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Breast phyllodes tumor: A review of literature and a single center retrospective series analysis

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Contents

Abstract

Purpose: Complete surgical resection is the standard treatment for localized breast phyllodes tumors. Post-surgical treatments are still a matter of debate. We carried out an overview of the literature to investigate the clinical outcome of patients with phyllodes tumor. A retrospective analysis of mono-institutional series has been included as well.

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Methods: We reviewed all the retrospective series reported from 1951 until April 2012. We analyzed cases treated at our institution from 1999 to 2010.
Results: Eighty-three articles (5530 patients; 1956 malignant tumors) were reviewed. Local recurrences were independent of histology. Distant recurrences were more frequent in the malignant tumors (22%). A total of 172 phyllodes tumors were included in the retrospective analysis.
Discussion: Prognosis of phyllodes tumors is excellent. There are no convincing data to recommend any adjuvant treatment after surgery. Molecular characterization may well provide new clues to permit identification of active treatments for the rare poor prognosis cases.

Keywords: Phyllodes tumor; Breast tumors; Literature overview; Retrospective analysis; Prognosis

1. Introduction

Phyllodes tumor of the breast are rare neoplasms with an incidence <1% of all primary breast tumors [1]. In 1982, the World Health Organization declared the term "phyllodes tumor" as the most appropriate among more than 60 synonyms [2]. After Trevor, Norris and Azzopardi the World Health Organization sub-classified them histologically as benign, borderline, or malignant [3–5]. Benign tumors are more frequent having an incidence of 35–64% while malignant tumors comprise about 25% of cases [1,6,7]. The median age of occurrence of disease is 40–50 years [1,7,8]. Histologically, they are fibroepithelial tumors, likely originated from the terminal ducto-lobular unit and considered as stroma-derived [5]. Microscopically, the stromal component may be bland resembling that of fibroadenoma, or atypical, resembling that of soft-tissue sarcoma, or it can vary between these extremes, often resembling low-grade sarcoma. Grading is usually based on a semi-quantitative evaluation of the following criteria in the stromal component: nuclear pleomorphism, mitotic rate, overgrowth, cellularity and aspects of tumor margins. Ward firstly reported the presence of stromal overgrowth as putative additional factor of prognosis [9]. In 1991 Cohen-Cedermark included tumor necrosis and the presence of stromal elements other than fibromyxoid tissue among the prognostic factors [10].

Complete surgical resection offers high rates of local control and disease-free survival [1]. Mastectomy has recently been replaced by conservative surgery with adequate negative surgical margins [6,7,11–14]. The potential role of adjuvant radiotherapy is still debated as only a minor fraction of patients have received this treatment and also there is an absence of large prospective trials [1,12,15–17].

We carried out an overview of literature to investigate the prognosis of phyllodes tumor according to tumor grade. We have also included a retrospective analysis of 172 consecutive patients with this tumor from our institute.

2. Overview of the literature

2.1. Methods

References were obtained from the major indexed literature database Medline, using the keywords breast phyllodes tumor. We reviewed all the cases of breast phyllodes tumors reported from 1951 (after Trevis' publication) until April 2012 [4–84]. We included only the articles in English which focused on clinical reports convincingly documenting the diagnosis, and which clearly reported the treatments administered and follow-up data. The analysis also included four reports written in their original language since their abstract reported all requested information [74–77].

2.2. Results

Eighty-three articles were reviewed with a total of 5530 patients (malignant 1956, 35%). Comprehensively, the mean number of patient per article was 67 (median 37.5; range 1–605).

2.2.1. Description of overall results

Table 1 reports the most representative studies with about more than 75 patients. These retrospective analyses collected cases treated in a period from 1930 to 2010. The mean size was 7.3 cm (median 6.5, range 0.4–29). The mean rate of mastectomies performed was 40% (range 0–67%). The median follow-up was 5 years (range 0.4–43). The mean local recurrence rate was 19.1% (median 17%; range 0–67%). The mean distant recurrence rate was 8.9% (median 5%; range 0–39%). Table 2 summarizes the details of the analysis. Local recurrences were independent of histology, but more frequent in the malignant group. Distant recurrences are almost never encountered in the benign group, whilst they are rare for borderline tumors (except for the report by Reinfuss [7] reporting an incidence of 22%). The malignant group relapsed with a mean and median rate of almost 25% (up to 60% in the 8 cases described by Halverson [24] and in the 13 cases described by Hawkins [43]). In the publications reporting positive surgical margins the mean local recurrence rate reached 31.5% (median 14.5%; range 1–67%) [5–7; 10, 11, 14, 16, 18, 35, 38–40; 42–44; 48–57; 59, 60, 62–65; 67–71; 74, 75; 80–84]. Fifty-eight progressions (from grade 1 or 2 to upper grade) out of 3574 cases (benign + borderline) were described (1.6%). Eighteen (0.3%) bilateral cases were recorded. A number of reports demonstrated the putative relationship between stromal overgrowth and pathological features (proliferative fraction) or clinical outcome (local and distant relapse, or

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Table 1
Selected retrospective investigations on the management of phyllodes tumors of the breast. Pts = patients; size expressed in cm; *M* = mastectomy (%); Mal. = malignant (number); LR locale recurrence (%); DR distant recurrence (%); Asia–Austr = Asia–Australia.

Author	Year	Period	Pts	Country	Size	*M* (%)	Mal.	LR	DR
Treves	1951	1930–1949	77	USA	10	42	18	67.0	11.6
Norris	1967	Before 1967	94	USA	6.4	59	NR	35.0	NR
Hajdu	1976	1932–1976	199	USA	4	23	49	16.0	1.5
Briggs	1983	1960–1980	83	USA	5	12	3	0.0	0.0
Chua	1988	1978–1984	106	Singapore	5	8	3	19.0	0.9
Cohn-Cedermark	1991	1958–1986	77	Swedish	5	69	49	19.0	21.0
Grimes	1992	1983–1990	187	USA	4.4	NR	50	28.0	8.0
Zurrida	1992	1970–1989	216	Italy	NR	9	14	12.5	NR
Reinfuss	1996	1952–1988	170	Poland	7	42	59	8.0	16.0
Zissis	1998	1981–1995	84	Greece	6	29	15	2.3	1.0
Chaney	2000	1944–1998	101	USA	6	53	29	4.0	8.0
Niezabitowski	2001	1952–1998	120	Poland	NR	60	44	8.0	9.0
Tse	2004	1988–2001	179	Asia–Austr.	4.8	NR	NR	NR	NR
Chen	2005	1985–2003	172	Taiwan	5.8	27	29	11.0	1.7
Tan	2005	1992–2002	335	Singapore	5.4	8	31	12.8	2.0
Abdalla	2006	1988–2003	79	Egypt	11	42	21	20.0	14.0
Ben hassouna	2006	1986–2001	106	Tunisia	8.3	23	28	12.2	7.5
Barrio	2007	1954–2005	293	USA	6	16	90	8.5	1.7
Guillot	2011	1994–2008	165	France	3	6	14	10.0	1.2
Pimiento	2011	1999–2010	124	USA	4.5	NR	19	6.5	1.6
Tan	2012	1992–2010	605	Singapore	5.2	19	54	11.2	1.1

overall survival) [9–11; 40, 42, 43, 49, 55, 57, 59, 63, 68, 70].

2.2.2. *Post-surgical treatments*

A total of 278 (14.2% of malignant cases) patients received complementary radiotherapy. The mean local recurrence rate and the median distant recurrence rate were 9% (mean 8%, range 0–22%) and 13.5% (mean 16.3, range 0–38%), respectively, in the 6 studies where at least 15 patients (an arbitrary cut-off chosen by the authors) had received radiotherapy [10, 12, 15–18; 75]. The median follow-up of these studies was of 13.25 years (mean 16.2, range 4, 6–43). Indeed none of these studies proved that radiotherapy can affect the distant spread of tumor and overall survival. Importantly, Christensen did not reveal any difference in overall survival between the group who was treated with radiotherapy and the group treated with surgery alone in a retrospective series [15]. In 2009 Barth published the first non-randomized prospective trial of radiotherapy for 46 consecutive patients with malignant tumors and demonstrated that radiotherapy can reduce the local recurrences (0%), although there were two distant metastases [17]. Chaney et al. compared in a retrospective series the patients (6) treated with adjuvant radiotherapy with other patients treated with surgery alone (23): the former had a lower risk of local relapse (9% at 10 years of follow up) [18]. This data was confirmed by an Indian experience (Pandey et al.) where 25 out of 37 patients received adjuvant radiotherapy. Unfortunately, 20 of the 37 patients had positive/unknown surgical margins and the actuarial local failure was 22%[16]. In our opinion this study places greater emphasis on the importance of negative margins than on the role of radiotherapy. Overall, only 72 patients were treated with chemotherapy (36 in adjuvant setting). Among the four studies reporting adjuvant chemotherapy the follow-up is too short (mean 2.6; median 2.1; range 1–5.4 years) and indeed there was a higher rate of surgical positive margins (0.3–39%): the distant recurrence rate was not lower relative to the other publications with a range of 1.2–40% [53,71,74,80]. The most significant trial is represented by that by Morales–Vasquez (a non-prospective trial) which demonstrated that the addition of adjuvant chemotherapy (doxorubicin/dacarbazine) to surgery did not reduce the risk of disease recurrence [71].

Table 2
Patient demography and clinical outcome according to tumor histology.

Patients (5530)	
Benign	2861 (52%)
Borderline	713 (13%)
Malignant	1956 (35%)
Mean size (range)	7.3 cm (0.4–29)
Median size	6.5 cm
Mean rate of mastectomy	40% (0–67%)
The mean local recurrence rate (median, range)	
All	19.1% (0–67)
Benign	15% (12.5, 0–42)
Borderline	17% (19, 0–50)
Malignant	28% (21, 0–100)
The mean distant recurrence rate (median, range)	
All	8.9% (0–39%)
Benign	0.1% (0; 0–2%)
Borderline	0.2% (0; 0–33%)
Malignant	22% (22; 0–62.5%)

2.2.3. *Biomarkers involved on tumor progression from fibroadenoma to malignant phyllodes tumor*

Numerous studies (preclinical or retrospective reports) have investigated some biomarkers that can be involved in

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Table 3
Molecular features which were described in tumor progression from benign to malignant tumor and could be putative prognostic factor. EGFR: epidermal growth factor receptor; c-kit: kit oncogene; p16INK4a: cyclin-dependent kinase inhibitor 2A; Wnt5: similar to wingless-type MMTV integration site family, member 5B precursor; pRB: retinoblastoma protein; RASSF1A: Ras association (RalGDS/AF-6) domain family 1 protein; TWIST1: twist homolog 1 (Drosophila); EPS15: EGFR pathway substrate 15; FA: fibroadenoma; PT: phyllodes tumor.

Molecule/pathway	Mechanism	Findings	Reference (Ref *N*)
EGFR amplification	EGFR/EPS15/caveolin-1 interplay in the carcinogenesis	Preclinical	Agelopoulos ′07 [85]
EGFR expression	Progression to borderline/malignant	Positive	Tse ′09 [89]
		Negative	Yonemori ′06 [61]
C-kit expression	Progression to borderline/malignant	Positive	Noronha ′11 [93]
			Esposito ′06 [62]
		Negative	Yonemori 2006 [61]
C-kit mutations	A ‘druggable target’	Negative	Bose ′10 [91]
Increased number of chromosomal gains (e.g4q12)	Progression to borderline/malignant	Positive	Lu ′08 [86]
9p deletion (loss of p16INK4a)	Progression to borderline/malignant	Positive	Jones ′08 [87]
Wnt5a expression	Role for progression and epithelial/stromal interactions	Positive	Karim ′09 [88]
Stromal p16 and stromal/epithelial pRb expression	Progression to borderline/malignant	Positive	Karim ′10 [90]
Methylation of RASSF1A and TWIST1	Progression from FA to PT	Positive	Huang ′10 [92]; Kwon ′11 [94]
CD10 expression	Prediction of occurrence of metastasis	Positive	Al-Masri ′11 [95]

tumor progression from fibroadenoma to malignant phyllodes tumor (Table 3) [61,85–95]. Most were focus on the role of Epidermal Growth Factor Receptor, c-kit and Wnt pathways: unfortunately they produced almost contrasting results.

3. Retrospective series

3.1. Methods

Data from 172 patients with breast phyllodes tumors (out of 203 patients with all breast sarcomas) [96] treated at the European Institute of Oncology in Milan from 1999 to 2010 were collected retrospectively. Diagnosis was confirmed histologically on the surgical specimens. Stromal overgrowth was defined as an absence of ductal elements in a 40× low-power field. Follow-up was obtained by internal data base clinical collection and interviews. The principal end-point was 10-year cumulative incidence of phyllodes-specific events. Disease-related events were defined as: ipsilateral breast recurrence, recurrence in the breast and axilla, and distant metastases. Secondary end-points included 10-year cumulative incidence of specific-phyllodes deaths and overall survival. Cumulative incidences were compared across different subgroups by means of the Gray test [97]. Multivariate Cox proportional hazards regression models were used to identify the prognostic independent clinico-pathological parameters associated with the risk of phyllodes-related events. The variables which showed some statistical significance ($P < 0.10$) in the overall univariate analysis were tested in the multivariable model with a forward selection method. Adjusted hazard ratios (HR) with 95% confidence intervals (CIs) were reported. All analyses were carried out with the SAS software (SAS Institute, Cary, NC) and the R software (http://cran.r-project.org/). All the reported *P*-values were two sided.

3.2. Results

From 1999 to 2010 172 cases with phyllodes tumor were retrieved. Patients treated in our institution (167) and those referred for consultation (5) to our site from other hospitals were included in the analysis (Table 4). There were 68

Table 4
Patient demographics (EIO series).

Patients (172) (%)	
Age (median years)	44
Age (range years)	11–82
Female/male	175/1
Histology	
Benign phyllodes	68 (39.5)
Borderline phyllodes	42 (24.5)
Malignant phyllodes	62 (36)
Size	
≤2 cm	19 (11.9)
2- ≤ 5 cm	82 (51.6)
>5 cm	58 (36.5)
Not available	13
Surgery	
Mastectomy	35 (20)
Conservative	137 (80)
Adjuvant treatments	
Chemotherapy	3 (1.7)
Radiotherapy	9 (5.0)

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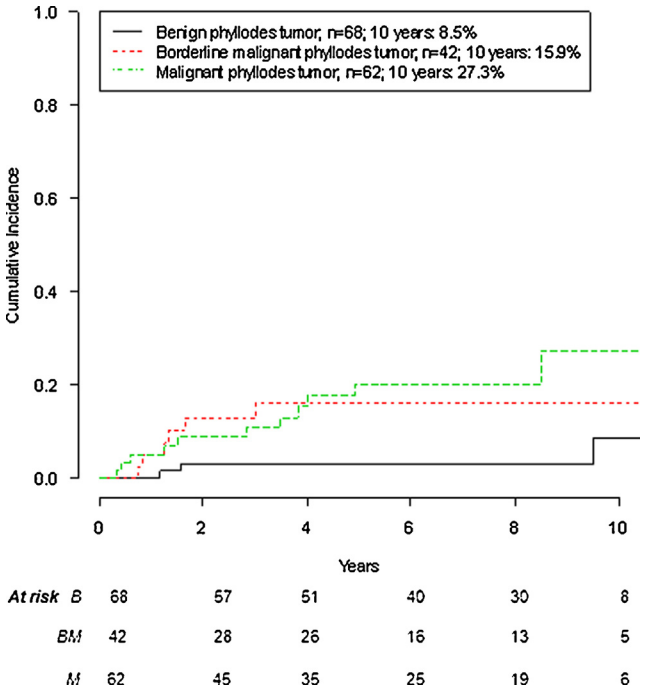

Fig. 1. Cumulative incidence of phyllodes-related events by histotype. Breast-related events: (a) Benign phyllodes tumor group: ipsilateral breast recurrence ($n = 3$); (b) borderline malignant phyllodes tumor group: ipsilateral breast recurrence ($n = 6$); (c) malignant phyllodes tumor group: ipsilateral breast recurrence ($n = 8$), recurrence in the breast and axilla ($n = 1$), distant metastases ($n = 2$).

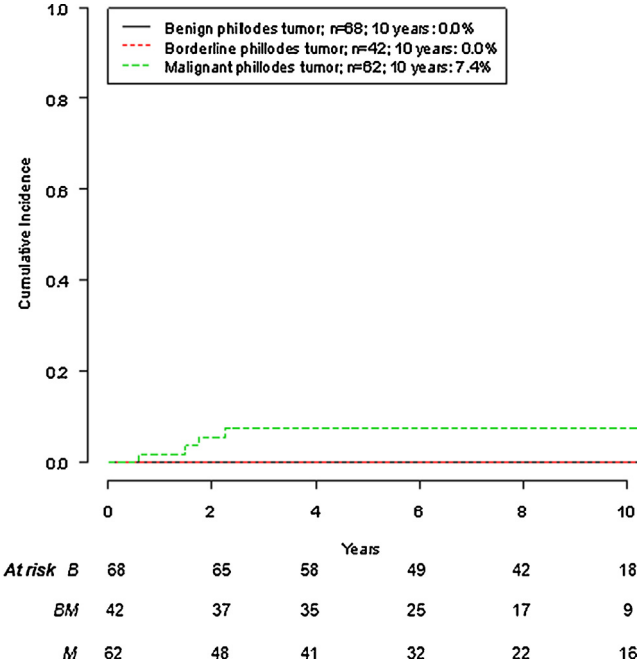

Fig. 2. Cumulative incidence of phyllodes-related deaths by histotype.

benign, 42 borderline and 62 malignant phyllodes. Median follow-up was 85 months (4.5–268 months). Most of the patients (137, 80%) underwent conservative surgery, while 35 (20%) underwent mastectomy, of which 20 benefited from breast reconstruction. We observed 20 phyllodes-related first events: 17 local recurrences, one chest-wall involvement and two distant events. The 10-year cumulative incidence of phyllodes-related events was 16.6% (95% CI 9.7–27.2). Four phyllodes-related deaths and 3 deaths from other causes were observed. The 10-year cumulative incidence of phyllodes-related deaths was 2.5% (95% CI 0.9–6.6%). The 10-year overall survival was 94.6% (95% CI 88.5–97.5%).

3.2.1. Benign tumors

Figs. 1 and 2 depict the 10-year cumulative incidence of phyllodes-related events according to tumor grade and the 10-year cancer-specific survival according to tumor grade, respectively. Sixty-eight (39.5%) cases out of 172 were benign. All but three of them underwent conservative surgery. We recorded three (4.5%) events among these patients and all consisted of local recurrences which were well managed with further surgery. Two patients died from causes unrelated to the tumor.

3.2.2. Borderline tumors

Forty-two (24.5%) patients had a borderline tumor. About 80% of the patients underwent breast-sparing surgery. We recorded 6 (14.2%) events out of these 42 patients and all consisted of local recurrences treated either with conservative surgery or mastectomy. All patients were alive at the analysis cut-off except for one who died from head and neck cancer.

3.2.3. Malignant tumors

Sixty-two (36%) patients had a malignant phyllodes tumor. Thirty-seven patients (59.6%) were treated with a conservative approach. Two patients with malignant phyllodes with unfavorable features received 5 courses of epirubicin/ifosfamide. Eight patients with the same features received radiotherapy after radical surgery. One patient received both chemotherapy and radiotherapy. None of these patients relapsed after a median follow-up of 3.5 years (range 0.5–10). Thirteen (21%) events were recorded in 11 (17.7%) of 62 patients. These consisted of 8 (13%) local recurrences, 1 (1.6%) chest wall infiltration and four (6.5%) distant metastases. Four patients died from disease progression (3 with a metastatic disease, one for a chest wall infiltration). The 10-year phyllodes-specific survival was 92.6%.

3.2.4. Uni- and multi-variate analyses

Univariate analysis (Table 5) identified age as a prognostic factor for all phyllodes-related events, with the risk decreasing with increasing age. The subgroup of malignant tumors showed a similar trend, but the association was not statistically significant. Presence of necrosis, stromal overgrowth and positive surgical margins were putative negative prognostic factors for recurrence in the overall population ($P < 0.10$). Despite the sparse number of events, surgical margin status was a significant prognostic factor in the malignant tumor subgroup. In the multivariable analysis (Table 6),

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Table 5
Uni-variate analysis for phyllodes-related events for all patients and according to tumor grade.

		All			Benign			Borderline malignant			Malignant		
		No. (%)	Events (10-year cum inc%)		No. (%)	Events (10-year cum inc%)		No. (%)	Events (10-year cum inc%)		No. (%)	Events (10-year cum inc%)	P
Age	Total	172	20 (16.6)		68	3 (8.5)		42	6 (15.9)		62	11 (27.3)	
	<35	35 (20.4)	9 (37.6)	0.01	15 (22.1)	1 (7.7)	0.56	8 (19.0)	4 (50.0)	<0.01	12 (19.4)	4 (54.5)	0.29
	35–49	83 (48.3)	7 (15.5)		37 (54.4)	2 (14.6)		23 (54.8)	1 (5.0)		23 (37.1)	4 (20.0)	0.12[c]
	≥50	54 (31.4)	4 (8.6)		16 (23.5)	0 (0.0)		11 (26.2)	1 (9.1)		27 (43.6)	3 (14.1)	
Tumor size [a]	≤2 cm	20 (12.0)	2 (20.8)	0.88	14 (20.6)	2 (22.6)	0.25	3 (7.3)	0 (0.0)	0.51	3 (5.2)	0 (0.0)	0.70
	2.1–5 cm	85 (50.9)	11 (15.0)		39 (57.4)	1 (2.9)		21 (51.2)	4 (22.2)		25 (43.1)	6 (27.6)	
	>5 cm	62 (37.1)	7 (18.2)		15 (22.1)	0 (0.0)		17 (41.5)	2 (13.2)		30 (51.7)	5 (35.6)	
Necrosis [a]	No	161 (94.2)	16 (15.2)	0.09	68 (100.0)	3 (8.5)	–	41 (97.6)	6 (16.3)	0.67	52 (85.3)	7 (24.9)	0.23
	Yes	10 (5.9)	3 (31.7)		0 (0.0)	–		1 (2.4)	0 (0.0)		9 (14.7)	3 (35.6)	
Overgrowth [a]	No	104 (68.0)	8 (11.6)	0.07	58 (93.6)	3 (9.7)	0.74	29 (80.6)	4 (15.3)	0.32	17 (30.9)	1 (7.7)	0.18
	Yes	49 (32.0)	8 (26.8)		4 (6.4)	0 (0.0)		7 (19.4)	0 (0.0)		38 (69.1)	8 (34.5)	
Surgical margins [a,b]	Negative	161 (94.2)	16 (15.1)	0.09	67 (98.5)	2 (7.0)	<0.01	39 (95.0)	5 (14.5)	0.57	55 (88.7)	9 (28.6)	0.74
	Positive	10 (5.9)	3 (30.0)		1 (1.5)	1 (100.0)		2 (5.0)	0 (0.0)		7 (11.3)	2 (28.6)	
Surgery	BCS	137 (79.7)	14 (14.1)	0.21	65 (95.6)	3 (8.6)	0.75	35 (88.1)	6 (19.5)	0.21	37 (59.7)	5 (17.1)	0.22
	Mastectomy	35 (20.3)	6 (28.9)		3 (4.4)	0 (0.0)		7 (11.9)	0 (0.0)		25 (40.3)	6 (43.5)	

[a] Information was missing for one or more patients.
[b] Tumor present on the surgical margin ($n = 5$) or within 1 mm or less from the margin ($n = 5$).
[c] Testing the trend. BCS: breast conservative surgery. Breast-related events: (a) benign phyllodes tumor group: ipsilateral breast recurrence ($n = 3$); (b) borderline malignant phyllodes tumor group: ipsilateral breast recurrence ($n = 6$); (c) malignant phyllodes tumor group: ipsilateral breast recurrence ($n = 8$), recurrence in the breast and axilla ($n = 1$), distant metastases ($n = 2$).

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Table 6
Multivariate survival analysis of tumor-related events.

Parameters		HR (95% C.I.)
Age (years)	<35 vs ≥50	5.4 (1.5–19.6)
	35–49 vs ≥50	1.5 (0.4–5.5)
Necrosis	Present vs absent	3.9 (1.1–14.1)
Surgical margins	Positive vs negative	3.9 (1.1–14.3)

young age (<35 years), presence of necrosis and positive surgical margins were associated with a significant increase of risk of phyllodes-related events. When limiting the analysis to borderline and malignant phyllodes, age remained the only significant prognostic factor.

4. Discussion

This is an overview of the English literature since 1951 with a total of 5530 patients and a median follow-up of 5 years. This overview is augmented with a presentation of new 172 cases of breast phyllodes treated at our Institution from 1999 to 2010 with a median follow-up of 7 years.

This tumor is clearly more frequent in women: in our series, there was only one case in a man, few cases have been reported in men and these have invariably been associated with gynecomastia [23,98].

Multi-focality (2–5 lumps) has been variably reported in literature where the highest incidence (up to 12%) was reported by Ben hassouna [65], whereas bilateral cases are rare being from 0 to 3.5% [70]. In our series we did not encounter multi-focality or bilateral cases.

Regarding the distribution of histology: benign tumors are more frequent (52% in the literature, about 40% in our series). The risk of local recurrence is irrespective of histology, although the events are more frequent in the malignant and borderline tumors than in benign group. Among the benign and borderline tumors all local relapses can be well managed by further surgery (either breast-conserving surgery or mastectomy). In this group (benign/borderline) positive surgical margins do not seem to predict a worse outcome. Two aspects must be taken in account during the recurrence after resection of benign or borderline tumor: the risk of distant recurrence and the sarcomatous progression (from benign/borderline to malignant tumor). The risk of distant relapse is very low (<0.5% in the literature, no events in our series). Tumor progression has been reported with wide range of percent (3–33%) in different reports with a median of 4% [3,4,7,18,20,23,25,27,32,59,65,70]. The highest incidence of events was reported in a small series [25], whereas the largest series reported a lower incidence (3%) [59,65,70]. Accordingly, the standard treatment for these tumors is a breast conserving surgery with negative margins. Based on the fact that local recurrences are usually well managed with breast sparing surgery and that the risk of tumor progression is low, a policy of 'wait and see' should be safely considered in cases with positive surgical margins, as already stated by Zurrida [14].

Different aspects are encountered in the malignant group, where there is a higher incidence of local relapse (about 30% both in the literature and in our series) and there is the chance of distant relapse: in our series we recorded one chest wall involvement and four distant metastases (6.4%) with four phyllodes-related deaths. In the literature overview the risk of systemic spread for malignant tumors was higher (22%). In any case, the extent of surgery did not affect long-term survival, so far the main standard of treatment is represented by breast spearing surgery (when feasible according to tumor and breast dimensions) with mandatory surgical negative margins. The role of adjuvant radiotherapy is also a matter of debate. In our series only nine patients received adjuvant radiotherapy and none of them relapsed. In the literature, radiotherapy has been shown to reduce the risk of local but not of distant relapse in malignant tumors. All these reports, however, were retrospective series with the exception of the study by Barth [10,12,15–18;75]. At this time, the indication for radiotherapy should be limited to patients with malignant tumors and positive surgical margins when a surgical radicalization cannot be performed.

The role of adjuvant chemotherapy is even more questionable and it is not indicated [71].

Beyond histology, different parameters (clinical or molecular) has been investigated to predict a higher risk of relapse. In our series, according to the multivariable analysis, young age (<35 years), tumor necrosis and positive surgical margins were associated with a significant increase of phyllodes-related events. Many reports dealt with young age as a putative prognostic factor [4,20–22,33,99]. Except for the report by Chua [34], all other studies identified young age as a favorable prognostic factor contrary to our data.

In the near future, the molecular characterization of these unusual breast tumors might well allow the identification of high risk tumors for distant relapse. Numerous studies have attempted to determine whether immunohistochemical markers may be useful to predict the clinical outcome of the patients, but so far all these markers have failed to attain any clinical validation [61,85–95]. It would be also extremely important to identify 'druggable targets' for this type of tumor, that it is notably chemorefractory.

In conclusion, we confirm that the prognosis of benign and borderline phyllodes tumors is excellent. They are cured with surgery alone. Most, but not all malignant phyllodes tumors also have a good prognosis. The main standard of treatment is adequate surgery with negative margins. No convincing data are available to suggest any adjuvant treatment. For the rare poor prognosis tumors in the near future molecular characterization may well provide new clues to permit identification of more active treatments.

Conflict of interest disclosure

None.

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