***Original Research Article***

**Value of Adjuvant radiotherapy in borderline-malignant phyllodes tumors :Mansoura university experience**

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ABSTRACT

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|  **Introduction:** Phyllodes tumors are rare type of breast cancer. Surgery still the first option of treatment; post-operative treatment is a matter of debate specially when considering radiotherapy. Many risk factors could affect the incidence of local recurrence. **Aim:** Study the impact of adjuvant radiotherapy on recurrence rate, local recurrence free survival and overall survival for cases of borderline and malignant phyllodes tumors and to study the risk factors associated with high incidence of local failure. **methods:** A retrospective study done on cases of breast border line or malignant phyllodes tumors. Patients were divided into two groups; group A received adjuvant radiotherapy; group B underwent surveillance after surgery. **Results:** 90 cases were documented in group A and 86 cases in group B. 7 cases (7.8%) in group A developed local recurrence compared to 18 cases (20.9%) in group B with significant P value. comparing failed cases, LRFS was 42.00± 4.32 months in group A compared to 29.16± 5.89 months in group B. P value (≤0.001\*). OS was 102.82± 42.53 months in group A compared to 93.01± 43.07 months in group B. P value was insignificant. Tumor size and pathological type affect LRFS. The cumulative survival after 50 months is 92% when the tumor is less than 8 cm compared to 78 % when the tumor is more than 8 and was 98% when the tumor is borderline compared to 74 % when the tumor is malignant. **Conclusion:** Adjuvant radiotherapy for borderline and malignant phyllodes tumors decreases recurrence rate and improves DFS. |

*Keywords:* phyllodes, radiotherapy, local recurrence.

1. INTRODUCTION

 Phyllodes tumors are non-common pathological type of breast cancer representing about 1% of diagnosed breast tumors (Bernstein L et al., 1993). The WHO identified a sub-type of these tumors according to pathological assessment which include pure benign, borderline or malignant sub-types (Tan PH et al., 2012). Surgery still the first option of treatment for all cases (Guillot E et al., 2011) but post-operative treatment is still a matter of debate specially for cases diagnosed with borderline and malignant pathology (Chaney AW et al., 2000). Using radiotherapy as adjuvant treatment for phyllodes tumors is still a point of discussion between researchers with no confirmed end results. This could be explained by the rarity of prospective trials and the small numbers of cases treated with adjuvant radiotherapy (Haberer S et al., 2009). When thinking about giving adjuvant radiotherapy to phyllodes tumors, many risk factors should be put in consideration. Those factors include pathological type (benign, borderline or malignant), age of the patient, surgical intervention (either breast conservative surgery or radical mastectomy) and size of the tumor. The aim of the current study is to show the experience of clinical oncology and nuclear medicine department, Mansoura university hospital about the impact of adjuvant radiation therapy on recurrence rate, local recurrence free survival (LRFS) and overall survival (OS) for cases of borderline and malignant phyllodes tumors and to study the risk factors associated with high incidence of local failure in patients diagnosed with these tumors.

2. material and methods

 This is a retrospective study done at clinical oncology and nuclear medicine department, Mansoura university hospital on cases of breast border line or malignant phyllodes tumors.

 Patients were divided into two groups; group A received adjuvant radiotherapy 50 gy over 25 ttt for whole breast or chest wall and group B underwent just surveillance after surgery. Both groups were compared for local recurrence rate, recurrence free survival (LRFS) and overall survival (OS) and the risk factors associated with the high incidence of local failure.

 Our study started at September 2008 and ended at August 2022. Cases with benign pathology were excluded, Cases who lost follow up or developed distant metastasis were excluded. Cases who completed the whole duration of follow up were examined clinically every 3 months and assessed radiologically every 6 months by breast ultrasound with or without mammogram annually (if indicated) for development of local recurrence.

**Statistical analysis**

 Data were analyzed using the Statistical Package of Social Science (SPSS) program for Windows (Standard version 26). The normality of data was first tested with one-sample Kolmogorov-Smirnov test.

 Qualitative data were described using number and percent. Association between categorical variables was tested using Chi-square test while continuous variables were presented as mean ± SD (standard deviation) and the two groups were compared by independent t test. Kaplan- Meier test was used for survival analysis and statistical significance of differences among curves was determined by Log-Rank test.

For all mentioned statistical tests done, the threshold of significance is fixed at 5% level (p-value). The results were considered significant when the p ≤0.05 . The smaller the p-value obtained, the more significant are the results.

3. results

At the end of the study there were 90 cases documented in group A who received adjuvant RTH and 86 cases in group B who were under just follow up after surgery. Period of follow up ranged between 24 and 164 months (median 94 months).

 Table 1 shows patients characteristics in both groups. Group A included 36 cases (40%) younger than 50 years and 54 cases (60%) older than 50 years while group B included 36 cases (41.9%) younger than 50 years and 50 cases (58.1%) older than 50 years. Considering tumor size, 44 cases (48.9%) in group A had tumors larger than 8 cm and 46 cases (51.1%) had tumors less than 8 cm while in group B, there were 40 cases (46.5%) with tumors larger than 8 cm and 46 cases (53.5%) with tumors less than 8 cm. regarding type of surgery, there were 50 cases (55.6%) in group A were operated with CBS and 40 cases (44.4%) were operated with MRM. In group B, there were 38 cases (44.2%) operated with CBS and 48 cases (55.8%) operated with MRM. Pathological assessment was done after surgery and there were 42 cases (46.7%) in group A diagnosed with borderline tumor and 48 cases (53.3%) diagnosed with malignant tumor. In group B there were 43 cases (50%) diagnosed with borderline tumor and 43 cases (50%) diagnosed with malignant tumor.

**Table (1):** Patients characteristics

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Group (1) (no=90) | Group (2) (no=86) | Test of significance | p value |
| Age (Years)<50 y≥50 y | 36 (40.0%)54 (60.0%) | 36 (41.9%)50 (58.1%) | χ2= 0.063 | 0.802 |
| Size<8 cm>8 cm | 44 (48.9%)46 (51.1%) | 40 (46.5%)46 (53.5%) | χ2= 0.10 | 0.752 |
| SurgeryConservative Modified radical | 50 (55.6%)40 (44.4%) | 38 (44.2%)48 (55.8%) | χ2= 2.27 | 0.132 |
| PathologyBorderlineMalignant | 42 (46.7%)48 (53.3%) | 43 (50.0%)43 (50.0%) | χ2= 0.196 | 0.658 |
| RecurrenceYesNo | 7 (7.8%)83 (92.2%) | 18 (20.9%)68 (79.1%) | χ2= 6.24 | **0.012\*** |
| Time of rec (m)Mean ± SD | 42.00± 4.32 | 29.16± 5.89 | t= 5.21 | **≤0.001\*** |
| Time of death or end f.u (m)Mean ± SD | 102.82± 42.53 | 93.01± 43.07 | t= 1.52 | 0.130 |

 t: Independent t-test, χ2 : Chi square test, \*significant p≤0.05

 When comparing previous characteristics, both groups were matched as regards age, tumor size, type of surgery and pathology with non-significant P value.

 When comparing recurrence rate between both groups, there were 7 cases (7.8%) in group A developed local recurrence compared to 18 cases (20.9%) in group B. the difference was significant with P value 0.012.

 When comparing the cases who developed local recurrence between both groups, the local recurrence free survival was 42.00± 4.32 months in group A compared to 29.16± 5.89 months in group B. P value was significant (≤0.001\*). This was not the same when comparing the overall survival where it was 102.82± 42.53 months in group A compared to 93.01± 43.07 months in group B and P value was non-significant (0.130).

 All previous data confirms the significant effect of giving adjuvant RTH to decrease the recurrence rate and improving LRFS in cases of phyllodes tumors of the breast, however this effect was not reflected significantly on the OAS.

 our study aimed also to assess the risk factors associated with developing local recurrence in phyllodes tumors. In group A and as shown in table 2, there were 4 cases (11.1%) in subgroup of patients below the age of 50 developed local recurrence compared to 3 cases (5.6%) in patients more than 50. With non-significant P value (0.335). when the tumor size was more than 8 cm, 5 cases (11.4%) developed local recurrence compared with only 2 cases (4.3%) in cases with tumor size less than 8 cm also with non-significant P value (0.214). Between cases who underwent CBS, 4 cases (8%) developed local failure compared to 3 cases (7.5%) in cases underwent MRM. Again, the P value was non-significant (0.930). the only significant P value was documented when comparing the recurrence rate in different pathological types. No cases (0%) were reported to develop local recurrence when the tumor was borderline compared to 7 cases (14.6%) when the tumor was malignant with P value 0.01.

**Table (2):** Association between recurrence and other parameters among group (A)

|  |  |  |  |
| --- | --- | --- | --- |
|  | Group (1)  | Test of significance | p value |
| Recurrence (no=7) | No recurrence (no=83) |
| Age (Years)<50 y≥50 y | 4 (11.1%)3 (5.6%) | 32 (88.9%)51 (94.4%) | χ2=0.929 | 0.335 |
| Size<8 cm>8 cm | 5 (11.4%)2 (4.3%) | 39 (88.6%)44 (95.7%) | χ2=1.54 | 0.214 |
| SurgeryConservative Modified radical | 4 (8.0%)3 (7.5%) | 46 (92.0%)37 (92.5%) | χ2=0.008 | 0.930 |
| PathologyBorderlineMalignant  | 0 (0%)7 (14.6%) | 42 (100%)41 (85.4%) | χ2=6.64 | **0.01\*** |
| Time of death or end f.u (m) | 70.85±21.59 | 105.52±42.83 | t=2.11 | **0.038\*** |

doing the same for group B and as shown in table 3, there were 9 cases (25%) in patients less than 50 years developed local failure compared to 9 cases (18%) in cases more than 50 with non-significant P value (0.43). when the tumor size was more than 8 cm, 12 cases (30%) developed local recurrence compared to 6 cases (13%) in cases with tumor less than 8 cm. although considerable difference but it did not reach significant value (P value 0.054). 10 cases (26.3%) developed local recurrence when the surgery was CBS compared to 8 cases (16.7%) when the surgery was MRM also with non-significant P value (0.275). like group A, the only significant P value was detected when considering the pathological type. Only 3 cases (7%) developed recurrence when the pathology was borderline compared to 15 cases (34.9%) in cases with malignant tumor. P value was 0.001.

**Table (3):** Association between recurrence and other parameters among group (B)

|  |  |  |  |
| --- | --- | --- | --- |
|  | Group (2)  | Test of significance | p value |
| Recurrence (no=18) | No recurrence (no=68) |
| Age (Years)<50 y≥50 y | 9 (25.0%)9 (18.0%) | 27 (75.0%)41 (82.0%) | χ2=0.620 | 0.431 |
| Size<8 cm>8 cm | 12 (30.0%)6 (13.0%) | 28 (70.0%)40 (87.0%) | χ2=3.72 | 0.054 |
| SurgeryConservative Modified radical | 10 (26.3%)8 (16.7%) | 28 (73.7%)40 (83.3%) | χ2=1.19 | 0.275 |
| PathologyBorderlineMalignant | 3 (7.0%)15 (34.9%) | 40 (93.0%)28 (65.1%) | χ2=10.12 | **0.001\*** |
| Time of death or lost f.u (m) | 65.78±19.46 | 100.22±44.78 | t=3.17 | **0.002\*** |

 considering those results, we can conclude that the only factor associated with significant increased risk of developing local recurrence in breast phyllodes tumor either received adjuvant RTH or not is the malignant pathological type.

 Table 4 showed the Kaplan meier disease free survival for every suspected risk factor in all cases either received adjuvant RTH or not. Cases with age less than 50 years had mean LRFS time 137.06 months compared to 151.26 months in cases more than 50 years with non-significant P value (0.3). also, the type of surgery did not affect the mean LRFS significantly, it was 145 months in cases underwent CBS compared to 146.6 months in cases underwent MRM with P value 0.53

 The significant values were detected in the other 2 risk factors; tumor size and pathological type.

 Although the different in size did not affect the recurrence rate significantly, but the difference was significant when comparing the mean LRFS where it was 135.19 months when the tumor is more than 8 cm compared to 155.27 months when the tumor was less than 8 cm with P value 0.048.

 Regarding the pathological type, and as the effect was significant on the rate of local recurrence, it was also significant on the mean LRFS. when the tumor was borderline, the mean LRFS was 162.77 months compared to 134.42 months when the tumor was malignant with P value ≤0.001\*

**Table (4):** Kaplan meier disease free survival

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Mean survival time | SE | 95% CI | Log rank test | P value |
| Age (Years)<50 y≥50 y | 137.06151.26 | 5.974.54 | 125.3-148.7142.3-160.1 | 1.07 | 0.300 |
| Size<8 cm>8 cm | 135.19155.27 | 5.784.29 | 123.8-146.5146.8-163.6 | 3.92 | **0.048\*** |
| SurgeryConservative Modified radical | 145.065146.621 | 5.5844.899 | 134.1-156.0137.0-156.2 | 0.379 | 0.538 |
| PathologyBorderlineMalignant | 162.77134.42 | 2.966.21 | 156.9-168.5122.2-146.5 | 13.74 | **≤0.001\*** |
| Overall disease free survival | 147.636 | 3.761 | 140.2-155.01 | - | - |

Figure 1 shows the curve of survival function for the size of the tumor less or more than 8 cm. from the curve we can discover that the cumulative survival after 50 months is 92% when the tumor is less than 8 cm compared to 78 % when the tumor is more than 8 cm.



**Figure 1** survival function for the size of the tumor

Figure 2 shows the curve of survival function for the pathological type of the tumor. from the curve we can discover that the cumulative survival after 50 months is 98% when the tumor is borderline compared to 74 % when the tumor is malignant.



**Figure 2** survival function for the pathological type of the tumor.

**4.Discussion:**

 Phyllodes tumor are rare type of breast cancer and although it has a good prognosis in general but still has a risk of local recurrence. Options for treatment specially after surgery is still unclear. Also, tumor characteristics and risk factors associated with high recurrence rate remain need more research (Gnerlich, J.L et al., 1998).

 The effect of giving radiotherapy after surgery on survival and local control is still debatable. We can explain that by the small number of cases receiving adjuvant radiotherapy in most of researches (Pezner RD et al., 2008).

 Our study was done to show our experience about the impact of adjuvant radiation therapy on recurrence rate, LRFS and OS of phyllodes tumors. We also tried to identify the risk factors affecting LRFS in patients diagnosed with border line or malignant phyllodes tumors.

 We concluded that incidence of local recurrence is lower when giving adjuvant radiotherapy with significant P value. Also, the LRFS was better even if developed local recurrence in the group who received adjuvant radiotherapy. However, the OS was non-statistically significant between the two groups.

 The Adjuvant radiation therapy for Phyllodes tumors was investigated by Boutrus et al. The number of patients was 108 and according to pathological type they were divided into 3 groups according to pathological type. The researcher found that there was insignificant difference in LRFS when comparing patients who received adjuvant radiotherapy and those who did not when the pathological type was benign. but in the borderline and malignant group, giving radiotherapy after surgery improved five-year LRFS with significant effect when compared to the group that did not receive adjuvant radiotherapy (90% vs. 42% P= 0.005). when comparing the difference in OS between both groups, they found that there was insignificant difference (60 months OS was 52% vs. 45%, P= 0.54) (Boutrus RR et al., 2021). That results matches completely with the results of our study.

 Another study done by Zeng S et al which was a systematic review for 8 studies on the impact of radiotherapy after surgery on borderline and malignant phyllodes tumors. Like our study, it concluded that giving radiotherapy markedly decrease the relative risk of local recurrence with hazard ratio of 0.43 and 95% confidence interval 0.23‑0.64. when assessing the OAS and DFS, they found that there were no significant differences (Zeng S et al., 2015). That was conflicting with our study regarding the effect on DFS which was significant in our results.

 A prospective study done by Richard J et al on the effect of adjuvant radiotherapy after surgery on 46 cases with malignant phyllodes tumors. The results showed that between all patients no cases developed a local recurrence (Richard J et al., 2009). That results reflects the strong effect of adjuvant radiotherapy to decrease the recurrence rate in phyllodes tumors.

 Although manifest effect on decreasing recurrence rate and improving DFS significantly, many researches did not confirm a significant effect on improving OAS. Balasubramanian et al had a retrospective study on 54 patients with malignant phyllodes tumor. Patients divided into 2 group, group 1 included 29 cases received adjuvant radiotherapy and group 2 included 25 patients did not receive radiotherapy. Although the survival was better in group 1 (10-year overall survival 62% in Group 1 compared to 51% in Group 2) but the results was insignificant (P value=0.989). our study confirmed the same results (Balasubramanian et al., 2021).

 Regarding the risk factors associated with developing local recurrence in phyllodes tumors, our study found that the statistically significant risk factor associated with increasing local recurrence in all cases either received radiotherapy or not is the pathological type. but when assessing LRFS for all cases, we found that pathological type and tumor size are associated with significant decrease in LRFS when the pathology is malignant and when the tumor size is more than 8 cm. while other risk factors including younger age, and type of surgery did not show significant effect.

 After analysis of about 50 studies, Yu CY et al concluded that malignant pathological type in phyllodes tumors was the most independent prognostic factor associated with local failure. Which is matched with our results. But when comparing the difference in recurrence rate between cases more or less than 5 cm in size, they found no significant effect (Yu CY et al., 2022). That was matched with our study despite the different cut point used in our study as we compared tumors more or less than 8 cm.

 Our study signifies the excellent prognosis of borderline phyllode tumors with cumulative survival after 50 months is 98% compared to 74 % when the tumor is malignant. Ibraheem et al had a research included 127 cases with 26.8% borderline and 26% malignant type and tried to study the effect of different risk factors on developing local recurrence in phyllodes tumors. They confirmed the same results as our study when considering the pathological type as they found that the 36 months overall survival for borderline tumors was 85.5 % versus 49.8% in malignant type and the difference was significant (Ibreaheem, M.H et al., 2020).

 The same research also tried to study the effect of other risk factors on developing local recurrence. regarding the borderline type, they found that neither the type of surgery nor the addition of radiotherapy affected DFS, however in malignant type, negative surgical margin was the most important factor affecting the DFS (p < 0.007). Also, the type of surgery affected the DFS in malignant type favoring mastectomy over WLE and lumpectomy (p < 0.001). while the addition of radiotherapy did not significantly affect the DFS (Ibreaheem, M.H et al., 2020). These results were different completely with our study as regarding the effect of giving adjuvant radiotherapy reflecting the debate about that point. Also, all cases in our study was operated with negative margin and there was no significant difference in developing local recurrence or DFS according to type of surgery.

 the study done by Balasubramanian et al tried to assess risk factors for recurrence in phyllodes tumor, local recurrence observed more in tumor size of more than 10 cm with a non-statistically significant effect (p-value of 0.774), while other risk factors of age, type of surgery, margin distance and adjuvant radiotherapy were not predictive for local recurrence (Balasubramanian et al., 2021). Again, conflicting with our study as regards effect of adding radiotherapy.

 The study done by Boutrus et al also demonstrated that the 5year estimated LRFS for borderline/malignant phyllodes with tumor size more than 8 cm was 47% vs. 90% in patients with tumors <8 cm (p 0.032) (Boutrus RR et al., 2021). Our study showed similar results where the cumulative survival after 50 months is 92% when the tumor is less than 8 cm compared to 78 % when the tumor is more than 8 cm with significant P value (0.048).

 All previous data show the great debate about the effect of giving adjuvant radiotherapy for borderline and malignant phyllodes tumors. Also, the conflicting results about the different risk factors associated with local recurrence for that tumors.

5. Conclusion

Our study strongly recommends giving adjuvant radiotherapy for borderline and malignant phyllodes tumors to decrease the recurrence rate and improve the DFS. Also, we confirm the effect of type of pathology and size of the tumor as a prognostic factor for LRFS. However, prospective studies with larger number of cases are needed for more confirmation.

Consent

 Not applicable as it is a retrospective study

Ethical approval (where ever applicable)

 The study has the approval of the IRB committee of the faculty of medicine (MFM-IRB), Mansoura university, Egypt, code number is “R.24.12.2952”

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