

Phyllodes Tumour of the Breast

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Background

Phyllodes tumour of the breast are rare; they represent approximately 1% of breast tumours. Many clinical characteristics of phyllodes tumours are like fibroadenomas (benign tumours), making them difficult to diagnose. Diagnostic imaging and histopathology are critical in establishing a diagnosis to guide patient management.

The World Health Organization (WHO) classifies phyllodes tumours as benign, borderline, or malignant based on a combination of histologic features presented in Table 1.^{1,2} Benign phyllodes tumours are the most common. Approximately 20% of phyllodes tumours are borderline or malignant.³ Risk for local recurrence (LR) in patients with benign phyllodes tumours is approximately 10–20% and increases to 30% in patients with borderline or malignant phyllodes tumours.³ Metastatic spread in patients with malignant phyllodes tumours occurs in 10–35% of cases.^{3,4}

Table 1. Histologic features of phyllodes tumours

Phyllodes Classification	Histologic Features
Benign	<ul style="list-style-type: none">- Increased stromal cellularity and mild-to-moderate cellular atypia- Low mitotic rate- Absence of stromal overgrowth- Circumscribed tumour margins
Borderline	<ul style="list-style-type: none">- Greater degree of stromal cellularity and atypia- High mitotic rate- Presence of stromal overgrowth- Microscopic infiltrative borders
Malignant	<ul style="list-style-type: none">- Marked stromal cellularity and atypia- High mitotic rate- Presence of stromal overgrowth- Infiltrative margins

Standard management for phyllodes tumours is surgical excision. Less clear is whether patients should be managed by breast or sarcoma specialists, what is considered an adequate surgical margin, and under what circumstances there is a role for adjuvant therapies.

Due to the rarity of phyllodes tumours, there is no high-level evidence (i.e., randomized controlled trials) to guide patient management. A scoping review of the available literature concluded that there is significant heterogeneity between studies, and that consensus-based guidelines or decision aids are needed.⁵ Thus, the objective of this guideline is to provide best practice recommendations, based on the available evidence and local expert opinion, about how to manage patients who present with a suspected phyllodes tumour.

Guideline Questions

1. How should patients with a suspected phyllodes tumour be diagnosed and staged?
2. How should patients with biopsy confirmed phyllodes tumour be managed?
3. What is the optimal post-therapy surveillance?

4. How should recurrent and/or metastatic disease be managed?

Search Strategy

The PubMed database was searched for relevant studies, guidelines and consensus documents published up to December 2021. The specific search strategy, search terms, and search results are presented in Appendix A, and evidence tables are available upon request. Online resources from oncology-based health organizations and guideline developers were also systematically searched. The only relevant guideline was published by the National Comprehensive Cancer Network (NCCN).⁶

Target Population

The following recommendations apply to adult cancer patients (≥18 years of age) with phyllodes tumours.

Recommendations

Diagnosis

1. A phyllodes tumour should be suspected in patients who present with a large (>3 cm), fast growing, and palpable painless breast mass. Peak incidence occurs in the fourth decade of life.
2. Patients should have a breast ultrasound (US) if there is clinical suspicion of a phyllodes tumour or a suspected phyllodes tumour is detected with screening mammography. (*Level of Evidence: IV⁷⁻⁹; Strength of Recommendation: B*).
3. Breast masses thought to be a phyllodes tumour should undergo core needle biopsy followed by excision/wide local excision. (*Level of Evidence: IV¹⁰⁻¹²; Strength of Recommendation: B*).

Staging

4. For patients diagnosed with benign or borderline phyllodes tumours there is no need for additional staging investigations; studies report low metastatic rates (about 0.13% and 1.62%, respectively). (*Level of Evidence: IV⁴; Strength of Recommendation: B*).
5. For patients diagnosed with malignant phyllodes tumours, lung is the most common metastatic site. Thus, routine baseline chest computed tomography (CT) is recommended. Additional imaging tests including abdominal CT or bone scan should only be ordered if the patient is symptomatic because of the much lower frequency of metastases in other anatomical sites. (*Level of Evidence: IV^{4, 13-15}; Strength of Recommendation: B*).

Organization of Care

6. Surgical expertise for management of phyllodes tumours is within the Provincial Breast Tumour Team. Cases with indications for Radiation Oncology or Medical Oncology consultations should

be referred to the Provincial Sarcoma Tumour Team for multidisciplinary case review and consultations (Calgary or Edmonton). (*Level of Evidence: V; Strength of Recommendation: C*).

Management

7. Surgery is considered primary management for all classifications of phyllodes tumours. While surgical margin status (positive or negative) is accepted as a key risk factor for LR malignant phyllodes tumours, adequate margins for all types of phyllodes tumours remain a topic of debate. Acknowledging limitations of the current literature (i.e., lack of prospective data), we recommend the following management strategy:
 - a) Complete gross resection (R1 resection/marginal resection while avoiding piecemeal resection) is recommended for benign and borderline tumours. (*Level of Evidence: benign III¹⁶IV¹⁷⁻²⁰ borderline III^{16, 21}IV¹⁹; Strength of Recommendation: B*)
 - b) Wide local excision with ≥ 1 cm surgical margins is recommended for malignant tumours. (*Level of Evidence: III^{16, 21}V⁶; Strength of Recommendation: B*) If needed, excision of the pre-pectoral fascia should be considered.
 - c) Mastectomy is generally not indicated unless a patient has a large tumour-to-breast volume ratio. (*Level of Evidence: IV²²; Strength of Recommendation: C*)
 - d) Axillary node enlargement is common, but nodal involvement is not (roughly 2.2%).⁵ Therefore, routine axillary node dissection is not recommended unless biopsy proven node positive. (*Level of Evidence: IV^{18, 22, 23} V⁶; Strength of Recommendation: B*)
 - e) Review of resection specimens should include reporting of the following elements in accordance with the College of American Pathologists' protocol,²⁴ which includes:
 - Tumour features (specimen laterality, tumour site, tumour size, histologic type, stromal cellularity, stromal atypia, stromal overgrowth, mitotic rate, histologic tumour border, and malignant heterologous elements)
 - Margin status
 - Regional lymph node status
 - Distant metastasis (DM)
 - Pathologic stage classification (pTNM, AJCC 8th Edition) for malignant tumours only
8. Patients with a large (≥ 4 cm) malignant phyllodes tumour should be referred to the Provincial Sarcoma Tumour Team for local multidisciplinary case review and discussion about whether to refer to an oncologist for a consult about the risks and benefits of adjuvant therapy. (*Level of Evidence for Adjuvant Radiotherapy (RT): III^{25, 26} IV^{27, 28} V⁶; Strength of Recommendation: B*)

(Level of Evidence for Adjuvant Chemotherapy: III^{29, 30}IV³¹⁻³³; Strength of Recommendation: C)

Surveillance

9. The chances of phyllodes tumours recurring are highest in the first two years after removal.³⁴ Therefore, for patients with borderline phyllodes tumours, ipsilateral breast US every 6 months in the first two years is recommended. (Level of Evidence: V; Strength of Recommendation: C)
10. For patients with malignant tumours, regular follow-up visits are recommended for at least three years. Surveillance imaging should begin with chest CT, and then transition to chest x-ray according to Alberta Health Services (AHS) guidelines for [follow-up surveillance of soft tissue sarcoma](#). Annual ipsilateral breast US/bilateral mammogram are also recommended during this time. If the patient has had a mastectomy, a chest wall exam without breast imaging is recommended. (Level of Evidence: follow-up frequency V⁶; Strength of Recommendation: C)

Recurrent and/or Metastatic Disease

11. Metastatic phyllodes tumours are very uncommon. Evidence about to how best to manage them is limited to case reports and small case series. It is recommended that patients with recurrent and/or metastatic disease be assessed on a case-by-case basis in Sarcoma Rounds. (Level of Evidence: IV^{13, 14}, Strength of Recommendation: C)

Discussion

This section will focus on the key evidence, and the justification for our recommendations on the management of phyllodes tumours only. Specifically, the discussion will focus on the recommendations to facilitate routine management with respect to surgical margins and the use of adjuvant RT.

Surgical Margins. No randomized trials are available to address the question of adequate margins. A local population-based retrospective study in Calgary, AB, examined the appropriate surgical management of patients with benign phyllodes tumours (n=119).¹⁷ After a median follow-up of 4.9 years, the authors found no association between final margin status and local recurrence rate (LRR) (odds ratio [OR] 0.97, 95% confidence interval [CI] 0.18–4.40, p>0.99). Additionally, they found no association between re-excision surgery and LRR (OR 0.24, 95% CI 0.02–2.04, p=0.23). Recurrences on final pathology were benign phyllodes tumours without progression of histological grade. Time to recurrence was on average 14.7 (range 8–22) months. Additionally, a low re-excision rate was noted (42%) after benign phyllodes tumour diagnosis was made. A larger multi-institutional retrospective study (n=379) also concluded that most patients with phyllodes tumours are benign and can be managed successfully with breast conservation with an overall low risk of LR, which is not significantly impacted by margin status or width.¹⁸

Two meta-analyses of retrospective case series studies also provide some direction for clinicians regarding adequate margins.^{16, 21} In the first meta-analysis the authors synthesized the best available evidence (13 retrospective studies) in which a link was made between margin width, tumour type, and the LR and DM rates (summarized in Table 1).¹⁶ For patients with benign and borderline phyllodes tumours, data suggests factors other than margin width may be more of a risk factor for LR. For patients with malignant phyllodes tumours, margin width ≥ 1 cm was clearly associated with a lower LR and DM rate. Current recommendations from the NCCN recommend obtaining surgical margins ≥ 1 cm for malignant disease.⁶

Table 1. Pooled data of relationship between phyllodes tumour type, width of margins, and recurrence

Phyllodes Tumour Type	Margin ≥ 10 mm		Margin 1-10 mm		Margin < 1 mm	
	LR%	DM%	LR%	DM%	LR%	DM%
Benign	4.95	0	8.09	0.58	2.04	0
Borderline	34.21	2.63	10.94	0	12.5	0
Malignant	15.03	5.20	41.67	16.67	-	-

In the second meta-analysis, the authors looked at LR, metastasis and survival for borderline and malignant tumours only resected with either ≥ 1 cm or < 1 cm margins.²¹ Ten retrospective studies were included. Meta-analysis pooling showed no statistically significant difference between < 1 cm and ≥ 1 cm margins in terms of LRRs (relative risk [RR] 1.43, 95% CI 0.70 - 2.93; $p=0.33$, $n=456$), DM (RR 1.93, 95% CI 0.35 - 10.63; $p=0.45$, $n=72$) or mortality (RR 1.93, 95% CI 0.42 - 8.77; $p=0.40$, $n=58$). The authors hypothesized that histopathological margin status (the presence or absence of tumour cells at the edge of excised tissue), rather than margin size plays an important role in recurrence. However, they also cautioned that current data is limited, and that practically it's fair to assume that less extensive surgery would result in an increased risk of positive margins, an important consideration for phyllodes tumours with infiltrative borders or nodules.

Adjuvant RT. No randomized trials have addressed the question of adjuvant RT following resection. Only one prospective, multi-institutional trial has evaluated the addition of adjuvant RT in patients with phyllodes tumours.²⁵ In the study, 46 patients with borderline (35%) and malignant (65%) received breast conserving surgery (BCS) with negative margins followed by adjuvant RT. During a median follow-up of 56 months, no patient developed a LR. Adjuvant RT began within 12 weeks of local excision or breast re-excision. Fields included the whole breast using standard tangent technique for a total dose of 50.4 Gy at 1.80 Gy per fraction over 28 treatments provided 5 days a week followed by a boost to the tumour bed area, including the resection site plus a 2-cm margin, for a further 10 Gy in five fractions of 2 Gy each.

Several retrospective studies have also evaluated the addition of adjuvant RT in patients with phyllodes tumours but demonstrated inconsistent outcomes. Two analyses have pooled data from these studies to better understand the effects of adjuvant RT.^{26, 30} The first meta-analysis included eight studies investigating the outcomes of postoperative borderline and malignant phyllodes tumours

with and without RT (~90 of patients had negative resection margins).²⁶ Patients who received adjuvant RT were found to have a lower relative risk of LR [hazard ratio [HR]=0.43, 95% CI: 0.23–0.64] with an I^2 of 0%. The 5-year absolute risk of a LR among patients who received adjuvant RT was 19.3% (95% CI: 11.6–29.1) compared to 29.4% (58 of 197, 95% CI: 23.1–36.3) among patients who did not receive RT. In a subgroup analysis of patients undergoing BCS and mastectomy, the pooled HR of LR in the BCS group showed a lower relative risk of LR in patients with RT compared to those without RT (HR=0.31, 95% CI: –0.10–0.72). However, the combined HR for LR in the mastectomy group did not show that adjuvant RT was superior to no RT (HR=0.68, 95% CI: –0.28–1.64). No significant differences were observed in overall survival (OS) or disease-free survival (DFS) between the two groups.

The most recent meta-analysis included 17 studies with borderline and malignant patients receiving adjuvant RT.³⁰ The group that received adjuvant RT had a lower LRR (8%, 95% CI: 1–22%) compared with the pooled LRR 19% (95% CI: 16–32%; test for heterogeneity: $I^2 = 24.5%$, $p=0.19$) for the group that had surgery alone, with statistical heterogeneity ($I^2 = 86.6%$, $p<0.01$). The metastasis rate of 4% (95% CI: 0–11%) for patients receiving RT without significant heterogeneity was also lower than the rate for the group that underwent surgery group (8%, 95% CI: 3–15%). Subgroup analysis results suggested that adjuvant RT may be more effective in younger patients, larger tumours, malignant tumours, and wider excision. The meta-regression analysis also confirmed the importance of margin status in local control, emphasizing the importance of adequate surgical margins. Surgery type (BCS vs. mastectomy) showed less impact on disease control. Of note, there was significant heterogeneity in the data.

The Surveillance, Epidemiology, and End Results (SEER) database was used to examine the role of adjuvant RT in patients with malignant phyllodes tumours ($n=1353$).²⁷ Less than a quarter (16.7%) of patients with malignant phyllodes tumours received adjuvant RT, of these 50.9% underwent BCS and 49.1% received mastectomy. Patients who received adjuvant RT were more likely white, with better differentiation and larger tumours ($p<0.05$). Multivariate analysis showed that poorer tumour differentiation grade, larger tumour size, and lymph node metastasis were associated with reduced survival while BCS was a protective factor of disease-specific survival (DSS) (HR 0.297; 95% CI 0.184–0.480) and OS (HR 0.445; 95% CI 0.321–0.616). After propensity-score matching, survival curves showed patients did not achieve an improved OS or DSS from adjuvant RT ($p>0.05$). In subgroup analysis, no subgroup benefited from adjuvant RT. Exploratory analysis showed a survival benefit trend from adjuvant RT in patients with tumour larger than 5 cm and undergoing BCS.

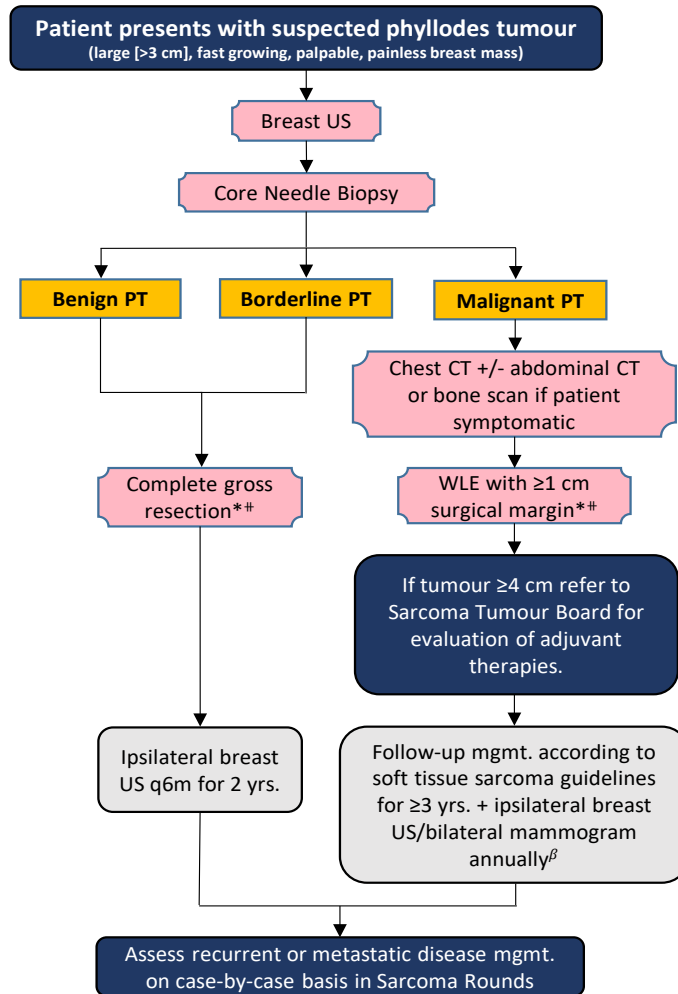
Finally, a retrospective review of 478 patients with malignant phyllodes tumours treated with mastectomy alone reported a five-year local control rate for patients with 0–2 cm, 2–5 cm, 5–10 cm, and 10–20 cm tumours of 100%, 95%, 88%, and 85%, respectively.²⁸ Analyses of locoregional recurrence for other malignancies such as breast cancer, suggest that a 15% risk of locoregional recurrence is an appropriate level of concern to consider adjuvant RT. This is supported by NCCN

recommendations that state in the setting where additional recurrence would create significant morbidity (e.g., chest wall recurrence following mastectomy), RT may be considered following the same principles that are applied to the treatment of soft tissue sarcoma.⁶

Adjuvant chemotherapy. A review of the available data for chemotherapy in the treatment of phyllodes tumours found a negligible role.³⁰ The authors highlighted the only prospective observational trial that evaluated adjuvant chemotherapy in patients with malignant phyllodes tumours, which showed no effect on patient survival.²⁹ In the study, 28 patients received chemotherapy with doxorubicin and dacarbazine. Eleven patients were observed. The median tumour size was 13 cm. At a median follow-up of 15 months, there were seven recurrences and five deaths. The 5-year recurrence-free survival (RFS) rate was 58% (95% CI=36% and 92%) for the patients who received adjuvant therapy and 86% (95% CI=63% and 100%) for the patients who were observed (p=0.17). The median survival after recurrence was 6.5 months. Several retrospective studies have also evaluated the role of adjuvant chemotherapy with mixed results.³¹⁻³³ In one of these studies, four patients were referred for adjuvant therapy secondary to large tumour size, tumour cut through prior resection, or close or positive microscopic surgical margins.³¹ Patients received doxorubicin- and ifosfamide-based chemotherapy and none developed distant disease. As part of the larger study, stromal overgrowth was found to be the strongest predictor of DM and ultimate outcome. Thus, the authors recommended that the role of adjuvant chemotherapy should be examined systematically in patients with stromal overgrowth. However, in another study where 8 of 70 patients with malignant phyllodes tumours received adjuvant chemotherapy no improvement was seen in OS (p=0.250) or DFS (p=0.659).³² A newer and larger retrospective study with 24 patients, also showed no improvement with adjuvant chemotherapy on metastasis-free survival.³³

Chemotherapy for metastatic disease. Two retrospective studies have looked at the role of chemotherapy in patients with metastatic disease.^{13, 14} In one study, 37 patients received chemotherapy. At a median follow-up of 5.2 years, clinical benefit of chemotherapy rate was 31.4% and 16.7% for the first and second lines. Polychemotherapy was not superior to single-agent therapy, and alkylating-agent-based chemotherapy was associated with a better rate than anthracyclines alone (p=0.049).¹⁴ In the other study, 31 patients with metastatic phyllodes tumours received systemic therapy.¹³ Median OS was 10.7 months (95% CI: 8.67, 16.5). Adriamycin/ifosfamide therapy had a progression-free survival (PFS) of 9.10 months (95% CI: 5.03, 14.2), other ifosfamide regimens had a PFS of 5.10 months (95% CI: 0.67, 12.1), other anthracycline regimens had a PFS of 3.65 months (95% CI: 1.17, 7.90), gemcitabine-based regimens had a PFS of 2.80 months (95% CI: 1.83, 4.60), and finally other regimens had a PFS of 1.67 months (95% CI: 1.13, 7.77).

Treatment Algorithm: Phyllodes Tumour Management



Notes:

*Mastectomy indicated for patients with a large tumour-to-breast volume.

#Axillary node dissection recommended if biopsy proven node positive.

^βIf patient has had mastectomy, chest wall exam without breast imaging recommended.

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Development and Revision History

This guideline was reviewed and endorsed by the Alberta Provincial Breast and Sarcoma Tumour Teams. Members include surgical oncologists, radiation oncologists, medical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Breast and Sarcoma Tumour Teams and a methodologist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Resource Unit Handbook](#).

This guideline was originally developed in June 2022.

Levels of Evidence

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small, randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinion

Strength of Recommendations

A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally, not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Maintenance

A formal review of the guideline will be conducted in 2025. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

AHS, Alberta Health Services; BCS, breast conserving surgery, CI, confidence interval; CT, computed tomography; DFS, disease-free survival; DM, distant metastasis; DSS, disease-specific survival; HR, hazard ratio; LR, local recurrence; LRR, local recurrence rate; NCCN, National Comprehensive Cancer Network; OR, odds ratio; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; RR, relative risk; RT, radiotherapy; SEER, Surveillance, Epidemiology, and End Results; US, ultrasound; WHO, World Health Organization

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Breast and Sarcoma Tumour Teams and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest Statements

Ericka Wiebe (guideline lead) has nothing to disclose.

Antoine Bouchard-Fortier has nothing to disclose.

Xiaolan Feng reports involvement in CCTG sarcoma IND committee.

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