

Management of Phyllodes Tumour of the Breast at Ain Shams University Hospital, Egypt: A Retrospective Review of a Rare Disease

Mohamed G Qassem MD, MRCS; Karim Fahmy, MD; MRCS; Rania Elahmady, MD

Department of General Surgery, Ain Shams University, Egypt

Background: Phyllodes tumors are rare distinctive fibro-epithelial tumors of the breast and their management continues to be questioned. Between 10% and 40% of phyllodes tumors have a tendency for LR and general dissemination. The aim of our study was to review the management of Phyllodes Tumour (PT) and to examine the determinants of local recurrence (LR).

Methods: A retrospective cohort study of female patients with histologically proven PT who presented to Ain Shams University Hospital (ASUH) between August 2014 and August 2018. Data collected from their files were analyzed to correlate LR after surgical intervention to demographic characteristics, tumour site, tumour size, tumour pathological grade, safety margin and type of performed surgery.

Results: Our study included 24 patients who presented to ASUH and were diagnosed to have PT, with follow up a mean of 30 months \pm 10. Only 6 patients (25%) demonstrated LR after the surgical intervention by a mean of 1.250 years \pm 0.354 (range 1-1.5 years). In the recurrent group, the mean age was 39.333 (range 27-51) (P 0.636), the lesion size was between 5-15 cm (mean 11.667) (P 0.016), and safety margin was exceeding 10mm (P 0.422).

Conclusion: Benign and small PTs should be removed with safety margin rather than simple excision, and their malignant potential should be considered. Wider-scale studies are vital in understanding the recurrence behavior of this rare disease.

Key words: Phyllodes tumour, local recurrence, safety margin.

Introduction

Phyllodes tumor is a rare tumor of the breast in comparison to other histologic subtypes, however, itself, is not a rare tumor, accounting for <1% of all breast malignancies,¹ and has an incidence of about 2.1 per million. Most of these tumors are benign, but some have a malignant potential. These tumors commonly occur in females during the 4th or 5th decade of life. Phyllodes tumors usually present as mobile painless breast masses, however, approximately 20% of tumors are identified on screening mammography and are non-palpable.²

Although phyllodes tumors are similar to fibroadenomas, suspicion for a phyllodes tumor is based on large size, a rapid growth rate, and findings of stromal hyperplasia and atypia on microscopic examination.² The stromal cellularity, atypia and mitotic index are the main parameters in the differentiation of phyllodes tumors from fibroadenomas and in distinguishing a benign from a malignant phyllodes tumor.³ The World Health Organization (WHO) categorizes phyllodes tumors according to the degree of stromal hyperplasia and atypia, as benign, borderline and malignant with malignant tumors accounting for 25% of resected tumors.⁴

Till now, Surgery is the main line of treatment.

National Comprehensive Cancer Network (NCCN) guidelines for the management of phyllodes tumors recommend wide excision with margins \geq 1cm and recommend no axillary intervention.⁵

Main determinants of local recurrence in phyllodes tumors include mitotic activity, tumor margin, and stromal cellular atypia. The local recurrence rates following wide local excision are 8% for benign phyllodes tumors and 21–36% for borderline and malignant tumours.⁶ The objective of this retrospective study is to review the management of the rarely-occurring Phyllodes Tumour at our institution with special highlighting of the potential determinants of its local recurrence.

Patients and methods

Study eligibility criteria:

Following are characteristics of individual studies required for their inclusion in this study depicted into the PICOS format:

- **Participants:** All female adult patients with histologically proven Phyllodes Tumour (PT). Those patients presented to Breast Outpatient Clinic of Ain Shams University Hospital (ASUH) in the period between August 2014 and August 2018. They had triple assessment and routine pre-operative investigations (**Figure 1**). Management plans were based

upon the discussions in weekly-held Multi-disciplinary meetings (MDM). Follow up was arranged to be done bi-annually.

- **Intervention (Exposure):** Mastectomy, Wide Local Excision (WLE) or Oncoplastic Surgery (OS) (**Figure 2**).
- **Control:** Patients who did not show recurrence after the planned surgical intervention.
- **Outcomes:** Local recurrence (LR) after surgical intervention, with correlation to demographic characteristics, tumour site, tumour size,

tumour pathological grade, safety margin and type of performed surgery.

- **Study design:** Retrospective cohort study of prospectively collected data.

All patients were well informed and signed informed consent prior to surgery. This study was approved by the IRB of General Surgery Department at Ain Shams Faculty of Medicine.

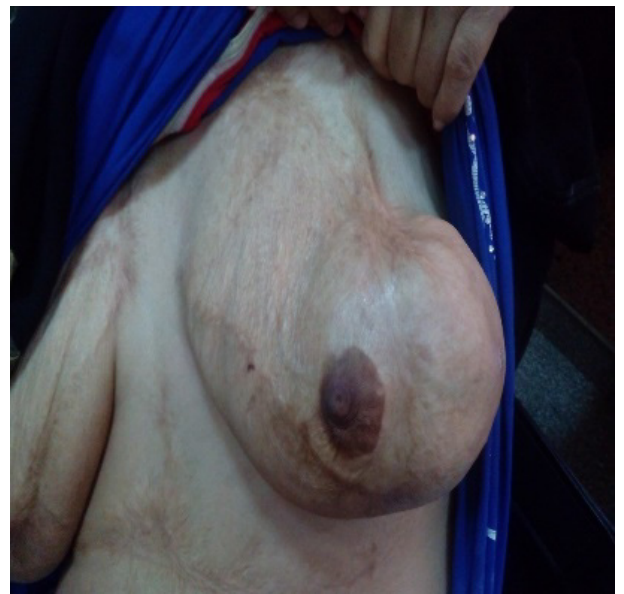


Fig 1: A variety of PT presentations.

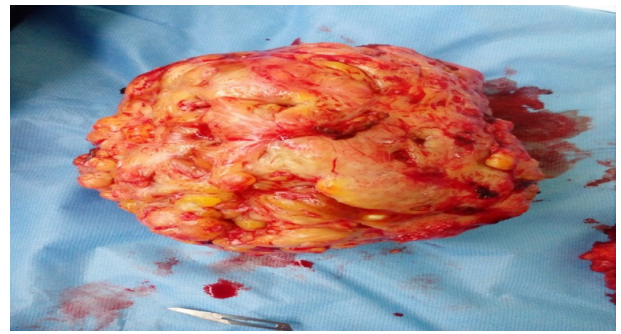
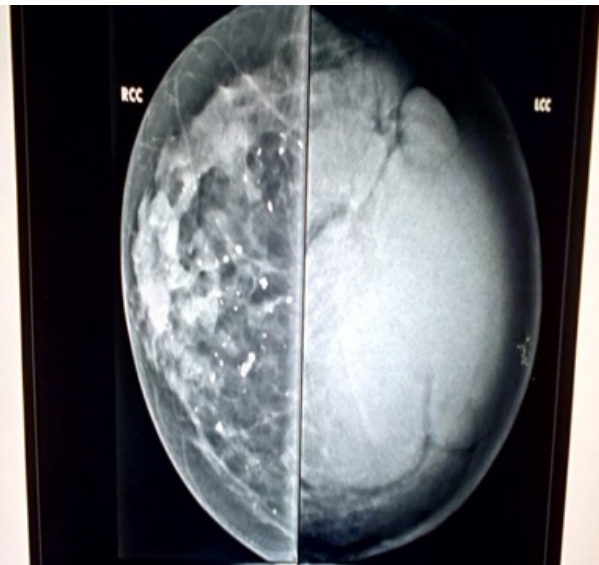


Fig 3: Specimen after WLE.

Statistical analysis of data:

Statistical presentation and analysis of the present study was conducted using the mean, standard deviation, student t- test, Chi-square tests by SPSS V17. Unpaired Student T-test was used to compare between two groups in quantitative data. P-value was considered significant when it was ≤ 0.05 .

Results

This study included 24 patients who presented to ASUH along four years starting from August 2014, and were diagnosed to have Phyllodes Tumour (PT). These patients were followed up for a mean of 30 months ± 10 (range between 20-40 months). Twenty patients (83.33%) presented with accidental discovery of a breast mass, whereas only 4 patients (16.67%) had pain at the time of assessment. Among our study population, 14 patients (58.33%) were recognized to have no associated co-morbidities, left-sided lesions, and benign post-operative histopathological results. Only 4 cases (16.67%) showed positive family history. Mastectomy was done in six patients (50.00%), while WLE and OS were done in 8 cases (33.33%) and in 4 cases (16.67%) respectively (**Table 1**). The mean age of our series was 43.333 ± 15.808 (range 21 – 74). Tumour size ranged between 3-15 cm (mean \pm SD 10.083 ± 4.231), while the safety margin in the histopathological reports exceeded 10 mm in 20 cases (83.33%), 3 mm and 1 mm in 2 cases and involved in 2 cases (**Table 2**).

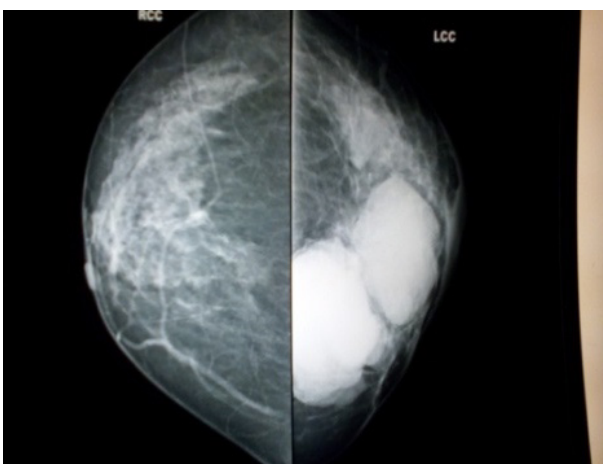
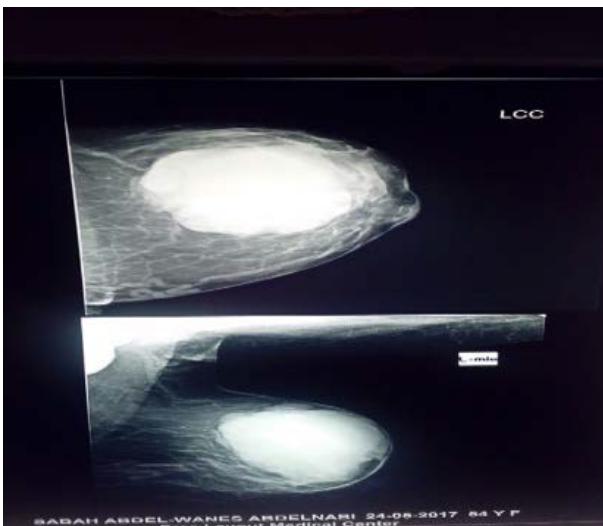


Fig 2: Different mammographic appearances.

Table 1: Demographic characteristics of study population

		N	%
Recurrence	Non-Recurrence	18	75.00
	Recurrence	6	25.00
Co-morbidities	No Co-morbidities	14	58.33
	Co-morbidities	10	41.67
FH	Negative	20	83.33
	Positive	4	16.67
Site	Right	10	41.67
	Left	14	58.33
Presenting symptoms	Lump	20	83.33
	Pain	4	16.67
Tru cut biopsy	Non-Phylloid	14	58.33
	Phylloid	10	41.67
Type of surgery	Mastectomy	12	50.00
	Conservative	8	33.33
	Oncoplastic Surgery	4	16.67
Revision	Re-excision	2	33.33
	Oncoplastic Surgery	4	66.67
Post op pathology type Grade	Benign	14	58.33
	Malignant	10	41.67
Radiotherapy	Benign	0	0
	Malignant	4	22.09
Safety margin	Negative	22	91.6
	Positive	2	8.33

Table 2: Demographic characteristics of study population, continued

	Range	Mean ± SD
Age (Years)	21 - 74	43.333 ± 15.808
Size of the tumor (cm)	3 - 15	10.083 ± 4.231
Disease free period (Years)	1 - 1.5	1.250 ± 0.354

Six patients (25%) demonstrated local recurrence after the surgical intervention by a mean of 1.250 ± 0.354 (range 1-1.5 years). Only one case of mortality was recorded during the follow up period. It is worth mentioning that this patient showed several times of recurrence after mastectomy, and then after Transversus Rectus Abdominis Myocutaneous Flap (TRAM), and then after LDF. During the last episode, she experienced life-threatening bleeding from the fungating tumour necessitated blood transfusion, haemostatic dose radiotherapy and angio-embolization.

**A) LR after MRM.**



B) LR after LDF.



E) After control by angio-embolization.



C)



D) Angio-embolization to control bleeding.

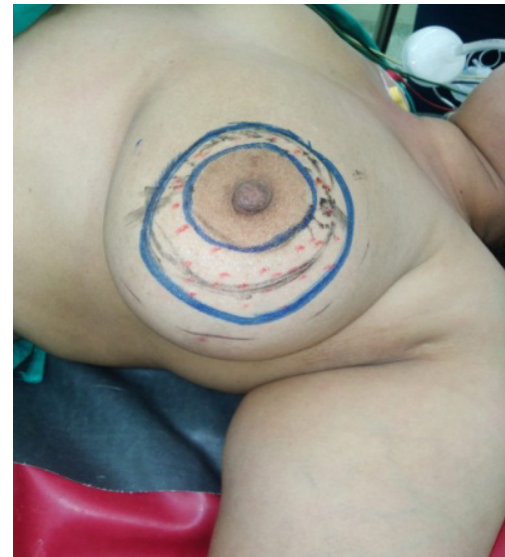


Fig 4: Aggressive local recurrence after surgical treatment of PT.

The disease-free period for the recurrent cases ranged between 1-1.5 years (mean±SD 1.250 ± 0.354). Among the recurrent cases, 2 cases (33.33%) were managed by r-excision and four cases (66.67%) by OS in the form of Round Block technique and Latissimus Dorsi Flap (LDF) (Figures 5-7).



Fig 5: Round Block technique.



Fig 6: Latissimus Dorsi Flap (LDF) technique.

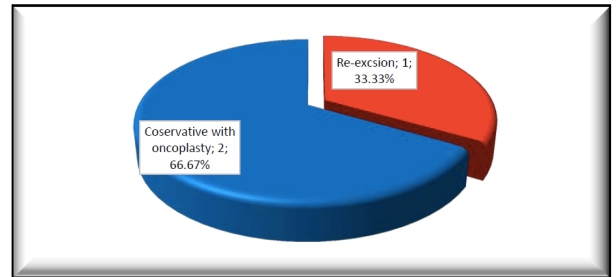


Fig 7: Management of LR following treatment of the primary lesion.

Only 2 recurrent cases (33.33%) had hypertension, while 4 recurrent patients (66.67%) did not have co-morbidities (P-value 0.735). Only 4 cases (16.67%) showed positive family history for breast cancer, half of them had local recurrence (P-value 0.371). PTs were located in the left side in 14 patients (58.33%), and in the right side in the remaining 10 patients (41.67%), P-value 0.735. As a part of triple assessment, tru-cut biopsy showed fibroepithelial lesion highly suggestive of phylloid in 10 patients with clinically suspicious masses (41.67%), while 14 patients (58.33%) tru-cut biopsy was not conclusive, P-value 0.091. Half of this cohort underwent Mastectomy, whereas 8 patients (33.33%) had WLE and the remaining 4 patients (16.67%) had OS in the form of Round Block technique, P-value 0.329. Post-operative histo-pathology revealed malignant PT in 10 patients (41.67%) and benign in 14 patients (58.33%), P-value 0.735. Recurrence occurred in the benign PT in 4 cases (66.67%). Inversely, 8 malignant PTs (44.44%) did not show any recurrence (**Table 3**). 4 patients with malignant pathology received RT based on MDT recommendations. The mean age of the study population was 44.667 (range 21-74) in the non-recurrent arm, and 39.333 (range 27-51) in the recurrent arm with P-value of 0.636. The longest diameter of the mass was ranging between 5-15 cm (mean 11.667) and 3-8 cm (mean 5.333) in the non-recurrent group and the recurrent group respectively, P-value 0.016 (**Figure 7**). (**Table 4**).

Table 3: Comparison between recurrent and non-recurrent groups regarding various factors

		Recurrence						Chi-Square	
		Non-Recurrence		Recurrence		Total		X ²	P-value
		N	%	N	%	N	%		
Co-morbidities	No Co-morbidities	10	55.56	4	66.67	14	58.33	0.114	0.735
	Co-morbidities	8	44.44	2	33.33	10	41.67		
FH	Negative	16	88.89	4	66.67	20	83.33	0.800	0.371
	Positive	2	11.11	2	33.33	4	16.67		
Site	Right	8	44.44	2	33.33	10	41.67	0.114	0.735
	Left	10	55.56	4	66.67	14	58.33		
Type of surgery	Mastectomy	10	55.56	2	33.33	12	50.00	2.222	0.329
	BCS	4	22.22	4	66.67	8	33.33		
	Round block technique	4	22.22	0	0.00	4	16.67		
Pos-op pathology Nature	Benign	10	55.56	4	66.67	14	58.33	0.114	0.735
	Malignant	8	44.4	2	33.33	10	41.67		

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ranging between 5-15 cm (mean 11.667) and 3-8 cm (mean 5.333) in the non-recurrent group and the recurrent group respectively, P-value 0.016 (**Figure 7**). (**Table 4**).

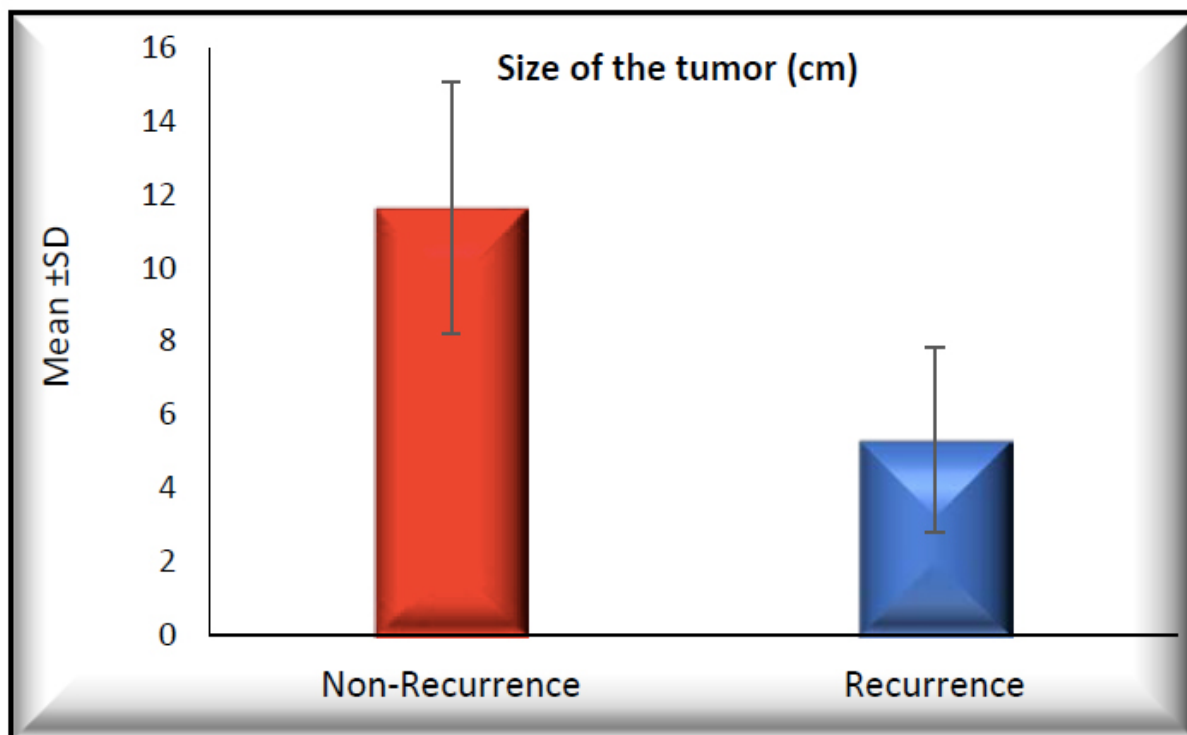


Fig 8: Relation between tumour size and its local recurrence.

Table 4: Impact of age, tumor size and safety margin on LR

		Recurrence		T-Test	
		Non-Recurrence	Recurrence	t	P-value
Age (Years)	Range	21-74	27-51	0.488	0.636
	Mean ±SD	44.667±17.306	39.333±12.014		
Size of the tumor (cm)	Range	5-15	3-8	2.909	0.016*
	Mean ±SD	11.667±3.428	5.333±2.517		

Discussion

Demographic characteristics, such as co-morbidities, family history, tumor site, type of surgery, tumor grade, age and safety margin, failed to prove statistical significance on the incidence of the LR after surgical management for PTs. However, tumor size alone was found to be independent risk factor for LR.

Our study indicates that LR can occur after surgical excision of benign PTs. There are reports of progression of benign PTs to more aggressive subtypes if they recur, this is extremely rare and its importance is possibly overestimated.⁷ This typically took place with one of the recurrent cases in this series. Her initial tru-cut pathology revealed benign PT. But within few months, PT recurred in a wild behavior for several times mandating repeated surgical revisions, adjuvant radiotherapy and even angio-embolization to control the cruel local disease. The biological behavior and pathological features of phyllodes tumors are variable, as benign phyllodes tumors may be associated with recurrence rate of 10–40%. meanwhile, malignant phyllodes tumors may show good clinical course.⁸

In an analysis of 70 patients with malignant phyllodes tumors, Mitus et al. observed patients who underwent mastectomy (82.4%) versus wide local excision (83.3%) with no evidence of recurrence after 5 years.⁹ In our series, LR occurred after 1-1.5 years. This might propose the Management of the large phyllodes tumors presents the surgeon with unique challenges. Complete excision, with accurate histological examination and continued follow-up care, is the best way to treat phyllodes tumors. In most cases wide local excision is indicated, with an adequate margin. Although no absolute consensus regarding margin size have been established a 1 cm macroscopic at the time of the operation and 1mm microscopic margin for most cases has been advocated as adequate.¹⁰ Most authors consider excision margin to be positive if the tumor was present at or close to (<1 mm) the inked tissue on histo-pathology. In fact, taking into account that local recurrence of phyllodes is high and that an affected margin is the single independent predictor of local recurrence is therefore understandable the

paramount significance of the wide excision in the local recurrence-free rate.¹¹

The value of negative margins was demonstrated in several studies, due to higher correlation with disease recurrence.¹²⁻¹⁴ In one of these studies, Spitaleri et al. reported that mean local recurrence rate reached 31.5% in patients with positive surgical margins.¹² Furthermore, Lim et al. identified margin status as the only parameter affecting overall survival at 5 years.¹³ Although the NCCN recommends a clearance of at least 1 cm, a recent literature review by Shaaban et al. found no statistically significant difference in recurrence regardless of 1 mm versus 10 mm margins.¹⁴ The latter study's results are consistent with our results which did not prove any significant difference between margins below 1cm and those higher than 1 cm. However, the authors noted that the possibility of recurrence based on margins status potentially differs depending on tumor behavior, and those with benign PTs do not mandate excision of >1 cm. however, more research is needed in this area.

In the literature the average size of phyllodes tumors is around 4–8 cm varying from 1 to over 40 cm at the extremes.¹⁵ In the study by Eugenie Guillot and his co-workers, the average size was 3 cm with a range of 0.5–15 cm, the largest tumors were of the highest grade. In the same series, univariate analysis showed tumor size to be a significant prognostic indicator for local control ($p = 0.02$), which is consistent with other authors.¹⁶ In our study, smaller PTs paradoxically demonstrate higher malignant potential than the larger ones, which is contradicting the classical conception of the proportional relationship between tumor size and its aggressiveness. Moreover, large sized masses were not associated with higher rate of recurrence mostly due to aggressive initial excision by our surgeon. This was consistent with evidence from literature that small Phylloid may be undertreated by simple enucleation may have higher potential of LR.

BCS with adequate margins (≥ 1 cm) is the mainstay primary therapy for non-metastatic PT.¹⁷ In the same review, it is worth to mention the fact that local recurrence rate between conservation

and mastectomy were not statistically significant provided the margins of excision were adequate.¹¹ This was consistent with our results which revealed no statistical impact of mastectomy versus WLE on LR rates. Axillary dissection was not performed in our series, except for axillary sampling of one case with axillary lymphadenopathy, since nodal metastases secondary to PT are very rare. Recent studies advocate the use of radiotherapy for borderline and malignant PT, recurrent tumors and in cases where it is not possible to achieve a greater than one-centimeter surgical margin.¹⁸ Given the rarity of PT, it might be challenging to derive a randomized controlled trial with adequate sample size.

Although limited in the literature, reports of immediate breast reconstruction have been produced. Immediate breast reconstruction with implant only autologous tissue alone or in combination with an implant did not warrant a higher recurrence rate compared to simple mastectomy and also it did not interfere with follow up or the detection of recurrent lesions. In the appropriate setting nipple sparing skin-sparing mastectomy can be applied without affecting recurrence rates something that is in the author's previous personal experience. The same applies for breast conservation Oncoplastic approach in the treatment of wide excisions and local recurrence being no different provided adequate margins are achieved.¹¹ In our series, only two patients underwent OS in the form of Round Block technique. In the recurrent patients, tumours were managed by Round Block technique and Latissimus Dorsi Flap (LDF).

In addition to the prognostic factors of PTs, several recent studies examining genetic characteristics of PTs have found correlations between varying genomic alterations and PTs.^{19,20} These alterations could potentially add a piece of knowledge regarding therapeutic targets and better management of this rare disease. Genetic analysis will potentially support histological evaluation for better understanding of the recurrence nature of this rare tumor.

Limitations of the study

There are several limitations in the present study. Due to low numbers and paucity of the disease, the significance of some parameters may not have been identified in under-powered analyses. This study represents a single institute experience of a relatively rare disease with the subsequent small sample size. Incidence of PTs could not be calculated because ASUH is a referral hospital from all over Egypt. Eventually, pathological details regarding prognostic factors such as stromal overgrowth, mitotic index and cellular atypia) were not available in the analysis.

Therefore, we recommend adoption of future

multi-centeric and prospective studies including full pathological details and highlighting both LR and distant metastases.

Conclusion

Benign and small PTs should be excised with adequate safety margin rather than simple enucleation, and their malignant potential and LR liability should be taken into consideration. However, multi-centeric studies with large population are considered a golden key in understanding the recurrence behaviour of this rarely-occurring disease.

Conflict of Interest

None to declare

Financial Support

None to declare

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