Review

Update on the diagnosis and management of malignant phyllodes tumors of the breast

Matthew Strode a, Thaer Khoury b, Christopher Mangieri d, Kazuaki Takabe, MD, PhD, FACS a, c, *

a Division of Breast Surgery, Department of Surgical Oncology, Roswell Park Cancer Institute, Buffalo, NY 14263, United States
b Department of Pathology, Roswell Park Cancer Institute, Buffalo, NY 14263, United States
c Department of Surgery, University at Buffalo the State University of New York, Buffalo, NY 14203, United States
d General Surgery Department, Eisenhower Army Medical Center, Fort Gordon, GA 30905, United States

ABSTRACT

Malignant phyllodes tumors of the breast are a rare entity. They occur infrequently but most often in younger women in comparison to typical epithelial-based breast cancers. Treatment of these tumors is not without controversy and in this review we will present an update on the diagnosis and management of malignant phyllodes tumors of the breast.

Keywords:
Malignant phyllodes tumors
Breast
Pathology

Introduction

Phyllodes breast tumors (PT) represent 0.5% of all tumors of the breast that translates into about 500 women annually diagnosed in the U.S [1]. The term “phyllodes” originates from the latin root, “Phyllodium” meaning leaf-like depicting its appearance on microscopy. In 1838, German physician Johannes Müller first described phyllodes tumors as cystosarcoma phyllodes despite the uncommon cystic component of these tumors and rarity of malignancy [2]. These fibroepithelial tumors are characterized as epithelial-lined spaces projecting into stromal elements on pathological examination [2]. The behavioral gamut ranges from that similar to a benign fibroadenoma (FA) to malignant lesions in 30% of patients that have the ability to metastasize distantly [3]. PTs are very rare in males and have been associated with gynecomastia [1]. The mean age of diagnosis is younger than typical breast carcinoma presenting at a mean age of 40 years old. The diagnosis of these lesions as malignant or benign with core biopsy or fine needle aspiration remains difficult pre-operatively [5]. Lumpectomy versus mastectomy remains the initial treatment of choice with 1 cm margins for all phyllodes tumors but the management of malignant tumors is controversial [3]. The key dilemma in the treatment and management of these tumors is local recurrence in both benign and malignant disease. We will review the current data available on the diagnosis, operative treatment and role of post-operative adjuvant treatment for malignant phyllodes tumors (MPTs).

Clinical presentation

The age of presentation of PTs are generally later than FAs and are typically present for an extended period of time prior to being evaluated. Clinical presentations are often preceded by a rapid increase in size but the growth rate has not been firmly associated with malignancy [2]. The size of the tumors is variable ranging between 4 and 7 cm and usually has a mobile, multinodular appearance that is non-painful [6]. Ulceration and fixation to the chest wall are rare even with malignancy [7]. Clinical adenopathy has been said to be present in 20% of patients, but true metastatic locally advanced disease in the axilla is very rare although distant metastatic disease has been reported in up to 20% of MPT. Local recurrence occurs in 15% of patients with R0 resections and is more common after inadequate excision [2]. The typical pattern of spread
is virtually always hemagenous and not lymphogenic so this finding is not unexpected. Any rapidly growing benign appearing breast mass in a female 35 years old or more should warrant concern for a PT and further investigation [8]. Risk factors for the development of PTs are not well published in the literature with exception of the described association with p53 germline mutations in Li-Fraumeni Syndrome [60].

Pathologic characteristics of PTs

The World Health Organization in 2012 revisited the division of subtypes of PTs; benign (Fig. 1A), borderline (Fig. 1B), and malignant (Fig. 1C) (Table 1) [53]. One fourth of PTs are classified as malignant, whereas benign PTs represent 60–75% of all PTs. Unlike FAs, they lack a true capsule, and possess increased mild stromal cellularity, mild nuclear atypia, rare mitosis and leafy architecture. The leafy architecture can be seen in FAs but is not well developed and tends to be focal. Despite these characteristics, pathologically differentiating between FAs and benign PTs consistently has been proven to be a daunting task which poses a significant issue as even benign PT have a local recurrence rate of up to 20%. Even with subspecialty breast pathologists, there has been little consensus as to distinguishing between these two lesions in direct comparison between observers [2,8,51]. There is some evidence in the literature pertaining to the use of surgical outcomes from FELCS in core biopsy specimens [14,19]. Labeling index of Ki-67, a proliferation marker, has been reported to be significantly different between FA and benign PT [13,19]. Another proliferation marker, topoisomerase 2, an enzyme that breaks and rejoins DNA [20,21], has been shown to correlate well with Ki-67 labeling index in breast tumors [20]. Increased p53 protein expression has been documented in malignant PT, but not in benign PT and FA [22]. In a large series by Læ et al., exon sequencing demonstrated that MED12 exon 1 and 2 somatic mutations tend to be present in more benign PTs and FA associating them with non-aggressive histology. While the mutations can be seen in MPTs in 27.6%, they are much more common in benign and borderline PTs at 58.3% and 63.3%, respectively. MED12 mutations can be seen with associated altered presence of genes seen on the WNT, TGFβ and THRA pathways. The presence of the MED12 mutations and mentioned altered gene pathways could not only provide diagnostic information for these difficult cases but also be a pathway for future therapeutic treatments [54].

In surgically excised specimens, nuclear pleomorphism, marked stromal cellularity or overgrowth, permissive margins, and >10 mitoses per 10 HPF distinguish MPT as do the presence of sarcomatous elements even in isolation [9,50]. Borderline PT characterizes a group of tumors that lie somewhere in between benign and MPT representing 12–26% of all PT’s. They tend to have some of the mentioned characteristics for MPT but lack all of them. Recurrence rates are similar to benign PT local recurrence rate at 14–25% after excision. The mitotic cutoff for diagnosis remains in the 5–9/10 HPF range just below the >10 mitoses for MPT [8]. Although these

![Fig. 1. A. Benign PT; B. Borderline PT; C. Malignant PT.](image-url)
Various types of mesenchymal metaplasia develop within the epithelial component of the MPT and mitotic count <5 per 10 HPF (benign PT) be classified? Azzopardi and Salvadori et al. first described a classification system in 1979 and 1989 that was similar to the 2012 WHO classification but lacked the stromal overgrowth component present in the WHO classification [2,16]. Components are all three subcategories of phyllodes tumors can be present in the same sample so careful sectioning of the samples is required. Each of the microscopic parameters consists of 2–3 levels of stratification and are difficult to reproduce accurately [9]. The stromal overgrowth can be so dense in malignant PT that it is difficult to distinguish the epithelial elements. The stroma is the most important aspect of the pathological appearance as it predicts a tumor’s behavior and metastatic potential. Latin American white females have an increased incidence of the development of malignant phyllodes tumors and are seen in increased frequency in immigrant women born in Mexico, Central America and South America [4].

The stromal component of the MPT is spindle shaped with either fibroblastic or myofibroblastic differentiation (Fig. 1C). Various types of mesenchymal metaplasia develop within the stroma including osseous, chondroid, lipoblastic, rhabdomyoblastic, and smooth muscle differentiation. More than one type of differentiation can be seen within the sarcomatoid component [23]. Therefore, included in the differential diagnosis of MPT are rare primary breast sarcoma, metastatic breast sarcoma, malignant phyllodes with sarcomatous overgrowth, and metaplastic spindle cell breast carcinoma with its varying subtypes [2,8]. Bland benign appearing epithelium and leaf-like pathologic architecture is more likely to be PT while metaplastic spindle cell carcinomas typically exhibit malignant epithelial components but are not always present. Ductal carcinoma in situ (DCIS) presence in proximity to spindle cell carcinoma favors metaplastic transformation. Immunohistochemistry (IHC) can be performed if the specimen lacks an epithelial component to aid in the diagnosis. Metaplastic spindle cell carcinomas have a varied staining pattern on IHC. CD34 is reported to be positive in 37–57% of malignant PT and lacking in metaplastic spindle cell carcinoma. The tumors are usually negative for epithelial markers (CAM5.2, EMA, CK7, and AE 1/3) and S100. The stromal cells could express p63 when the tumor has significant atypia but rare in tumors with low grade nuclei. CD10 and CD117 have been reported to be expressed in PTs [23].

Comparative genomic hybridization studies have identified recurrent large scale copy number variation, including gains of chromosome 1q, 5p, 7 and 8 and losses of chromosomes 6q, 9p, 10p and 13q, among others. There is an increase in the mean number of chromosomal alterations from benign to MPTs [24–30]. Liu et al. sequenced 510 cancer-related genes in 10 MPTs. Overall, genomic aberrations in FGFR/EGFR PI-3 kinase and RAS pathways were identified in 8 tumors. There were mutually exclusive and potentially actionable activating FGFR1, PIK3CA and BRAF V600E mutations, inactivating TSC2 mutation, EGFR amplification and PTEN loss. They included 5 cases with liposarcomatous differentiation, none of which had CDK4/MDM2 amplification, a finding shared by others [31]. They also found that there was intratumoral heterogeneity and evidence for divergent tumor evolution in MPTs with and without heterologous differentiation. Tumors with liposarcomatous differentiation revealed more chromosomal aberrations in non-heterologous components compared with liposarcomatous components [32]. Molecular studies have also shown that p53, Rb1, NF-1 mutations and EGFR, and IGF1 gene amplifications can also be detected in malignant tumors [8].

Tan et al. performed targeted deep sequencing in a cohort of 100 fibroepithelial tumors (21 FA and 34 benign, 35 borderline and 10 malignant PT). They found frequent recurrent mutations in two genes coding for the transcription factors MED12 (73%) and RARA (32%) in all subtypes of tumors, suggesting that mutations in these genes are early events in tumorigenesis. The fibroepithelial RARA mutations were highly clustered within the portion of the gene encoding the nuclear hormone receptor ligand-binding domain [52]. In other studies, however, both MED12 and RARA were found to be associated with estrogen-related transcription and signaling [62,63]. Interestingly, mutations in MED12 and RARA co-occurred at rates higher than expected by chance [54]. These results suggest that mutations in these genes are early events in FAs and PTs. In comparison to FA and benign PT, borderline and malignant PT exhibited additional mutations coupled with putative Copy Number Alterations in NF1, RB1, TP53, PIK3CA, ERBB4 and EGFR, though the frequency of these events was low (29%). These genes are known to have cancer driver function and have transforming ability. These findings are consistent with previous studies showing deregulation of TP53 and RB1 in malignant PT [64–66].

Primary breast sarcoma and metastatic breast sarcoma are both very rare but can appear very similar to MPT if no epithelial component is present. Angiosarcoma is the most common form of sarcoma in the breast accounting for less than 0.04% of all breast cancers. These angiosarcomas are typically high grade and have a very poor prognosis and have been associated with prior radiation or are sporadic in nature [33,49]. The treatment for either primary or metastatic sarcomas are similar in that both require wide local excision and have similar overall survival and disease free survival rates.

As stated previously, the metastatic rate of MPT has been stated at 22% with poor response to systemic therapy and most patients
dying within 3 years of initiation of treatment regardless of the regimen. The majority of the tumors metastasize to the lungs, followed by the skeleton, heart, and then liver. It has been reported to involve almost all organs including central nervous system, gastrointestinal (Fig. 2), adrenal gland, pancreas, spleen, among others [23].

Imaging

PT appear similar to FA on mammography and ultrasound as a smooth, well circumscribed, polylobulated, hypoechoic masses. Screening mammography can identify up to 20% of non-palpable PT. There is some low level evidence that T1 weighted images with high intensity, T2 images with low intensity and rapid enhancement may identify MPT but this has not been confirmed prospectively [34]. MRI may aid in surgical planning but does reliably differentiate between malignant and benign disease.

Treatment

Prior to the 1970s, mastectomy was the treatment of choice for all PTs regardless of subtype but without a documented survival advantage. Axillary dissection is not routinely recommended since lymph node involvement is very rare with less than 1% of patients as described [2]. The recommended NCCN guideline treatment of MPT is complete surgical excision with 1 cm margins without sentinel lymph node biopsy. Mastectomy at the index surgery is only recommended in the cases if the inability to adequately obtain 1 cm margins or if changes in the cosmetics of the breast would be unacceptable to the patient [47]. The recommended NCCN guideline treatment of MPT is complete surgical excision with 1 cm margins without sentinel lymph node biopsy. Mastectomy at the index surgery is only recommended in the cases if the inability to adequately obtain 1 cm margins or if changes in the cosmetics of the breast would be unacceptable to the patient [47]. The recommended NCCN guideline treatment of MPT is complete surgical excision with 1 cm margins without sentinel lymph node biopsy. Mastectomy at the index surgery is only recommended in the cases if the inability to adequately obtain 1 cm margins or if changes in the cosmetics of the breast would be unacceptable to the patient [47]. The recommended NCCN guideline treatment of MPT is complete surgical excision with 1 cm margins without sentinel lymph node biopsy. Mastectomy at the index surgery is only recommended in the cases if the inability to adequately obtain 1 cm margins or if changes in the cosmetics of the breast would be unacceptable to the patient [47]. The recommended NCCN guideline treatment of MPT is complete surgical excision with 1 cm margins without sentinel lymph node biopsy. Mastectomy at the index surgery is only recommended in the cases if the inability to adequately obtain 1 cm margins or if changes in the cosmetics of the breast would be unacceptable to the patient [47]. The recommended NCCN guideline treatment of MPT is complete surgical excision with 1 cm margins without sentinel lymph node biopsy. Mastectomy at the index surgery is only recommended in the cases if the inability to adequately obtain 1 cm margins or if changes in the cosmetics of the breast would be unacceptable to the patient [47]. The recommended NCCN guideline treatment of MPT is complete surgical excision with 1 cm margins without sentinel lymph node biopsy. Mastectomy at the index surgery is only recommended in the cases if the inability to adequately obtain 1 cm margins or if changes in the cosmetics of the breast would be unacceptable to the patient [47].

A study at Mayo Clinic confirmed that disease free survival and overall survival was not affected by extent of surgical margins in a small study of borderline and MPT. Adequate treatment of MPTs starts with the adequacy of surgical excision and negative margins. Local recurrence rates of 31.5% have been stated in the literature after positive resection margins at the index surgery [59]. The definition of a negative margin has been a point of contention in the literature. To prevent local recurrence, Tremblay-Lemay et al. suggested that at least 1 mm may be sufficient to prevent local recurrence while the NCCN recommends 1 cm as previously stated [58]. Breast conservation is appropriate for both malignant and benign variety of PT’s with re-excision of positive or close margins [34]. Local recurrence rate is the major challenge in borderline and malignant PTs, which is up to 60% when followed out to 9 years with the mean recurrence time of 20 ± 13.4 months in MPT, and is 21–36% even with 1 cm margins [35,39]. Again, it is very important to differentiate these tumors from metaplastic carcinoma because sentinel lymph node biopsy and neoadjuvant/adjuvant chemotherapy play a role in staging and treatment of those types of cancers while typically being omitted in MPT [8].

Radiation treatment for MPT is also controversial. Despite the lack of clear prospective randomized evidence of the efficacy of treatment with radiation on survival, a study using the Surveillance, Epidemiology, and End Results Program (SEER) database showed that from 2000 to 2012, the utilization of radiation for MPT increased substantially over time. Patients who had larger tumors, later year of diagnosis, and those who underwent axillary staging were more likely to have radiation [38]. Barth et al. conducted a prospective study of forty-six patients receiving radiation therapy for borderline and MPT. Forty-three of the patients had a resection of a primary PT while three patients had a local recurrence that was resected and all followed by radiation. Thirty of the forty-six patients had MPT with a median age of 49 years of age. The mean diameter of the tumors were 3.7 cm. No patients were lost to follow-up and mean time for surveillance post-operatively was 60 months. No local recurrence in any patient was observed at the conclusion of the study. This is in comparison to other previous studies of local recurrence rates after resection alone of malignant PT’s is relatively high with rates of 20% suggesting that radiation could be effective even in margin negative tumors [35,39–42].

Gnerlich et al. performed an analysis of the effects of radiotherapy on 3120 patients using the National Cancer Database and found no survival benefit, or disease free survival but confirmed a significantly reduced local recurrence rate in patients undergoing both lumpectomy and mastectomy for MPT [43]. The reduction of local recurrence but absence of disease free or overall survival has been the limiting factor in using radiotherapy routinely but despite the clear presence of a survival benefit, the usage of therapy appears to be increasing. Pezner et al. reviewed 478 patients with MPTs from the National Oncology Database suggested that adjuvant radiation be strongly evaluated in these patients as local recurrence was shown to impact overall survival differing from other available literature [55]. Pandey et al. reported a small study of 37 patients with MPTs reporting that the margin of excision was the only independent factor determining DFS or overall survival. They did, however, show some difference in 5 year DFS with adjuvant radiotherapy (61.2% versus 25.7%) but was limited by the small study size thus was not statistically significant [56]. Belkacemi et al. found using the Rare Cancer Network database that radiotherapy decreased local recurrence in MPT and borderline PTs at 10 years but did not affect overall survival [57]. Kim et al. performed a large study using the SEER database of 1974 patients with MPTs managed with both mastectomy and local excision. Similar percentages of patients (16% and 11%, respectively) underwent radiotherapy post-operatively and no difference in cancer specific survival was seen in those patients [61]. Future prospective, randomized trials would be helpful in providing possibly a subset of patients who would possible benefit more from radiotherapy aiding in the treatment algorithm for MPT.

Estrogen and progesterone receptor positivity have been described in 58% and 75% of PT, respectively but no defined benefit has been derived from hormone therapy [5] Hormone receptors of estrogen and progesterone have confirmed presence in epithelial tissue of all types of PT’s. Unfortunately, the estrogen receptor beta is the predominant receptor present rather than estrogen receptor alpha that is the most common estrogen receptor present in typical
invasive ductal carcinoma of the breast. At this point, hormone therapy has no role in the treatment of malignant PTs and should be omitted [44–46].

With the poor prognosis of metastatic disease and frequency of recurrence, the use of chemotherapy is controversial. There are no prospective trials of chemotherapy for MPT. Neoadjuvant Doxorubicin plus Dacarbazine versus no medical therapy has been examined in a small observational biased trial with no benefit of relapse-free survival [36]. The use of routine chemotherapy is not encouraged for MPT in the standard treatment algorithm but can be considered in extreme circumstances such as large tumors, or involvement of secondary structures such as the chest wall. The benefit, however, of such use is not well documented or recommended by the NCCN guidelines on the management of MPT. Metastatic PT’s are, however, treated accordingly to the NCCN sarcoma guidelines and are not discussed in this review [47].

Other modalities have been described with success on case-report basis. Hashimoto et al. reported the pre-operative chemotherapy preparation of a large MPT with successful avoidance of skin grafting after excision. Although not well described in the literature, this modality could be a possible treatment option in extreme circumstances [48].

Prognosis

Recurrence rates for MPTs alone are reported as 23–30% in the literature. Benign and borderline phyllodes tumors recurrence rates in comparison are 10–20% and 14–25%, respectively [9]. The mean time to recurrence of benign, borderline, and MPT’s are reported as 20.2 ± 12.1, 16.9 ± 10.8, and 20.3 ± 19.0 months, respectively [38]. Close follow-up of these lesions is essential to identify recurrences. Local recurrences are more common than metastatic recurrence, but are not associated with a decreased survival and can be cured with lumpectomy or mastectomy while metastatic disease has worse prognosis [3]. Metastatic disease most commonly occurs in the lung, abdominal viscera, and skeleton but other sites have been reported. The presence of metastatic disease usually indicates a bleak prognosis followed by death soon after with no long term survivors. Pathologically, the metastatic deposits typically have the malignant stromal elements that are present in the typical primary tumor and lack the epithelial aspect appearing more like a sarcoma. They typically occur without a local recurrence and the extent of the index surgery (i.e. mastectomy versus lumpectomy) has no effect on distant metastatic recurrence [9].

Spitaleri et al. published a large retrospective report and review of the literature of breast phyllodes tumors that demonstrated through multivariable analysis clinical features that predict relapse in these patients. The authors showed that age less than 35 years old, tumor necrosis, stromal overgrowth, and positive surgical margins were negative prognostic factors for recurrence. They also demonstrated that when benign and borderline tumors recur, they can generally be managed with repeat surgery with either wide excision or mastectomy with good success rates. Distant recurrence or benign and borderline PTs was not seen in this particular review but MPT was shown to have distant recurrences in 6.4% and up to 22% in the literature. The discrepancy in both distant spread and recurrence in the spectrum of PTs creates difficulty in follow-up strategies [59].

Conclusion

Malignant Phyllodes tumors represent an entity of breast cancer that has been elusive as to the best therapy for each patient. Surgical management with negative margins of at least 1 cm, or mastectomy without axillary lymphadenectomy is the treatment of choice for most patients. Although no difference in survival has been proven, we recommend post-operative radiotherapy in all MPT’s even with negative margins due to the substantial decrease in local recurrence rate. Consideration of radiotherapy can be given for close margins or proximity to critical structures for borderline MPT or for local recurrence of either MPT or borderline PT. Chemotherapy or hormonal therapy currently has little evidence in treating MPT’s although chemotherapy can be considered for high risk, large tumors or locally invasive with or without radiotherapy. Until clinical trials can produce a benefit for adjuvant chemotherapy, we recommend that it should be omitted from most patients’ treatment plans that lack this aggressive presentation.

Conflicts of interest

There were no conflicts of interest or funding required in the preparation of this manuscript.

Disclosure

The authors declare no conflict of interest.

Acknowledgements

Kazuaki Takabe is funded by United States National Institute of Health (R01CA160688) and Susan G. Komen for the Cure (Investigator Initiated Research Grant (IIR12222224)).

References


Lye PL, Bridge JA, Simpson JF, Cates JM, Sanders ME. Liposarcomatous differentiation in malignant phyllodes tumors is unassociated with MDM2 or CDK4 amplification. Histopathology 2016;68(7):1040–5.


