved by the ethical Review committee of hospital. Patients were well informed about the surgical procedure and a signed informed consent was taken prior to surgery.

Statistical Analysis

Categorical data are presented as frequency and percentage. Fisher's exact test was used for comparison of the two groups of categorical variables. Continuous data are presented as mean and standard deviation. Clinicopathoogical factors of prognostic significance, like patient age,

tumour size, histological type, type of surgery and postoperative radiotherapy were evaluated. Kaplan Meier method was used to estimate the overall survival rates for benign, borderline and malignant cases and those who received or not received radiotherapy. Patients without disease recurrence, and those who survived were censored at the end of study. A p value of <0.05 was considered significant. Data was analysed on R statistical software version 4.0.0.

RESULTS

We found mean age of our patients was 39.5 years (SD 6.95) with a range of 25-55 years. The mean tumor size was 6 cm (SD=2.48) with a range of 2.8–14.5 cm. Histologically, 15 patients had benign, 8 patients malignant and 6 borderline phyllodes. Table-I shows clinical features and treatment options in different histological types of phyllodes tumour.

Eleven patients (38%) were treated with mastectomy and 18 (62%) with breast conservative surgery (BCS). Axillary surgery was not carried out in any patients as no patient had clinical or radiological signs of nodal involvement. Figure-1 a & b shows a comparison of operative time and hospital stay in BCS and Mastectomy, showing a mean operative time of 50 min and a mean hospitals stay of 3.6 days in BCS as compared to 68.6 min and 6.2 days respectively in MRM group.

Regarding type of surgery and local recurrence (In borderline and malignant cases); 20% of BCS and 33.3 % of mastectomy cases developed local recurrence. We have seen that malignant histology and larger tumour size were other factors contributing to poor outcome in MRM group. All patients were followed at outpatient department (OPD) every 3 months in first year, every 6 months in second year and then annually for 5 years. Table-II shows predictive factors and their association with local recurrence. Fifty percent of the patients with malignant and borderline phyllodes received postoperative radiotherapy. After a mean follow-up period of 34.6 months (range 3–60 months), 4 patients of group A and 1 patient of group B developed local recurrence (p=0.2). Although p value of 0.2 is not significant (probably due to small sample size), Odds ratio of 0.147 signifies that pts who received radiotherapy have only 14.7 % chances of developing recurrence as compared to 85.3 % chance in non radiotherapy group. Regarding histological types, 4 malignant PT cases developed local recurrence, 1 borderline case developed recurrence. No benign case developed recurrence. (p=0.007). Out of recurrent cases Two patients with malignant histology developed distant metastasis to lung and both died within a year of recurrence and metastasis.

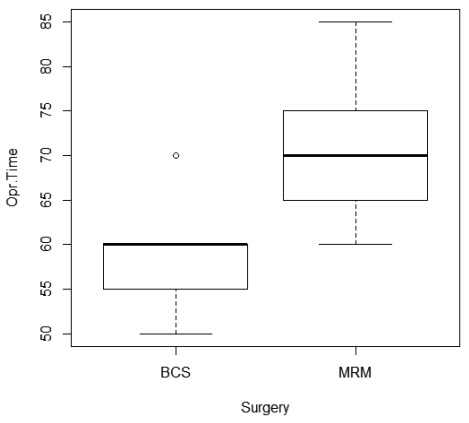

Figure-1a. Operation time vs surgery (BCS/MRM)

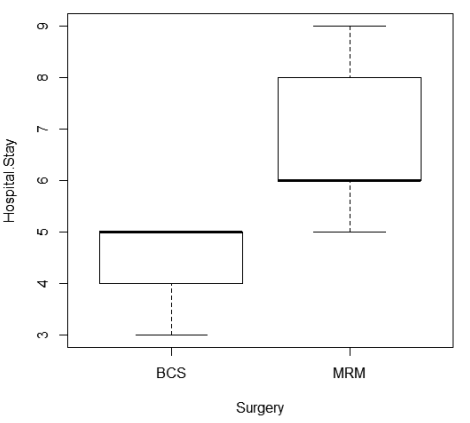

Figure-1b. Hospital Stay vs Surgery (BCS/MRM)

Variables	Benign Phyllodes	Borderline Phyllodes	Malignant Phyllodes
Age Mean: 39.5 (Range: 25-55)	 36.1 (25-46)	 39.2 (33-44)	 46.3 (38-55)
Clinical size of tumour Mean: 6cm (Range: 2.8-14.5)	 5 (3.2-9.8)	 5.4 (2.8-7.2)	 8.3 (5-14.5)
Site of tumour (%) UOQ (41.4%) LOQ (13.8%) UIQ (6.9%) LIQ (10.3%) Central (13.8%) >1 Quadrant (13.8%)	 7 3 1 2 1 1	 3 0 1 0 2 1	 2 1 0 1 1 2
Type of Surgery: Breast conservation (BCS) Mastectomy (MRM)	 13 (86.6%) 2 (13.3%)	 3 (50%) 3 (50%)	 2 (25%) 6 (75%)
Post op Radiotherapy Yes No	0 15	3 3	4 4

Table-I. Clinical features and treatment of different histological types of phyllodes tumour

Features	Total Cases (%)	LR cases (%)	P-Value	OR
Age (years) <40 >40	 15 14	 1 4	0.17	0.19
Tumour size <6 >6 (cm)	 18 11	 1 4	0.036	0.09
Histotype: Benign Borderline Malignant	 15 6 8	 0 1 4	0.007	Infinity
Type of Surgery BCS MRM	 18 11	 1 4	0.053	8.9
Radiotherapy Yes No	 7 7	 1 4	0.2	0.147

Table-II. Predictive factors association with Local recurrence

The distant metastasis and overall survival rate was 93.1%. Kaplein Meire curve (Figure-2) shows survival benefit of radiotherapy. Survival was 100% for irradiated patients compared to 88% for non irradiated patients.

We found that size of the tumour, malignant histology and no use of radiotherapy after surgery to be highest risk factors for tumour recurrence, distant metastasis and overall survival.

DISCUSSION

Phyllodes tumours are rare tumours of breast that exhibit a blend of epithelial component and connective tissue stroma, unlike more common breast cancers that are epithelial in origin.[12] Most of the tumors arise in women between 35 and 55 years of age, about 20 years later than fibroadenoma.[4] In our study mean age of the patients was 39.5 years that was similar to other loco regional studies.[10,13-15]

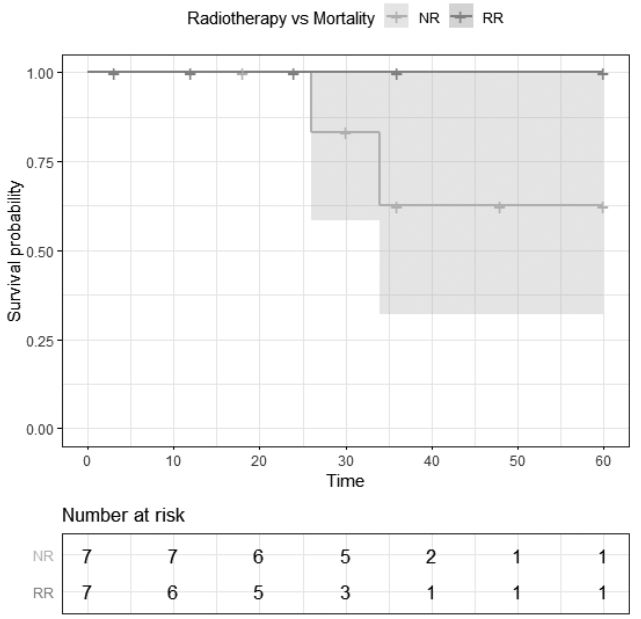

Figure-2. Effect of radiotherapy on 5 year survival of patients with phyllodes tumour.
Note: NR=No radiotherapy. RR= Received radiotherapy.

We found 15 cases of benign, 6 borderline and 8 malignant phyllodes that is similar to a pathological study conducted at Mayo Hospital, Lahore.[16]

PT vary in their size with a median size of 4-7cm[10] and tumours sizes of up to 40 cm has been reported in literature.[5,12] The mean size of phyllodes tumors in our study was 6 cm. In our study larger tumour size (>6cm) was commonly related to malignant histology (75%), similar to the observation of Ditsatham.[17]

A good diagnostic work up and surgical planning is needed to avoid chances of repeated surgery. Treatment can be either mastectomy or BCS if histologically tumour free margins are ensured.[4] BCS with wide tumour margins is considered a preferred treatment provided a good cosmetic and oncologic outcome is feasible.[18,19] A 1-cm margin is considered to be an adequate resection margin and different national and international series report an improved local recurrence and disease-free survival rate with a negative surgical margin.[12,13] We performed BCS (taking 1 cm surgical margin) in 18 cases, of which 12 were benign, 3 borderlines and 2 malignant cases. We did not observe any case of tumour recurrence in benign cases. This was similar to the observation of Ren J and colleagues who described no recurrence in benign tumours over a period of 8 years using wide local excision.[20] In our study mean operative time in BCS was 50 min and mean hospitals stay was 3.7 days. This was shorter than mastectomy. (Figure-2 a,b). Similar observations were reported by Ren J and colleagues.[20]

In most of the malignant cases and especially those with large tumour size, mastectomy was performed. Mastectomy rate for the malignant phyllodes tumours in this study was 75%. It was reported 81% by Demian from Egypt owing to larger size of tumor and a high positive margin rate.[10] It was also observed that most of the cases of mastectomy were performed in older patients and larger tumour size, as compared to BCS. This was similar to the observation of Adesoye T, et al.[7]

To date, a mean local recurrence rate of about 15 % is reported in most series with a range of 10% to 40%.[4] In our study 5 cases (17.2 %) developed local recurrence, 4 of which were malignant and one borderline case. Cases became recurrent at mean period of 22 months with a range of 16 to 30 months. Similarly, Tan EY and colleagues reported local recurrence at a median period of 22 months.[21] We found significant association of factors like size of the tumour, malignant histology and no use of radiotherapy with tumour recurrence (Table-III). Similarly, a study by Ditsatham and colleagues showed tumour size, malignant histology and patient age to be associated with local recurrence.[17]

Limited research is available about the role and effectiveness of adjuvant radiotherapy in reducing recurrences.[2,9] In our study radiotherapy group developed less recurrence with an odds ratio of 14.7 as compared to 85.3 of non radiotherapy however a p value of 0.2 was observed due to small sample size. Similar results were described by Pandey et al.[22] In our study 25% of malignant phyllodes tumour developed distant metastasis, both cases to lungs within a year of local recurrence. Literature also shows most common

site for distant metastasis to be lungs.[4,10,23] Mishra and colleagues reported that 25% of patients with histologically malignant tumors develop distant metastasis, most common site observed for the distant metastases was lungs (66%) followed by bones (28%) and brain (9%).[4] Similarly, Khosravi S described 22% of malignant tumors giving rise to haematogenous metastases.[24] Ramakant P from India reports a poor prognosis of metastatic phyllodes tumors with very few patients surviving more than a year after metastasis.[25] Both of our cases who developed distant metastasis also died within a year of metastasis.

Figure-2 shows Kaplein Miere curve of impact of radiotherapy on survival. The overall survival rate was 93.1%. It was 100% for irradiated patients (Group B) compared to 88 % for non irradiated patients. These results were similar to the study of Demian from Egypt.[10]

Small sample size, due to rarity of tumour was a limitation of this study. A multicentric study needs to be conducted to define the role of radiotherapy in preventing recurrence and improvement in overall survival of phyllodes tumour, on a larger scale.

CONCLUSION

Phyllodes tumour of breast has a propensity of local recurrence and distant metastasis. Malignant phyllodes tumour and large tumour size is associated with worse prognosis. Postoperative radiotherapy improves local recurrence, distant metastasis and overall survival rate.

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3	Farhan Javed	Proof reading.	
4	Irshad Ahmad	Review of literature & Proof reading.	