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Distant metastases in phyllodes tumours of the breast: an overview

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Abstract

Phyllodes tumours (PTs) of the breast are uncommon fibroepithelial neoplasms, comprising 0.3 – 1.0% of all primary breast malignancies in Western countries, but accounting for a higher proportion of primary breast tumours in Asian countries. They are graded as benign, borderline or malignant based on the World Health Organisation (WHO) classification, according to a constellation of 5 histologic parameters. While most PTs carry a good prognosis, malignant and occasionally borderline PTs have the potential to metastasize to distant sites. Although events of distant metastasis are few, the prognosis for such patients is dismal, as they are often unresponsive to chemotherapy with high mortality. This review seeks to provide an overview of this rare but important phenomenon of distant metastases in PTs of the breast.

Keywords: Fibroepithelial neoplasms, Phyllodes tumours, Metastasis, Distant metastases, Prognosis

Background

Phyllodes tumours (PTs) of the breast are uncommon fibroepithelial neoplasms morphologically characterised by benign double-layered epithelium surrounded by a hypercellular stroma, which together exhibit a leaf-like architecture [1]. They are classified into benign, borderline, and malignant according to the World Health Organisation (WHO) classification, based on the assessment of 5 histologic parameters – stromal cellularity, stromal atypia, mitoses, stromal overgrowth, and tumour margins. PTs comprise 0.3 – 1.0% of all primary breast tumours in Western countries. In Asian countries however, PTs account for a higher proportion of primary breast tumours and can also develop in younger patients [1].

The majority (60.0%–75.0%) of PTs are benign. Benign PTs carry a good prognosis, and are generally well managed with surgery, with a local recurrence rate of about 10.0%–20.0% [2–4]. Borderline and malignant PTs account for 15.0 – 20.0% and 10.0 – 20.0% of all PTs respectively [1]. Unlike benign PTs, malignant PTs, and occasionally borderline PTs, can behave in a clinically aggressive manner, with local recurrence rates of malignant PTs ranging from 15.0 to 40.0%. Distant metastasis is rare, occurring nearly exclusively in malignant PTs at a rate of 9.0 – 27.0%. Although a rare event, the prognosis of patients with metastasis is very poor, as many are unresponsive to standard chemotherapy with ensuing mortality [4].

As events of distant metastases in PTs are rare, there are limited studies on this clinically important phenomenon. This review seeks to provide a literature overview of PTs with distant metastases.

Rates of metastasis in PTs

A summary of studies containing PTs with distant metastases by various authors can be found in Table 1. The overall rates of distant metastases in PTs range from 1.7 to 27.1% [5, 6], with an average of 5.6%, and vary according to tumour grade. It is highly unlikely for benign PTs to metastasize to distant sites; however, rare exceptions do exist. Reinfuss et al. [7] documented 3 cases of benign PTs that developed metastases, while Mangi et al. [8], Chaney et al. [9], Asoglu et al. [10], and Abdalla et al. [11] each recorded 1 case of metastatic benign PT in their studies. In the study by Mangi and colleagues, the case of benign PT that later metastasized was initially treated with a simple excision. The lesion was 2 cm in size and the surgical margins were <1 mm. Distant metastasis (site not mentioned) developed 36 months later and the patient underwent a total mastectomy and radiotherapy, but eventually still succumbed

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Table 1 A summary of studies with metastatic PT

Authors, year of publication	No. of cases	Total metastatic rate, % (no. of cases)	Metastatic rate by tumour grade, % (no. of cases)			Site(s) of metastasis	PT-related death rate, % (no. of cases)	Metastatic death rate, % (no. of cases)	Time to metastasis from diagnosis (months)	Time to death (months)	Factors associated with metastasis	Axillary lymph node metastasis, % (no. of cases)
			Benign	Borderline	Malignant							
Lindquist et al. 1982 [16]	42	9.5 (4/42)	0/3[a]	0	4/7	Chest wall, liver, lungs, retroperitoneum	50.0 (5/10)	100 (4/4)	Range 0 - 84	PT diagnosis to death: Range 21-84	NA[b]	NA
Ward and Evans 1986[c] [19]	26	19.2 (5/26)	-	-	-	Gastrointestinal tract, lung, spleen, thyroid, uterus	26.9 (7/26)	100 (5/5)	NA	PT diagnosis to death: range 6 - 32	Stromal overgrowth	0
Hawkins et al. 1992[c] [26]	33	24.2 (8/33)	-	-	-	Bone, lung, mesentery, muscle or soft tissue, pleura, skin	21.2 (7/33)	87.5 (7/8)	Median 14 (range 2 - 31)	DM[d] to death: Median 10 (range 2 - 40) PT diagnosis to death: Median 25 (range 12 - 50)	Severe nuclear pleomorphism, stromal overgrowth, high mitotic count, infiltrating margins, large tumour size, presence of necrosis	NA
Rowell et al. 1993 [30]	18	5.6 (1/18)	0 (0/11)	0 (0/4)	33.3 (1/3)	Lung, muscles	5.6 (1/18)	100 (1/1)	NA	PT diagnosis to death: 23	NA	0
Reinfuss et al. 1996 [7]	170	15.9 (27/170)	3.3 (3/92)	21.1 (4/19)	33.9 (20/59)	Bone, brain, lung	15.9 (27/170)	100 (27/27)	Mean 18 (range 2 - 57)	Mean 4 (range 2 - 11)	NA	0.5 (1/70)
de Roos et al. 1999 [39]	38	10.5 (4/38)	0 (0/15)	0 (0/11)	33.3 (4/12)	NA	10.5 (4/38)	100 (4/4)	NA	Median 17 (range 12 - 125)	Size and grade related to metastatic death	NA
Mangi et al. 1999 [8]	40	2.5 (1/40)	2.9 (1/34)	0 (0/3)	0 (0/3)	NA	2.5 (1/40)	100 (1/1)	36	NA	None	NA
Chaney et al. 2000 [9]	101	7.9 (8/101)	1.7 (1/59)	0 (0/12)	23.3 (7/30)	Brain, lung, pelvis	NA	100 (8/8)	NA	NA	Stromal overgrowth, malignant histology, mastectomy	0
Kapiris et al. 2001[e] [6]	48	27.1 (13/48)	-	-	27.1 (13/48)	Bone, lung, pleura	35.4 (17/48)	92.3 (12/13)	Median 25.6 (range 6 - 120)	DM to death: mean 16.6 (range 1 - 24)	Tumour size, margins	0
Asoglu et al. 2004 [10]	50	26.0 (13/50)	6.3 (1/16)	33.3 (1/3)	35.5 (11/31)	Abdomen, bone, brain, liver, lung	32.0 (16/50)	100 (13/13)	Mean 53.4, median 36 (range 4 - 77)	DM to death: mean 7 (range 1 - 19)	Stromal overgrowth	2 (1/50)
Chen et al. 2005 [5]	172	1.7 (3/172)	0 (0/131)	8.3 (1/12)	6.9 (2/29)	Lung, soft tissue of neck	NA	100 (3/3)	NA	DM to death: 5 (patient 1), 6 (patient 2). No info on 3rd patient	Stromal cellularity, stromal overgrowth, stromal atypia, mitotic activity, tumour margin,	0

Table 1 A summary of studies with metastatic PT *(Continued)*

											heterologous stromal elements	
Sotheran et al. 2005 [27]	50	2.0 (1/50)	0 (0/29)	0 (0/12)	11.1 (1/9)	Musculoskeletal chest wall	2.0 (1/50)	100 (1/1)	18	NA	NA	NA
Abdalla et al. 2006 [11]	79	12.7 (10/79)	3.2 (1/31)	11.1 (3/27)	28.6 (6/21)	Bone, brain, lung	12.7 (10/79)	100 (10/10)	Median 14 (range 3 - 36)	DM to death: Mean 5 (range 1 - 11)	Histotypes and resection margins	1.3 (1/79)
Tan et al. 2006 [48]	37	16.2 (6/37)	0 (0/22)	0 (0/9)	100 (6/6)	Bone, lungs, pleura	8.1 (3/37)	50 (3/6)	NA	Mean 11.3	NA	NA
Cheng et al. 2006 [12]	182	2.2 (4/182)	0 (0/138)	7.7 (1/13)	9.7 (3/31)	Lungs	2.2 (4/182)	100 (4/4)	Mean 14	Mean 6 (range 5 - 9)	None	0
Belkacémi et al. 2008 [13]	443	3.4 (15/443)	0 (0/284)	2.5 (2/80)	16.5 (13/79)	Lung	NA	NA	NA	NA	NA	0.2 (1/443)
Lenhard et al. 2008 [24]	33	9.1 (3/33)	0 (0/13)	0 (0/9)	27.3 (3/11)	Liver, lung	3.1 (1/32) (1 lost follow-up)	50 (1/2) (1 lost follow-up)	Median 40 (range 4 - 56)	26 (DM at diagnosis)	Histopathological classification	0
Guillot et al. 2011 [49]	165	1.2 (2/165)	0 (0/114)	0 (0/37)	14.3 (2/14)	Bone, lung	1.2 (2/165)	100 (2/2)	NA	NA	NA	0
Al-Masri et al. 2012 [40]	43	14.0 (6/43)	0 (0/16)	0 (0/10)	35.3 (6/17)	NA	NA	NA	NA	NA	Expression of stromal CD10	NA
Jang et al. 2012 [50]	164	2.4 (4/164)	0 (0/82)	0 (0/42)	10.0 (4/40)	Bone, lung	1.8 (3/164)	75 (3/4)	NA	NA	NA	NA
Tan et al. 2012 [2]	605	2.0 (12/605)	0 (0/440)	0 (0/111)	22.2 (12/54)	Liver, lung, pleura, soft tissue, vertebra	2.0 (12/605)	NA	NA	NA	NA	NA
Do et al. 2013 [51]	179	2.8 (5/179)	0 (0/103)	0 (0/38)	13.2 (5/38)	NA	2.2 (4/179)	60 (3/5)	NA	NA	None	NA
Sawalhi and Shatti 2013 [20]	42	14.3 (6/42)	0 (0/16)	0 (0/9)	35.3 (6/17)	Bone, intestine, lung, thigh	NA	NA	Mean 15.9	NA	Histological grade	14.3 (6/42)
Spitaleri et al. 2013 [3]	172	2.3 (4/172)	0 (0/68)	0 (0/42)	6.5 (4/62)	NA	2.3 (4/172)	75.0 (3/4)	NA	NA	Young age (<35 years), presence of necrosis, positive surgical margins associated with	NA

Table 1 A summary of studies with metastatic PT *(Continued)*

											increased risk of all PT-related events	
Ren et al. 2014 [14]	140	7.1 (10/140)	0 (0/80)	6.7 (2/30)	26.7 (8/30)	NA	NA	NA	NA	NA	Tumour grade, expression of Axl and ST6GalNAcII	NA
Wei et al. 2014 [15]	192	6.3 (12/192)	0 (0/80)	6.3 (4/63)	16.3 (8/49)	Bone, liver, lung, pancreas, pleura, soft tissue, thoracic cavity	6.3 (12/192)	100 (12/12)	Median 26 (range 0 - 60)	DM to death: Median 10.0 (range 2.0 - 41.1) PT diagnosis to death: Median 34.3 (range 14.0 - 80.0)	Histotype, margin status	0
Bumpers et al. 2015 [52]	50	2.0 (1/50)	0 (0/40)	0 (0/3)	14.3 (1/7)	Lung	2.0 (1/50)	100 (1/1)	Lung metastasis found at time of presentation	PT diagnosis to death: 4	NA	4 (2/50)
Ramakant et al. 2015 [17]	167	4.2 (7/167)	0 (0/118)[f]		14.3 (7/49)	Adrenal, bone, brain, duodenum, lung, mediastinal nodes, para-aortic nodes	NA	85.7 (6/7)	Median 7 (range 0 - 156)	NA[g]	NA	1.2 (2/167) (para-aortic and mediastinal nodes)
Demian et al. 2016 [53]	35	2.9 (1/35)	0 (0/1)	0 (0/13)	4.8 (1/21)	Lung	Lost follow-up	Lost follow-up	NA	NA	-	0
Total	3516	5.6 (196/3516)	0.4 (7/1915)	2.9 (18/612)	20.0 (154/770)							

[a]Although the total number of patients with PT was 46, the study only looked at 10 patients with recurrence and/or distant metastasis, as such, the percentages of benign, borderline, and malignant PT were not tabulated and included in the total metastatic rates of benign, borderline, and malignant PTs

[b]*NA* Information was not available

[c]Cases were not specified to be benign, borderline, or malignant

[d]*DM* Distant metastasis

[e]This study looked only at high-grade malignant PTs

[f]As the exact breakdown of benign and borderline cases were not known, these numbers were not computed in the total metastatic rates of benign and borderline PTs

[g]The follow-up of each patient was detailed in the study, however the starting time points to death (i.e from diagnosis of PTs, or distant metastases or surgery etc.) were not consistent for all patients, therefore we were not able to tabulate a mean, median or range of time to death

to the disease. It is also noteworthy that the PT cases by Mangi et al. and Asoglu et al. were categorised as low grade, instead of benign. The average rate of metastasis amongst benign PT is 0.4%, based on literature reports (Table 1). It is acknowledged however, that accurate grading relies on diligent sampling of these usually large tumours, and it is possible that benign PTs that metastasized may have been under-graded.

There is potential for borderline PTs to metastasize, although the risk is very low. The rate of metastasis amongst borderline PTs averages around 2.9% (Table 1), as documented in 8 studies [5, 7, 10–15].

Although the occurrence of distant metastasis in benign PTs is a rare and aberrant phenomenon, metastases in malignant PTs have been recorded in quite a number of studies (All studies in Table 1). Even though events are still considered uncommon, the average metastatic rate of malignant PT is around 20.0% (Table 1).

Sites of metastasis

Metastasis occurs mostly through the haematogenous route [16]. The most common site of distant metastasis for PT appears to be the lungs. Of the 21 studies which mentioned sites of metastasis, 20 documented patients whose PTs had spread were to the lungs. The second most common site for PT metastasis is the bone, with 12 studies containing patients with bone metastases. A picture of a malignant PT and its lung metastasis is shown in Fig. 1.

Although the lungs and skeleton are the usual sites of distant metastasis for PT, almost all other organs have been shown to be afflicted, including the adrenal glands [17], brain [7, 9–11, 17, 18], gastrointestinal tract [17, 19–21], heart [22], kidney [23], liver [2, 10, 15, 16, 24, 25], mesentery [26], pancreas and pleura [15], retroperitoneum [16], soft tissues [2, 5, 15, 26, 27], spleen and thyroid [19], tonsil [28], uterus [19], and vulva [29].

Lymph node metastases are less frequent, although 10.0 – 15.0% of patients may present with clinical lymphadenopathy, they are usually as a result of reactive hyperplasia due to tumour necrosis or infection [11, 30]. In a study conducted by Gullett and colleagues [31], 9.0% of 1035 cases of patients with PT were subjected to an axillary sampling of ≥ 10 lymph nodes but nodal involvement was documented only in 9 patients. Of the 17 studies with information on lymph node metastasis in Table 1, 10 of them recorded no lymph node metastasis. With the exception of Sawalhi and Shatti [20], the remaining 6 studies displayed a lymph node metastatic rate of less than 5.0%. It is therefore not recommended to perform routine axillary dissection [32].

Histologically, the majority of the metastases contain only the stromal elements, without the epithelium [1, 32]. However, two unusual cases of metastatic PTs incorporating epithelial components have been documented by West et al. [33], and Kracht et al. [34]. The former described a case of PT metastasizing to the lungs with the pulmonary lesion containing the stroma, a well-differentiated myxoid fibrosarcoma, and the epithelium, which was mono-layered and appeared to be benign. The second case, recorded by Kracht and colleagues, detailed a malignant PT with liposarcomatous differentiation that metastasized to the lungs. The lung metastasis was a replication of the primary PT, displaying both the benign epithelium (bilayered ductal structures comprising luminal and basal cells) and malignant liposarcomatous stroma.

Prognosis of patients with metastasis in PT

The majority of PTs carry a good prognosis; however, patients who develop distant metastasis tend to have a very dismal clinical outlook, oftentimes leading to death. The time that it takes for distant metastasis to develop can be very varied, from as short as 2 months post-treatment [7, 26], to longer than a decade [17] (Table 1).

As patients with metastatic PTs may not respond well to standard chemotherapy, death often ensues [4]. As many as 15 studies summarized in Table 1 describe a 100.0% mortality rate amongst patients with metastatic PTs. The remaining studies displaying metastatic PT death rates had mortality rates exceeding 50.0%. The time to death is also relatively short, ranging from 1.0 to 41.1 months from the diagnosis of distant metastasis (Table 1).

Factors associated with metastasis

In 2012, a nomogram for predicting PT recurrences was developed by Tan and colleagues [2], based on the assessment of 4 predictive factors, namely, stromal atypia, mitoses, overgrowth, and surgical margins (AMOS). This nomogram was subsequently validated in two small case series [35, 36]. Its widespread use in clinical practice is limited by the rarity of PTs in general. Nevertheless, it is being further validated in 2 larger cohorts [37, 38]. Although several studies have looked into the various factors that may predict distant metastasis of PTs, none were successfully established and universally recognised as reliable predictors of PT metastasis, in part due to the limited number of such events. One of the earlier studies by Ward and Evans [19], which examined 26 cases of cystosarcoma phyllodes (synonymous with PTs), found that stromal overgrowth was significantly associated with metastasis ($p = 0.0014$). Stromal overgrowth as a predictor of PT metastasis was also supported by 4 other studies [5, 9, 10, 26].

Other clinico-pathological predictive factors for distant metastasis include severe nuclear pleomorphism [26], mitotic activity [5, 26], positive surgical margins [3, 5, 6, 11, 15, 26], large tumour size [6, 26, 39],

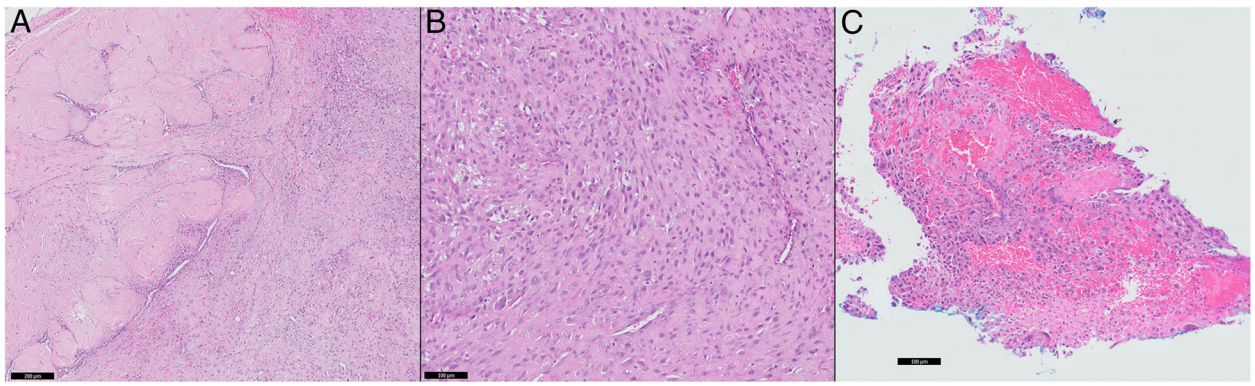

Fig. 1 **a** Primary malignant phyllodes tumour shows a fibroadenomatoid area juxtaposed to more cellular zones with pleomorphic cells. **b** Higher magnification of the phyllodes tumour displaying malignant stromal cells with stromal overgrowth. **c** Metastatic phyllodes tumour to the lung, composed only of malignant stromal cells

presence of necrosis [3, 26], tumour grade [9, 11, 14, 15, 20, 24, 39], stromal cellularity and atypia, heterologous stromal elements [5], and young age [3].

Studies investigating the predictive value of biomarkers for PT metastasis have also been performed. Al-Masri and colleagues [40] studied the expression of CD10 in 43 cases of PTs and found that positive CD10 expression was significantly associated with the development of distant metastasis ($p < 0.05$). Ren et al. [14] also noted in their study that positive expression of Axl ($p = 0.006$) and ST6GalNAc-cII ($p = 0.015$) correlated significantly with distant metastasis in PT. In another study by Tan et al. [41], high stromal cytoplasmic expression of Six1 was shown to be independently associated with distant metastasis and local recurrence ($p = 0.044$).

Recent molecular developments in PTs have revealed insights into the pathogenesis of PTs, in particular the identification of recurrent mediator complex subunit 12 (MED12) somatic mutations, found in fibroadenomas and all grades of PTs [42–45]. Mutations in FLNA (28.0%), SETD2 (21.0%) and KMT2D (9.0%) were also discovered, which are believed to contribute to tumour progression in PTs [46]. Currently, the genomic features of primary PTs and their metastases are not well understood. Molecular studies on malignant PTs are few [47], and to the best of our knowledge, no studies have focused on comparing the genomic profiles of primary PTs and their metastases.

Conclusions

The clinical behaviour of PTs can be very unpredictable, as seemingly benign PTs can recur as malignant PTs and develop distant metastasis, while cases with malignant histology may never exhibit metastatic behaviour at all. However, it is clear that malignant PTs stand the highest risk of developing distant metastases, compared to borderline and benign PTs. The most common sites of distant metastasis are the lungs and skeleton; however nearly all other organs have been shown to be affected as well. Patient prognosis is extremely poor after metastatic spread, with death oftentimes ensuing. Several factors, such as stromal overgrowth, have been shown to be significantly associated with the occurrence of distant metastasis, although there are still no established robust pathological characteristics to predict which cases of PTs are at risk of developing distant metastasis. Future work investigating the predictive factors of distant metastases in PTs will be another step closer in identifying patients who are at higher risk of developing distant metastasis, in order to optimize their management.

Abbreviations

DM: Distant metastasis; PT: Phyllodes tumour; WHO: World Health Organisation

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VK drafted the manuscript. AAT contributed to the content of the manuscript and also revised it. PHT revised it critically for important intellectual context and gave final approval of the version to be published.

Competing interests

The authors declare that they have no competing interest.

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