The Breast 43 (2019) 85–90

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Phyllodes tumors of the breast. The treatment results for 340 patients from a single cancer centre

J.W. Mitus [a, b, *], P. Blecharz [c], J. Jakubowicz [c], M. Reinfuss [d], T. Walasek [d], W. Wysocki [a]

[a] Department of Surgical Oncology, Centre of Oncology, Maria Sklodowska-Curie Memorial Institute, Cracow Branch, ul. Garncarska 11, 31-115 Cracow, Poland
[b] Department of Anatomy, Collegium Medicum, Jagiellonian University, ul. Kopernika 12, 31-034 Cracow, Poland
[c] Department of Gynecological Oncology, Centre of Oncology, Maria Sklodowska-Curie Memorial Institute, Cracow Branch, ul. Garncarska 11, 31-115 Cracow, Poland
[d] Department of Radiotherapy, Centre of Oncology, Maria Sklodowska-Curie Memorial Institute, Cracow Branch, ul. Garncarska 11, 31-115 Cracow, Poland

ARTICLE INFO

Article history:
Received 26 August 2018
Received in revised form
13 November 2018
Accepted 25 November 2018
Available online 26 November 2018

Keywords:
Phyllodes tumor
Breast
Surgery
Radiotherapy

ABSTRACT

Purpose: The primary treatment of choice for patients with phyllodes tumor of the breast (PTB) is surgery. Two major problems regarding the treatment of such patients remain unclear: what is the appropriate surgical margin and what role is played by adjuvant radiotherapy (ART).
Methods: The study provides a retrospective review of all patients with PTB treated between 1952 and 2013 at a single institute. The histology slides were re-examined based on WHO criteria. The clinical characteristics and therapy outcomes were obtained. The five-year survival with no evidence of disease (NED) was used as the end point.
Results: The study population comprised 340 women with PTB. Fifty-five percent of the patients were diagnosed with the benign, 11.8% with borderline and 33.2% with malignant PTB. All the patients received primary treatment with surgery (mastectomy–27.1%, and BCS– 72.9%). Local recurrence (LR) was found in 28 (9.1%) of these patients. Four patients with borderline and 8 with malignant PTB who were treated with BCS and had tumor-free margins < 1 cm received ART. None of these patients had LR and all survived 5 years NED. Of the 340 patients from our group, 294 (86.4%) survived five-years NED.
Conclusion: The prognosis for benign PTB is excellent and can be cured with surgery alone. A sufficient margin would be 0.1 cm (data from the literature) or 0.2–0.4 cm (our study). We recommend application of ART for such patients but the role of ART in patients with borderline and malignant PTB treated with BCS and with surgical margin < 1 cm remains uncertain.

1. Introduction

Phyllodes tumor of the breast (PTB) account for 0.2–2% of all breast tumors and 2–3% of all fibroepithelial tumors of the breast in women [1–10]. The World Health Organization (WHO) classifies PTB into benign, borderline, and malignant types, based on a microscopic evaluation of the following features: stromal overgrowth, mitotic activity, tumor borders and stromal cell atypia [11].

The primary treatment for patients with PTB is surgery, but the optimal extent of this treatment (breast conserving surgery – BCS or mastectomy) has been a matter of debate in the last few years [6–8,10,12–18]. Historically, mastectomy was the treatment of choice, principally in patients with a borderline or malignant PTB [10–17,19]. Nowadays, the generally accepted approach for patients with all PTB types is BCS with a clear margin of healthy tissue. A mastectomy is justified only when surgery cannot obtain an adequate tumor-free margin or satisfying aesthetic effect [7,10,13–16,20–29]. Metastases of PTB to the axillary lymph nodes are very rare. Hence, there are no indications for sentinel lymph node biopsy or elective resection of these lymph nodes [6,12,13,16,21,25].

The role of adjuvant or palliative radio- or chemotherapy in PTB is currently debatable [1,5–7,9,10,12–14,16,17,20–22,24,25,29] and there is no place for a hormone therapy in these patients [12,14,21,22,30].

* Corresponding author. Department of Surgical Oncology, Centre of Oncology, Maria Sklodowska-Curie Memorial Institute, Cracow Branch, Cracow, Poland ul. Garncarska 11, 31-115 Cracow, Poland.
E-mail address: jerzy.mitus@gmail.com (J.W. Mitus).

https://doi.org/10.1016/j.breast.2018.11.009
0960-9776/

At present, two main problems regarding the treatment of PTB patients remain unclear: what is the appropriate width for a tumor-free margin and the role of adjuvant radiotherapy [1,2,7,10,13,15,16,20–22,24,26,28–33]. In our study we have tried to contribute to the debate on both these controversial issues.

2. Material and methods

The present article provides a retrospective review of patients with PTB treated at the Maria Sklodowska-Curie Memorial Institute of Oncology Cancer Centre in Cracow, Poland. All the clinical characteristics, treatment options and therapy outcomes were obtained by reviewing the patients' charts (approved by Institutional review board). All the histology slides were re-examined and the PTB histotypes diagnosed and determined on the basis of WHO criteria [11].

The five-year survival rate with no evidence of disease (NED) was used as the endpoint for the analysis and was estimated by means of the Kaplan-Meier method. All the patients were followed up for at least 5 years (or until death). The mean follow-up time was 12 years. The statistical significance of the differences was set at $p \leq 0.05$ and determined by the log-rank test.

3. Results

3.1. Characteristics

Between January 1952 and June 2013, 340 women with PTB received primary treatment with surgery at the Cancer Centre in Cracow. The patients age ranged from 19 to 89 years, and the mean age was 51 years. One hundred and ninety-seven (57.9%) patients were <50 years of age, and 143 (42.1%) were ≥50 years. The tumor size, defined as the maximum dimension of the tumor reported in the pathology report, ranged from 2 to 40 cm (mean 6 cm). A total of 153 patients (45.0%) had breast tumors measuring <5 cm in diameter, 129 (37.9%) 5–10 cm, and 58 (17.1%) >10 cm. A total of 187 (55.0%) patients were diagnosed with benign PTB, 40 (11.8%) with borderline PTB, and 113 (33.2%) with malignant PTB. Metastases to axillary lymph nodes were found in only 3 (0.9%) patients.

3.2. Treatment

All 340 patients received primary treatment with surgery; 92 (27.1%) patients underwent a mastectomy, defined as the removal of all the breast tissue and including both simple (61 patients) and radical mastectomies (31 patients). BCS was the treatment used on 248 (72.9%) patients. The extent of the surgery performed according to the PTB histotype is shown in Table 1.

3.3. Status of the resection margin

Six (1.8%) patients with malignant PTB infiltration of the pectoralis major muscle and limited mobility in relation to the chest wall received postoperative irradiation, because the Halsted operation was not microscopically complete. In the remaining 334 (98.2%) patients the microscopic margins were tumor-free.

The tumor-free resection margin was ≥ 1.0 cm in three hundred and two (88.8%) patients and <1.0 cm (0.2–0.8 cm) in 32 (9.4%) patients.

The resection margin widths in 334 patients with tumor-free margin are presented in Table 2.

The benign PTB patients had surgical margins of 0.2–0.4 cm, with borderline – 0.3–0.6 cm, and malignant – 0.3–0.8 cm.

3.4. Adjuvant treatment

None of the 302 patients with tumor-free margins ≥1 cm received adjuvant treatment. Twenty patients with benign PTB treated with BCS and with tumor-free margins <1 cm did not receive adjuvant treatment. These patients had regular clinical and imaging follow-up only, in particular during the first 3 years following primary surgery.

Four patients with borderline PTB and 8 with malignant PTB treated with BCS who had tumor-free margins <1 cm, received adjuvant radiotherapy. A dose of 5.040 cGy in 28 fractions over 5 weeks was delivered to the entire breast using a tangential technique. This was followed by a boost to the tumor bed with 2 cm margins (1.000 cGy in 5 fractions).

3.5. Outcome

Of the 340 patients in our group, 294 (86.5%) survived NED for five years. The 5-year NED survival rate was 95.7% (179/187) for patients with benign, 82.5% (33/40) with borderline and 72.6% (82/113) with malignant PTB. Fig. 1 presents Kaplan-Meier 5-year NED survival curve.

These differences are statistically significant (benign vs. borderline and malignant PTB, log-rank test, $p < 0.01$). Five of our patients with benign PTB and one with borderline PTB died without PTB from a myocardial infarction or cerebral hemorrhage. In all the other deceased (3-benign, 6-bordeline and 31-malignant PTB) patients, death during the 5-year follow-up occurred due to metastases to the lungs (31 patients), the bone (8 patients), the brain (6 patients), and the liver (2 patients). These metastases occurred on average 21 months (2–57) after surgery.

3.6. Local recurrences (LR)

Cases of LR in the 334 patients with tumor-free margins are presented in Table 3.

LR was detected in 29 of our 334 patients (8.7%). in 6.4% (12/187) of patients with benign, in 12.5% (5/40) with borderline, and in 11.2% (12/107) with malignant PTB.

Of the 302 patients with tumor-free margins ≥1 cm, LR occurred in 28 (9.1%) patients; twenty of these were reoperated on: 10 patients with benign PTB, 2 with borderline PTB, and 8 with malignant PTB. Patients with benign or borderline PTB had wide local

Table 1
Extent of surgery.

Histotype of PTB	mastectomy		BCS		total	
	No.	%	No.	%	No.	%
Benign	22	11.8	165	88.2	187	100.0
Borderline	6	15.0	34	85.0	40	100.0
Malignant	64	56.6	49	43.4	113	100.0
Total	92	27.1	248	72.9	340	100.0

Table 2
Status of resection margins.

Width tumor-free margins	No.	%
Benign PTB: ≥1.0 cm	167	89.3
<1.0 cm	20	10.7
Borderline PTB: ≥1.0 cm	36	90.0
<1.0 cm	4	10.0
Malignant PTB: ≥1.0 cm	99	92.5
<1.0 cm	8	7.5
Total	334	100.0

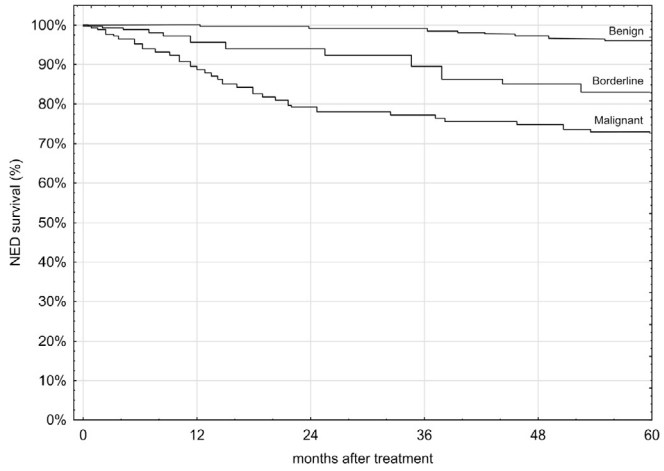

Fig. 1. Kaplan-Meier curve. 5-year NED survival rate.

excisions, while those with malignant PTB had a simple or radical mastectomy. All the patients survived 5-years NED.

All 32 patients with tumor-free margins <1 cm received primary BCS. In this group LR was observed in 1 (3,1%) patient with benign PTB who was reoperated on with BCS and survived 5 years NED, just like the other 19 patients with benign PTB and tumor-free margins <1 cm. Twelve patients with borderline or malignant PTB with tumor-free margins <1 cm received postoperative, adjuvant radiotherapy. None of these 12 patients had LR, and all survived 5 years NED.

4. Discussion

4.1. The appropriate width of a tumor-free margin following primary surgery

According to most authors, a correlation exists between the rate of LR and the type of PTB (benign, borderline, malignant) and the microscopic status of the resection margin [10,16,17,22,23,26,30,33–53].

4.1.1. Type of PTB

According to WHO 2012, LR can occur in all cases of PTB with an overall rate of 21%, within a range of 10–17% for benign, 14–25% for borderline, and 23–30% for malignant cases [11]. The majority of authors pointed out that the frequency of LR is higher in patients with malignant PTB [1,5,12,16,22,29,30,34,35,38,40,45,47,50,54–56]. In our group of patients, the frequency of LR was higher in borderline and malignant PTB than in benign cases, but the differences were not statistically significant. Hence, most authors contend that the risk of LR depends not so much on the microscopic type of PTB as on the margin status of the surgical procedures [15,16,20,23,30,34,35].

4.1.2. Status of surgical margin

In 2016 Zhou et al. summarized the results of 24 studies, and presented the prognostic factor for PTB LR. The most common factors cited were the status of the surgical margin (15 out of 24 studies) and histological grade (9 of 24 studies). The surgical approach (6/24), and the use of adjuvant radiotherapy (5/24) [57] were more rarely used.

Undoubtedly, the presence of tumor cells in the resection margin is a strong prognostic factor for LR in PTB, particularly in cases of borderline and malignant PTB [1,15,21–23,26,27,29–31,33,34,36–38,43–45]. In a large study of 605 cases of PTB conducted by Tan et al. the surgical margin status (positive or negative) appears to be an independent predictive factor of recurrence-free survival [48]. Spitaleri et al. reported a mean LR rate of 31.5% in patients with positive surgical margins [38]. According to Strode et al., the appropriate treatment for malignant PTB is surgical excision with a negative margin [6].

Thus, a clear margin has been identified as the key factor responsible for the low LR rate in cases of PTB. However, what remains a matter of debate is the appropriate width for tumor-free margins. NCCN and a large number of authors recommend a free-margin $\geq$ 1 cm [5,6,12,14–16,21,22,24,26,31,34,36,37], but often it is difficult to achieve both a positive cosmetic outcome and obtain a 1 cm margin [51] at the same time.

Currently, more and more authors suggest that a margin of at least 1 mm (one that is tumor-free) may be sufficient to prevent LR, especially in patients with benign or borderline PTB [1,4,17,23,27,31,34,38–43,45,47,51].

4.1.2.1. Benign PTB. Recent studies showed a low LR rate in patients with benign PTB (1.9–6.2%) [1,4,40,50,51]. Based on an analysis of 12 studies Shaaban and Barthelmes reported that the LR rate following excision of benign PTB was surprisingly low – 11% (range: 0–43%) (112 LR out of 1052 cases), despite a high percentage of margin involvement (7.6–43.7%) [43].

Based on an analysis of 76 patients, Moutte et al. (2016) recommended complete surgical resection with a safe margin in cases involving benign PTB or where it is unclear whether the tumor is a fibroadenoma or a benign PTB suspected on the basis of a core needle biopsy. Enucleation must be reserved for preoperative diagnoses of fibroadenomas [51].

Also, in 2017 Shaaban and Barthelmes published a review of the risk of LR in 12 studies covering the excision of 1052 benign PTB patients [43]. No statistically significant differences were observed between a 10 mm margin group – 7.9% (13/159) and a 1 mm margin group – 5.7% (12/211). Therefore, the presence of tumor cells on the margin doubled the LR rate compared to the 1 mm margin group (12.9%-90/696) [43]. The authors suggest that where a preoperative diagnosis following a core needle biopsy is such that

Table 3
Local recurrences.

Histotype of PTB	Tumor-free margin ≥1 cm			Tumor-free margin <1 cm			Total		
	No. of patients	Local recurrences		No. of patients	Local recurrences		No. of patients	Local recurrences	
		No.	%		No.	%		No.	%
Benign	167	11	6.6%	20	1	5.0%	187	12	6.4%
Borderline	36	5	13.9%	4	0	0%	40	5	12.5%
Malignant	99	12	12.1%	8	0	0%	107	12	11.2%
Total	302	28	9.1%	32	1	3.1%	334	29	8.7%

"benign PTB cannot be excluded" patients be offered the option of a wide local excision aimed at achieving a 1 mm margin. When tumor cells are found at the margins, re-excision is advised. According to the authors, their review shows that 87% of patients do not develop recurrences even with focal margin involvement and "a watch and wait policy" of close follow-ups can also be adopted [43].

A study of 114 PTB patients conducted by Tremblay-LeMay et al., in 2017 strongly suggests that the previously traditional 1 cm wide margin is unnecessary. The low recurrence rate showed that patients with PTB still received adequate treatment despite the margin not necessarily being wider than mm [1].

In our group of 20 patients with benign PTB treated with BCS and with a tumor-free margin of <1 cm, LR was found in one (3.1%) patient only; following reoperation this patient survived 5 years NED, as did the 19 other patients.

To summarize, a 1 mm tumor-free surgical margin has recently been proposed for patients with benign PTB [1,4,27,40,43,47,50] and a margin of ≥1 cm should not be required [1,41,43,51].

4.1.2.2. Borderline and malignant PTB. Currently, some authors suggest that in borderline and malignant PTB, a margin of at least 1 mm achieved all around the tumor is sufficient and that the previously traditional 1 cm wide margin is not necessary [1,31,39,40,42]. In contrast to benign PBT, in borderline and malignant PTB a negative margin is probably insufficient, which suggests that in patients with a margin of <1 mm, surgical revision of the margin might be necessary [1,4,39,52]. As a consequence, the ideal margin width for these patients remains to be determined [39]. Patients with borderline and malignant PTB should be followed up closely [1].

4.1.3. The role of adjuvant radiotherapy

Precisely determining the role of postoperative, adjuvant radiotherapy in patients with PTB is difficult and controversial for two essential reasons: the low incidence of PTB in general and its borderline and malignant types in particular, and the very small percentage of patients who qualify for this therapy [1,5,6,9,13,15,16,20–22,24–26,28–30,33–35,39,56–58].

At the turn of the twenty-first century the use of adjuvant radiotherapy increased in patients undergoing surgery, especially in borderline and malignant PTB, while in benign PTB the problem is practically nonexistent as LR is rare and reoperation almost always has a successful outcome [5,9,10,22,30,38,39,53–56,58,59]. An analysis of 3120 malignant PTBs from the US National Cancer Data Base, by Gnerlich et al. showed a pronounced increase in the use of radiotherapy (9.5% in 1998–1999 versus 19.5% in 2008–2009) [56]. In an analysis of SEER 18 data (1983–2013) the use of adjuvant radiotherapy in patients with malignant PTB, in which a mastectomy was performed increased from 2.3% (1983–1989) to 33.8% (2010–2013) and in patients treated with BCS from 1.6% to 43.4%, respectively [9].

In 2008 Belcacemi et al. presented a report by the Rare Cancer Network on the treatment of 159 patients with borderline and malignant PTB in multivariate analysis the only independent favorable prognostic factor was the application of adjuvant radiotherapy [10].

In 2013 Spitaleri et al. reviewed eighty-three articles from the literature covering a period from 1951 to 2012 and a total of 5530 patients (35% with malignant PTBs) and concluded that adjuvant radiotherapy should be limited to patients with malignant PTBs and a positive surgical margin, where radical surgery could not be performed [38].

In spite of a large number of publications that appeared between 2014 and 2018, the indications for, and the efficacy of, adjuvant radiotherapy, both of the chest wall and the breast, is a controversial issue [1,5,6,9,10,12,20,24,27,29,30,38,45,53,56,58–62]. Despite many doubts, most of the authors consider adjuvant radiotherapy to be effective in reducing LR but without any impact on OS (overall survival) and DFS (disease free survival) in patients with borderline and malignant PTB [1,5,6,9,10,12,30,56,58,62].

In 2014 Mitus et al. expressed the view that adjuvant radiotherapy should be considered for patients with malignant PTB where a tumor-free margin <1 cm is reported. The authors indicated a 5-year NED survival rate of 83.3% between patients who received BCS with a margin ≥1 cm and those who had margins of <1 cm and underwent adjuvant radiation [59].

Kim and Kim reviewed 1974 patients with malignant PTB using the Surveillance, Epidemiology and End Results Program (SEER) database (1983–2013). Of these, 825 (42%) and 1149 (58%) patients underwent mastectomy and BSC, respectively. In these two groups, 130 (16%) and 122 (11%) patients, respectively, received postoperative RT. Although patients with more adverse prognostic factors underwent postoperative RT. The RT group was not inferior to the non-RT group with regard to CSS (cancer specific survival), regardless of surgery [9].

No recurrence occurred in the 13 cases of malignant PTB analyzed in a study by Tremblay-LeMay et al. Five of these patients received adjuvant radiotherapy and they all had margins of ≤1 mm. In addition, all the patients with positive margins had surgical revision and/or adjuvant radiotherapy. The absence of recurrence in the cases of malignant PTB examined in this study may suggest that adjuvant radiotherapy could be beneficial to patients with malignant PTB [1].

In 2017 Varghese et al. analyzed 92 patients with PTB (60% benign, 23% borderline and 17% malignant) and concluded that for patients with borderline PTB, adjuvant radiotherapy is useful if the margins are close or positive. There is a trend towards improved local control with adjuvant radiotherapy in malignant PTB [5].

In a review from 2017 Strode et al. recommend post-operative radiotherapy for all patients with malignant PTB, even in the case of negative margins, due to a substantial decrease noted in the LR rate [6].

None of our 12 patients with borderline or malignant PTB, treated with BCS and adjuvant radiotherapy, and with a tumor-free margin of <1 cm, had LR, and all survived 5 years NED.

One way or another, most of the authors regard the role of adjuvant radiotherapy in patients with borderline or malignant PTB as still uncertain and more research (prospective, randomized trials?) is needed to elucidate this problem [1,6,9,20,27,29,38,39,45,49,59].

4.2. Limitations

Our study suffers from several limitations. The first is that we presented a retrospective review of patients treated over a long period of time (over 60 years). Secondly, a high percentage of our patients have surgical margins of >1 cm (88.8%) and only 9.4% have surgical margins of <1 cm (0.2–0.8 cm). Another drawback of the present study is the lack of patients with surgical margins within the range of 0–0.1 cm.

In our study we were unable to assess the role of surgical margin width in patients treated with mastectomy, because all these patients had surgical margins ≥1 cm.

The efficacy of adjuvant radiotherapy in 12 patients treated with primary BCS (surgical margins within the range of 0.2–0.8 cm) must be interpreted with caution due to the small number of patients (4 borderline and 8 malignant). We do not know whether the absence of LR in such patients is a result of adjuvant radiotherapy or whether the surgical margin (0.2–0.8 cm) was sufficient without radiotherapy.

5. Conclusion

The prognosis for patients with benign PTB is excellent and they are cured by means of surgery alone. The previously traditional tumor-free surgical margin of ≥1 cm is not necessary. Benign PTB is successfully treated with surgery alone, in borderline and malignant PTBs, with tumor-free margin < 1 cm, we recommend adjuvant radiotherapy.

Disclosure statement

Nothing to declare.

Conflicts of interest

The Authors declare that they have no conflict of interest to disclose concerning the topic of the present paper.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

Institutional review board approval was obtained.

References

[1] Tremblay-LeMay, R., J.C. Hogue, L. Provencher, B. Poirier, et al., How wide should margins Be for phyllodes tumors of the breast? Breast J, 2017. 23(3): p. 315-322. https://doi.org/10.1111/tbj.12727
[2] Amer, A., P. Ainley, R. Thompson, and H. Mathers, Postoperative follow-up practice of phyllodes tumour in the UK: results from a national survey. Surgeon, 2018. 16(2): p. 74-81. https://doi.org/10.1016/j.surge.2016.05.003
[3] Mitus, J.W., P. Blecharz, T. Walasek, M. Reinfuss, et al., Treatment of patients with distant metastases from phyllodes tumor of the breast. World J Surg, 2016. 40(2): p. 323-328. https://doi.org/10.1007/s00268-015-3262-7
[4] Moo, T.A., H. Alabdulkareem, A. Tam, C. Fontanet, et al., Association between recurrence and Re-excision for close and positive margins versus observation in patients with benign phyllodes tumors. Ann Surg Oncol, 2017. 24(10): p. 3088-3092. https://doi.org/10.1245/s10434-017-5955-7
[5] Varghese, S.S., B. Sasidharan, M.T. Manipadam, M.J. Paul, et al., Radiotherapy in phyllodes tumour. J Clin Diagn Res, 2017. 11(1): p. XC01-XC03. https://doi.org/10.7860/JCDR/2017/24591.9167
[6] Strode, M., T. Khoury, C. Mangieri, and K. Takabe, Update on the diagnosis and management of malignant phyllodes tumors of the breast. Breast, 2017. 33: p. 91-96. https://doi.org/10.1016/j.breast.2017.03.001
[7] Mitus, J.W., P. Blecharz, M. Reinfuss, J.K. Kulpa, et al., Changes in the clinical characteristics, treatment options, and therapy outcomes in patients with phyllodes tumor of the breast during 55 years of experience. Med Sci Monit, 2013. 19: p. 1183-1187. https://doi.org/10.12659/MSM.889687
[8] Ruvalcaba-Limon E, Jimenez-Lopez J, Bautista-Pina V, Ramirez-Bollas J, et al. Phyllodes tumor of the breast: 307 treated cases, the largest Mexican experience at a single breast disease institution. Iran J Pathol 2016;11(4):399–408.
[9] Kim, Y.J. and K. Kim, Radiation therapy for malignant phyllodes tumor of the breast: an analysis of SEER data. Breast, 2017. 32: p. 26-32. https://doi.org/10.1016/j.breast.2016.12.006
[10] Belkacemi, Y., G. Bousquet, H. Marsiglia, I. Ray-Coquard, et al., Phyllodes tumor of the breast. Int J Radiat Oncol Biol Phys, 2008. 70(2): p. 492-500. https://doi.org/10.1016/j.ijrobp.2007.06.059
[11] Lakhani SR, E.I, Schnitt SJ, Tan PH, van der Vijver MJ. WHO classification of tumours of the breast. fourth ed. IARC Lyon; 2012. p. 142.
[12] Bouhafa, T., O. Masbah, I. Bekkouch, S. Afqir, et al., [Phyllodes tumors of the breast: analysis of 53 patients]. Cancer Radiother, 2009. 13(2): p. 85-91. https://doi.org/10.1016/j.canrad.2008.11.007
[13] Haberer, S., M. Lae, V. Seegers, J.Y. Pierga, et al., [Management of malignant phyllodes tumors of the breast: the experience of the Institut Curie]. Cancer Radiother, 2009. 13(4): p. 305-312. https://doi.org/10.1016/j.canrad.2009.05.001
[14] Guillot, E., B. Couturaud, F. Reyal, A. Curnier, et al., Management of phyllodes breast tumors. Breast J, 2011. 17(2): p. 129-137. https://doi.org/10.1111/j.1524-4741.2010.01045.x
[15] Chen, W.H., S.P. Cheng, C.Y. Tzen, T.L. Yang, et al., Surgical treatment of phyllodes tumors of the breast: retrospective review of 172 cases. J Surg Oncol, 2005. 91(3): p. 185-194. https://doi.org/10.1002/jso.20334
[16] Reinfuss M, Mitus J, Duda K, Stelmach A, et al. The treatment and prognosis of patients with phyllodes tumor of the breast: an analysis of 170 cases. Cancer 1996;77(5):910–6.
[17] Ben Hassouna, J., T. Damak, A. Gamoudi, R. Chargui, et al., Phyllodes tumors of the breast: a case series of 106 patients. Am J Surg, 2006. 192(2): p. 141-147. https://doi.org/10.1016/j.amjsurg.2006.04.007
[18] Mitus, J.W., J. Jakubowicz, T. Walasek, A. Szadurska, et al., Are patients with phyllodes tumor of the breast good candidates for breast conserving therapy? A single center experience. Eur J Gynaecol Oncol 2018. XXXIX(4): p. 641-644. https://doi.org/10.12892/ejgo4220.2018
[19] Verma, S., R.K. Singh, A. Rai, C.P. Pandey, et al., Extent of surgery in the management of phyllodes tumor of the breast: a retrospective multicenter study from India. J Cancer Res Ther, 2010. 6(4): p. 511-515. https://doi.org/10.4103/0973-1482.77085
[20] Pezner, R.D., T.E. Schultheiss, and I.B. Paz, Malignant phyllodes tumor of the breast: local control rates with surgery alone. Int J Radiat Oncol Biol Phys, 2008. 71(3): p. 710-713. https://doi.org/10.1016/j.ijrobp.2007.10.051
[21] Telli ML, Horst KC, Guardino AE, Dirbas FM, et al. Phyllodes tumors of the breast: natural history, diagnosis, and treatment. J Natl Compr Canc Netw 2007;5(3):324–30.
[22] Khosravi-Shahi, P., Management of non metastatic phyllodes tumors of the breast: review of the literature. Surg Oncol, 2011. 20(4): p. e143-e148. https://doi.org/10.1016/j.suronc.2011.04.007
[23] Barrio, A.V., B.D. Clark, J.I. Goldberg, L.W. Hoque, et al., Clinicopathologic features and long-term outcomes of 293 phyllodes tumors of the breast. Ann Surg Oncol, 2007. 14(10): p. 2961-2970. https://doi.org/10.1245/s10434-007-9439-z
[24] Macdonald, O.K., C.M. Lee, J.D. Tward, C.D. Chappel, et al., Malignant phyllodes tumor of the female breast: association of primary therapy with cause-specific survival from the Surveillance, Epidemiology, and End Results (SEER) program. Cancer, 2006. 107(9): p. 2127-2133. https://doi.org/10.1002/cncr.22228
[25] Reinfuss M, Mitus J, Stelmach A. Phyllodes tumor of the breast. Strahlenther Onkol 1995;171(1):5–11.
[26] Asoglu, O., M.M. Ugurlu, K. Blanchard, C.S. Grant, et al., Risk factors for recurrence and death after primary surgical treatment of malignant phyllodes tumors. Ann Surg Oncol, 2004. 11(11): p. 1011-1017. https://doi.org/10.1245/ASO.2004.02.001
[27] Ganesh, V., L. Drost, J. Lee, B.A. Wan, et al., A retrospective review of phyllodes tumours of the breast: a single institution experience. Breast, 2018. 38: p. 52-57. https://doi.org/10.1016/j.breast.2017.12.008
[28] Adesoye, T., H.B. Neuman, L.G. Wilke, J.R. Schumacher, et al., Current trends in the management of phyllodes tumors of the breast. Ann Surg Oncol, 2016. 23(10): p. 3199-3205. https://doi.org/10.1245/s10434-016-5314-0
[29] Zhou, Z.R., C.C. Wang, X.J. Sun, Z.Z. Yang, et al., Prognostic factors in breast phyllodes tumors: a nomogram based on a retrospective cohort study of 404 patients. Cancer Med, 2018. 7(4): p. 1030-1042. https://doi.org/10.1002/cam4.1327
[30] Barth, R.J., Jr., W.A. Wells, S.E. Mitchell, and B.F. Cole, A prospective, multi-institutional study of adjuvant radiotherapy after resection of malignant phyllodes tumors. Ann Surg Oncol, 2009. 16(8): p. 2288-2294. https://doi.org/10.1245/s10434-009-0489-2
[31] Jang, J.H., M.Y. Choi, S.K. Lee, S. Kim, et al., Clinicopathologic risk factors for the local recurrence of phyllodes tumors of the breast. Ann Surg Oncol, 2012. 19(8): p. 2612-2617. https://doi.org/10.1245/s10434-012-2307-5
[32] Reinfuss M, Mitus J, Smolak K, Stelmach A. Malignant phyllodes tumours of the breast. A clinical and pathological analysis of 55 cases. Eur J Cancer 1993;29A(9):1252–6.
[33] Cheng, S.P., Y.C. Chang, T.P. Liu, J.J. Lee, et al., Phyllodes tumor of the breast: the challenge persists. World J Surg, 2006. 30(8): p. 1414-1421. https://doi.org/10.1007/s00268-005-0786-2
[34] Chaney AW, Pollack A, McNeese MD, Zagars GK, et al. Primary treatment of cystosarcoma phyllodes of the breast. Cancer 2000;89(7):1502–11.
[35] Barth Jr RJ. Histologic features predict local recurrence after breast conserving therapy of phyllodes tumors. Breast Cancer Res Treat 1999;57(3):291–5.
[36] Mangi, A.A., B.L. Smith, M.A. Gadd, K.K. Tanabe, et al., Surgical management of phyllodes tumors. Arch Surg, 1999. 134(5): p. 487-492; discussion 492-3.
[37] Gradishar WJ, Anderson BO, Balassanian R, Blair SL, et al. Invasive breast cancer version 1.2016, NCCN clinical practice guidelines in Oncology. J Natl Compr Canc Netw 2016;14(3):324–54.
[38] Spitaleri, G., A. Toesca, E. Botteri, L. Bottiglieri, et al., Breast phyllodes tumor: a review of literature and a single center retrospective series analysis. Crit Rev Oncol Hematol, 2013. 88(2): p. 427-436. https://doi.org/10.1016/j.critrevonc.2013.06.005
[39] Tan, B.Y., G. Acs, S.K. Apple, S. Badve, et al., Phyllodes tumours of the breast: a consensus review. Histopathology, 2016. 68(1): p. 5-21. https://doi.org/10.1111/his.12876
[40] Yom, C.K., W. Han, S.W. Kim, S.Y. Park, et al., Reappraisal of conventional risk stratification for local recurrence based on clinical outcomes in 285 resected phyllodes tumors of the breast. Ann Surg Oncol, 2015. 22(9): p. 2912-2918. https://doi.org/10.1245/s10434-015-4395-5
[41] Teo, J.Y., C.S. Cheong, and C.Y. Wong, Low local recurrence rates in young Asian patients with phyllodes tumours: less is more. ANZ J Surg, 2012. 82(5): p. 325-328. https://doi.org/10.1111/j.1445-2197.2012.06045.x
[42] Onkendi, E.O., R.E. Jimenez, G.M. Spears, W.S. Harmsen, et al., Surgical treatment of borderline and malignant phyllodes tumors: the effect of the extent

of resection and tumor characteristics on patient outcome. Ann Surg Oncol, 2014. 21(10): p. 3304-3309. https://doi.org/10.1245/s10434-014-3909-x
[43] Shaaban, M. and L. Barthelmes, Benign phyllodes tumours of the breast: (Over) treatment of margins - a literature review. Eur J Surg Oncol, 2017. 43(7): p. 1186-1190. https://doi.org/10.1016/j.ejso.2016.10.019
[44] Lim, S.Z., S. Selvarajan, A.A. Thike, N.D. Nasir, et al., Breast sarcomas and malignant phyllodes tumours: comparison of clinicopathological features, treatment strategies, prognostic factors and outcomes. Breast Cancer Res Treat, 2016. 159(2): p. 229-244. https://doi.org/10.1007/s10549-016-3946-1
[45] Rodrigues, M.F., P.T. Truong, E.C. McKevitt, L.M. Weir, et al., Phyllodes tumors of the breast: the British Columbia cancer agency experience. Cancer Radiother, 2018. 22(2): p. 112-119. https://doi.org/10.1016/j.canrad.2017.08.112
[46] Nishimura, R., P.H. Tan, A.A. Thike, M.H. Tan, et al., Utility of the Singapore nomogram for predicting recurrence-free survival in Japanese women with breast phyllodes tumours. J Clin Pathol, 2014. 67(8): p. 748-750. https://doi.org/10.1136/jclinpath-2014-202215
[47] Kim, S., J.Y. Kim, D.H. Kim, W.H. Jung, et al., Analysis of phyllodes tumor recurrence according to the histologic grade. Breast Cancer Res Treat, 2013. 141(3): p. 353-363. https://doi.org/10.1007/s10549-013-2684-x
[48] Tan, P.H., A.A. Thike, W.J. Tan, M.M. Thu, et al., Predicting clinical behaviour of breast phyllodes tumours: a nomogram based on histological criteria and surgical margins. J Clin Pathol, 2012. 65(1): p. 69-76. https://doi.org/10.1136/jclinpath-2011-200368
[49] Kapiris, I., N. Nasiri, R. A'Hern, V. Healy, et al., Outcome and predictive factors of local recurrence and distant metastases following primary surgical treatment of high-grade malignant phyllodes tumours of the breast. Eur J Surg Oncol, 2001. 27(8): p. 723-730. https://doi.org/10.1053/ejso.2001.1207
[50] Borhani-Khomani, K., M.L. Talman, N. Kroman, and T.F. Tvedskov, Risk of local recurrence of benign and borderline phyllodes tumors: a Danish population-based retrospective study. Ann Surg Oncol, 2016. 23(5): p. 1543-1548. https://doi.org/10.1245/s10434-015-5041-y
[51] Moutte, A., N. Chopin, C. Faure, F. Beurrier, et al., Surgical management of benign and borderline phyllodes tumors of the breast. Breast J, 2016. 22(5): p. 547-552. https://doi.org/10.1111/tbj.12623
[52] Barth R, J., Margin negative, breast conserving resection: adequate for benign phyllodes tumors, but inadequate therapy for borderline and malignant phyllodes tumors. Breast Cancer Res Treat, 2013. 142(2): p. 463-464. https://doi.org/10.1007/s10549-013-2750-4
[53] Pandey M, Mathew A, Kattoor J, Abraham EK, et al. Malignant phyllodes tumor. Breast J 2001;7(6):411–6.
[54] Ramakant, P., S. Chakravarthy, J.A. Cherian, D.T. Abraham, et al., Challenges in management of phyllodes tumors of the breast: a retrospective analysis of 150 patients. Indian J Cancer, 2013. 50(4): p. 345-348. https://doi.org/10.4103/0019-509X.123625
[55] Narayanakar, R.P., D.M. Gangaiah, S. Althaf, K. Dev, et al., Cystosarcoma phyllodes: pathological enigma: a retrospective review of 162 cases. Indian J Cancer, 2015. 52(3): p. 365-368. https://doi.org/10.4103/0019-509X.176698
[56] Gnerlich, J.L., R.T. Williams, K. Yao, N. Jaskowiak, et al., Utilization of radiotherapy for malignant phyllodes tumors: analysis of the National Cancer Data Base, 1998-2009. Ann Surg Oncol, 2014. 21(4): p. 1222-1230. https://doi.org/10.1245/s10434-013-3395-6
[57] Zhou, Z.R., C.C. Wang, Z.Z. Yang, X.L. Yu, et al., Phyllodes tumors of the breast: diagnosis, treatment and prognostic factors related to recurrence. J Thorac Dis, 2016. 8(11): p. 3361-3368. https://doi.org/10.21037/jtd.2016.11.03
[58] Zeng, S., X. Zhang, D. Yang, X. Wang, et al., Effects of adjuvant radiotherapy on borderline and malignant phyllodes tumors: a systematic review and meta-analysis. Mol Clin Oncol, 2015. 3(3): p. 663-671. https://doi.org/10.3892/mco.2015.503
[59] Mitus, J., M. Reinfuss, J.W. Mitus, J. Jakubowicz, et al., Malignant phyllodes tumor of the breast: treatment and prognosis. Breast J, 2014. 20(6): p. 639-644. https://doi.org/10.1111/tbj.12333
[60] Carlson RW, A.B., Burstein HJ et al. , The NCCN breast cancer clinical practice guidelines in Oncology, version 1, 2007. Available at: http://www.ncnn.org/professionals/physican-gls/pdf/breast.pdf. Accessed January 30, 2007.
[61] Chaney, A.W., A. Pollack, M.D. McNeese, and G.K. Zagars, Adjuvant radiotherapy for phyllodes tumor of breast. Radiat Oncol Investig, 1998. 6(6): p. 264-267. https://doi.org/10.1002/(SICI)1520-6823(1998)6:6<264::AID-ROI3>3.0.CO;2-J
[62] Ossa CA, Herazo F, Gil M, Echeverri C, et al. Phyllodes tumor of the breast: a clinic-pathologic study of 77 cases in a Hispanic cohort. Colomb Méd 2015;46(3):104–8.