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ORIGINAL ARTICLE – BREAST ONCOLOGY

Long-Term Outcomes After Surgical Treatment of Malignant/ Borderline Phyllodes Tumors of the Breast

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Journal Club 6/2/20

Learning Objectives

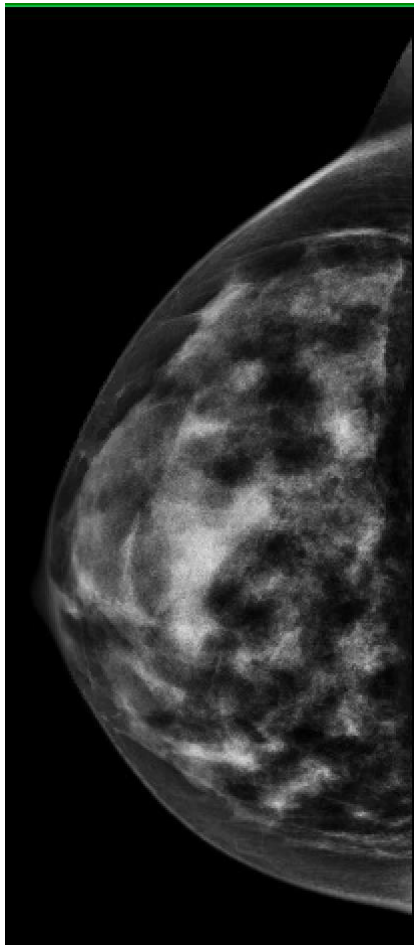
By the end of this journal club, participants will be able to:

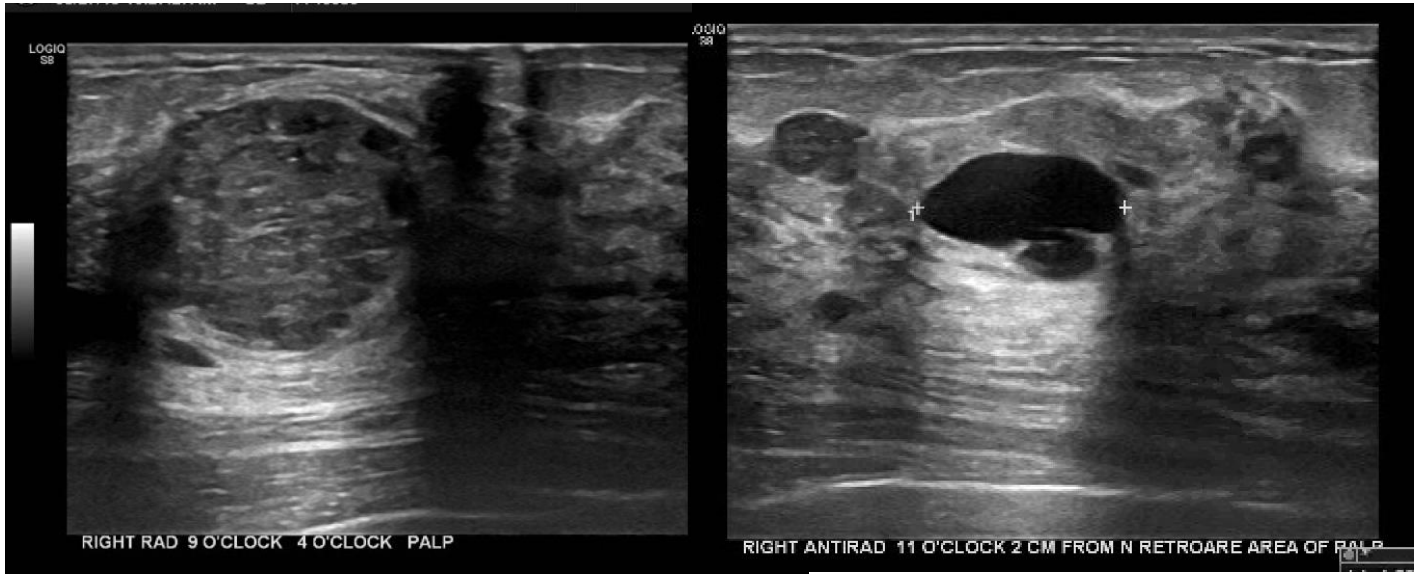
1. List the WHO-classified types of fibroepithelial lesions
2. Understand differences between benign, borderline and malignant Phyllodes tumor (PT)
3. Identify high risk features of a pathology report for PT
4. Know risk factors for distant recurrence (DR) for PT
5. List treatment options for women with PT

Module Outline

I. **Case**
II. Background
III. Article Overview
IV. Clinical Questions
V. Key Points

UNC Case: 40 yo female presents for diagnostic workup for right breast mass at the 9:00 position





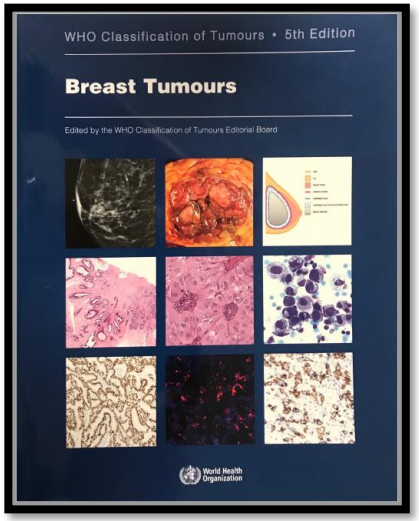
1. What is your differential diagnosis for palpable breast mass in 40yo F?
2. What is your impression of the mammogram? the US?
3. Possible next steps?

Case – Pathology Report

- Underwent **excisional biopsy**
- Diagnosis: **Phyllodes tumor**
  - Histologically ***borderline,*** 4 cm, located at anterior, posterior, superior and lateral inked margins, and < 1 mm from anterior, medial and inferior inked ***margins.***
  - Atypical ductal ***hyperplasia*** (ADH) and columnar cell changes with ***atypia***, both involving the phyllodes tumor.
  - Fibrocystic and fibroadenomatoid changes associated with calcifications.
  - Pseudoangiomatous ***stromal hyperplasia***

    Note: The tumor is composed of ***hypercellular stroma*** and benign epithelium in a pattern typical of phyllodes tumor. The tumor exhibits a ***mild mitotic rate*** and ***moderate cytologic atypia*** with ***infiltrative borders***; stromal overgrowth and necrosis are not identified.

Case – WHO Fibroepithelial lesions



- WHO classifies all tumors in monographs “blue books”
- WHO Breast new edition published end 2019
- Fibroadenoma, Fibroepithelial lesion, Benign Phyllodes, Borderline Phyllodes, Malignant Phyllodes
- This distinction is very important (based on histopath) because FA is the most common solid breast mass in patients of all ages *esp in young pts*

Case – Questions to Consider

- What makes this a histologically ***Borderline*** PT vs a ***Malignant*** or benign PT?
- What histological features in this report are most worrisome?
- What is our patient's chance for local recurrence or distant metastases?
- If further surgical intervention is discussed, what would be the next best step?
  - Close follow up with mamo or US?
  - Re-excision partial mastectomy?
  - Nipple sparing mastectomy?
  - Radical Mastectomy?

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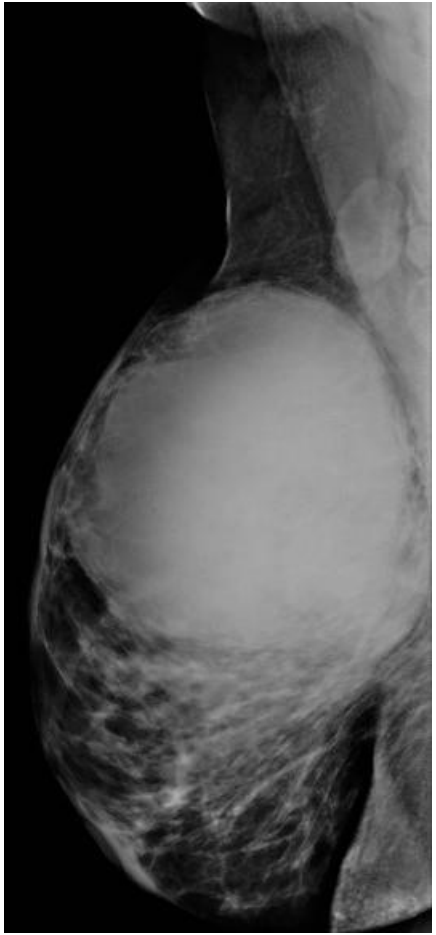
Background on the Phyllodes Tumor

What is a Phyllodes tumor?

- **Sarcoma** (tumor of the soft tissues or bone)
  - Specifically fibroepithelial
- **Rare** – 2.1 per 1,000,000 women
- **Usually Benign** – 35% -64%.
  - borderline/malignant
- **Demographics –** Most common in 6th decade of life

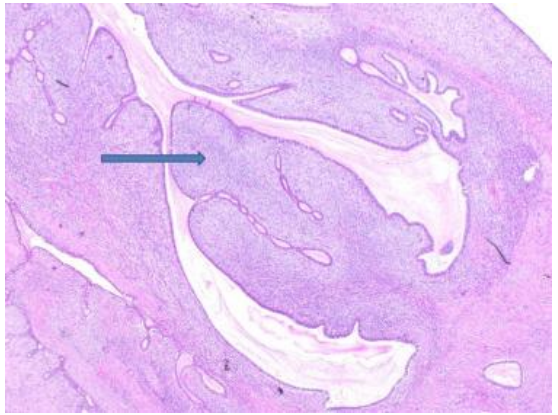
Presentation

- Rapidly Growing Breast Mass
- Size from 1 cm – 20 cm
- Well circumscribed or lobulated on MG imaging
  - Usually heterogeneous mass on US



Pathology

- **Gross Exam:** firm, circumscribed, grey/white color
- **H&E: cystic spaces** with characteristic **leaf-life** projections
- **Benign Characteristics**
  - Mild to moderate hypercellular stroma
  - Normal (ish) cytologic atypia
  - Few mitoses
- **Malignant Characteristics**
  - Very hypercellular
  - Easily identifiable pleomorphisms
  - Abundant mitoses (>10/high power field)
  - Stromal Overgrowth
  - **Difference between malignant and borderline?**



Clinical Treatment and Outcome

- **Benign:** Local Resection
  - Small risk of local recurrence
- **Malignant:** Greater risk of local recurrence and Distant Mets
  - **Treatment:** BCS or mastectomy
  - **Adjuvant chemo? Radiation?**
  - **Prognosis:** not well defined
- **Current Issues of Malignant PT**
  - Rare - limited clinical data of malignant cases
  - Factors associated with recurrence or metastasis
  - Defining characteristics of malignant vs borderline

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Article Nuts and Bolts

Purpose: A study of malignant/borderline PTs to evaluate recurrence rates and survival, and to identify factors associated with local and distant failure

Journal: Annals of Surgical Oncology. 2019

Study Type: Retrospective review of cases at the Memorial Sloan Kettering Cancer Center between 1957 – 2017

Number of Cases: 124 patients with definitive surgery

Data: Pathology slides re-reviewed by breast pathologists (43 of 125 cases) otherwise based on original path report

Borderline
vs
Malignant

KEY ELEMENTS

1. Stromal Cellularity
2. Stromal Overgrowth
3. Tumor Border
4. Mitoses
5. Necrosis

Stromal Cellularity: areas of densely overlapping stromal nuclei – marked, moderate or mild

Stromal Overgrowth: presence of stroma without epithelium in at least one low power field

Tumor Border: infiltrative (invasion noted) vs circumscribed/pushing vs no displacement

Mitoses: stratified according to a cutoff of 10 or more mitoses per 10 high powered field

Necrosis: Presence of ghosts of tumor cells retaining phyllodes architecture within tumor

Material and Methods Continued

- Clinical Metrics – Utilizing Survival Curve
  - Distant Recurrence free survival (DRFS): Kaplan-Meier Method
  - Disease Specific Survival (DSS): Time from surgery to overall death from disease
  - Overall Survival (OS), Local Recurrence (LR), Distant Disease

- Uniformly Poor Pathologic Features
  - Marked stromal cellularity, stromal overgrowth, infiltrative borders and 10 mitoses or more per 10 hpf

TABLE 1 Clinicopathologic characteristics of the study cohort stratified by histology

Characteristic	Total (n = 125)	Malignant (n = 86)	Borderline (n = 39)	p value
Median age: years (range)	44 (13–83)	43 (13–83)	44 (14–77)	0.8
Median pathologic tumor size: cm (range)	5 (0.9–35)	5.3 (0.9–35)	3 (0.9–22)	< 0.001
Stromal cellularity[a], n (%)				< 0.001
Mild/moderate	37 (30)	16 (19)	21 (54)	
Marked	70 (56)	55 (64)	15 (39)	
Stromal overgrowth[a], n (%)				0.001
No	58 (46)	31 (36)	27 (69)	
Yes	45 (36)	38 (44)	7 (18)	
Borders[a], n (%)				0.006
Circumscribed/pushing	43 (34)	23 (27)	20 (51)	
Infiltrative	68 (54)	54 (63)	14 (36)	
Mitosis[a], n (%)				< 0.001
< 10	53 (42)	24 (28)	29 (74)	
≥ 10	48 (38)	44 (51)	4 (10)	
Necrosis[a], n (%)				0.03
No	93 (74)	58 (67)	35 (90)	
Yes	19 (15)	17 (20)	2 (5)	
Uniformly poor pathologic features[a], n (%)				< 0.001
No	67 (54)	38 (44)	29 (74)	
Yes	25 (20)	25 (29)*	0 (0)	
Surgery, n (%)				0.003
Breast-conserving surgery	71 (57)	41 (48)	30 (77)	
Mastectomy	54 (43)	45 (52) *	9 (23)	
Final margin, n (%)				0.09
Negative	109 (87)	78 (91)	31 (79)	
Close/positive	16 (13)	8 (9)	8 (21)	

[a]Unknown, stromal cellularity (n = 18), stromal overgrowth (n = 22), borders (n = 14), mitosis (n = 24), necrosis (n = 13), uniformly poor pathologic features (n = 33)

TABLE 2 Factors associated with locoregional recurrence

Characteristic	10-year LRR cumulative incidence % (95% CI)	HR (95% CI)	*p* value
Age (years)			0.02 *
< 40	21 (7–33)	1.00	
≥ 40	7 (1–13)	0.3 (0.1–0.89)	
Histology			0.87
Borderline	11 (0–21)	1.00	
Malignant	13 (5–21) *	0.91 (0.31–2.72)	
Stromal cellularity			0.25
Mild/moderate	8 (0–17)	1.00	
Marked	17 (6–26)	2.11 (0.58–7.67)	
Stromal overgrowth			0.79
No	11 (2–19)	1.00	
Yes	13 (0–24)	0.84 (0.25–2.9)	
Borders			0.55
Circumscribed/pushing	15 (3–26)	1.00	
Infiltrative	13 (3–22)	0.73 (0.26–2.08)	
Mitosis			0.93
< 10	12 (3–21)	1.00	
≥ 10	15 (1–27)	1.06 (0.33–3.35)	
Necrosis			0.47
No	12 (5–19)	1.00	
Yes	32 (0–62)	1.75 (0.38–8.13)	
Surgery			0.11
Breast-conserving surgery	16 (6–24)	1.00	
Mastectomy	8 (0–16)	0.37 (0.1–1.31)	
Final margin			0.001 *
Negative	9 (3–15)	1.00	
Close/positive	33 (5–53)	4.97 (1.66–14.88)	

LRR, locoregional recurrence; CI, confidence interval; HR, hazard ratio

Results – Distant Mets and Survival

- Of the 124 patients, 7 developed distant disease, 6 within 5 years of surgery.
  - Two of the seven distant recurrences (DRs) were preceded by an LR
- DR occurred ***only*** in patients whose tumors had ***uniformly poor pathologic features***
  - Six of the seven patients with distant disease died of their disease a median of 5 months (range, 1–10 months) after diagnosis of metastasis.

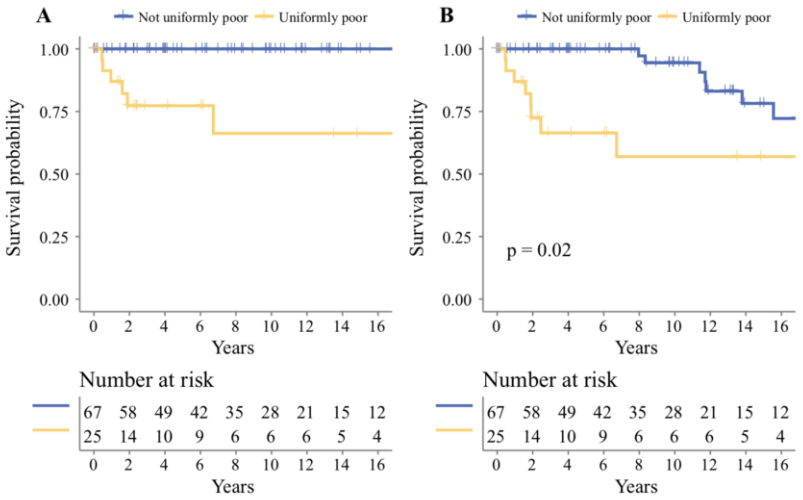

FIG. 3 **a** Disease-specific survival and **b** overall survival by pathologic features

Discussion – Local Recurrence (LR)

- 10-year incidence of LRR was 12% and ***did not vary*** between tumors classified as ***borderline vs malignant***
  - individual histologic characteristics were not important predictors of local failure.
- LRR incidence was significantly higher for the patients younger than 40 years of age and for those with close/positive final surgical margins.
  - Authors do not suggest that these patients warrant more aggressive management other than obtaining negative surgical margins.
  - Continued surveillance with annual breast imaging
  - the ***ideal negative margin width after excision of PT has yet to be defined***
- ***Margin of at least 1 mm*** after BCS or mastectomy was associated with a significantly lower 10-year risk of LR
- ***No significant reduction in LR with mastectomy***, which potentially has the widest negative margin that can be obtained, compared with BCS

Discussion – Distant Recurrence

- DRs ***only*** occurred in patients with malignant PT whose tumors had uniformly poor pathologic features
  - The majority (80%) of the patients with malignant/borderline PT did not have uniformly poor histologic features
  - predicted a poor prognosis: 10-year DSS of 63% and a 10-year OS of 57%.
- Authors suggests that the difference in prognosis observed between patients with and without uniformly poor features show that ***current classification system may be inadequate*** for prognostication
  - Idea: only tumors with ***uniformly poor features*** are considered ‘‘malignant’’ given their significant metastatic potential
- No systemic therapy regimen that is known to improve outcome in patients with malignant PT.

Hold On!

- Single Academic Institution
  - External Validity?
- Retrospective
  - In addition to small sample size and even smaller sample of malignant PT with uniformly poor features
- Difference in grading schemes over ***five decades***
  - Some pathology slides were unable to be rereviewed for this study
  - only one-third of pathology slides were available for re-review

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Clinical Questions

- At UNC – how do we define Malignant PTs?
- Do these data sway your thought process of malignant vs borderline vs benign PTs considering some of the limitations (ie small sample size)?
- At UNC – What is the standard surgical recommendation for PTs? (BCS vs Mastectomy)
- The article states that “The ideal negative margin width has yet to be defined”. What margins at UNC are acceptable?

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Key Points

- Obtaining negative margins is critical for reducing risk of local recurrence
- Distant recurrence (those with highest mortality risk) occurred in patients with malignant PT whose tumors had uniformly poor pathologic features
- Young age does not mandate mastectomy for patients with malignant/border- line PT (no difference between mastectomy vs BCS). However these patients should be monitored closely
- Further study needed for better classification and treatment of these malignant tumors.

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