EVALUATION OF A PALPABLE BREAST MASS
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Week 5

Educational Objectives:

1. Recognize history and physical exam findings that may increase risk for breast malignancy in a patient presenting with a palpable breast mass
2. Generate a differential diagnosis for a palpable breast mass
3. Compare and contrast indications for breast imaging and tissue biopsy for the evaluation of breast masses

CASE ONE:

Ms. B is a 25-year-old woman seeing you with a two-month history of a palpable breast mass that she detected after experiencing right breast tenderness. She is otherwise healthy, takes a progestin-only oral contraceptive pill, and has no family history of cancer.

Questions:

1. What aspects of her history are helpful in assessing the risk of her breast mass being malignant?

Breast cancer remains the most prevalent malignancy in women (CDC, 2019). When detected by patients, breast masses can cause significant distress, and make up 40% of office visits for breast-related concerns in women ages 40-70 (Wood, 2016). Approximately 10% of breast masses are found to be malignant after evaluation (Pearlman, 2011). A thorough history, followed by a careful physical exam, can help identify patients at higher risk for breast malignancy and inform patient counseling and management.

Initial history should inquire about the patient’s breast mass itself, including chronicity of the mass and how it was first detected; changes in size; any associated symptoms like pain, bloody nipple discharge, or skin changes; and if the mass seems to fluctuate with menstruation. Most masses detected by patients are benign. However, a chronic, slowly enlarging, non-tender mass that does not fluctuate with menses, or a mass detected with bloody nipple discharge or skin dimpling is more concerning for malignancy (Salzman, 2019).

When taking a history from patients presenting with breast mass, it is also important to ask about risk factors for breast malignancy, which can be categorized as reproductive, genetic, or exposure risk factors (Table 1 from the Pearlman article).
Reproductive Factors:

- Factors that increase length of estrogen exposure have been associated with an increased risk of breast cancer, these include: early age of menarche (less than 11 years old), late onset menopause, nulliparity, onset of first pregnancy after age 35, and long-term estrogen hormone therapy.
- Conversely, factors that interrupt estrogen exposure are protective against breast cancer: multiparity, breastfeeding for more than three months, and early menopause (less than 40 years old).

Genetic Factors:

- The relative risk of breast cancer in women who have one or more first-degree relatives with breast cancer is 1.5-6.9. The lifetime risk of breast cancer is 17.5% for women with a sister and mother with breast cancer.
- Women with a family history of BRCA gene mutations have 40-85% lifetime risk of developing breast cancer. Certain ethnic populations have higher prevalence of BRCA gene mutations. In Ashkenazi men and women, 1 in 40 carry a BRCA gene mutation (as compared to roughly 1 in 900 in the general population) and 10% of Ashkenazi women with breast cancer have a BRCA mutation (NCI, 2018).

Exposure Factors:

- History of high-dose thoracic radiation confers a relative risk of 55.5 for breast cancer.
- Observational studies suggest that women actively using combination oral contraceptive pills had a relative risk for developing breast cancer of 1.24 compared to women not using combined OCPs. This higher risk in combination OCP users did not increase with duration of use; additionally, risk increase was no longer evident with 10 years of use (Collaborative Group on Hormonal Factors in Breast Cancer, 1996).

Additional factors to consider are the patient’s age and prior history of breast lesions. Breast cancer is rare before age 20; incidence rises significantly for women starting in their 50s and 60s and increases with increasing age. Prior non-proliferative lesions like simple cysts confer no increase in risk of breast cancer. Proliferative lesions without atypia like fibroadenomas and intraductal papillomas confer a relative risk of 1.3-1.9 for future breast cancer risk. Atypical ductal or lobular hyperplasia confers a relative risk of 4-5 for future breast cancer (Pearlman, 2011).

Risk calculators are available to quantify a patient’s breast cancer risk. The Gail Model is a commonly-used risk model that calculates a five-year and lifetime risk of breast cancer based upon the patient’s genetic and reproductive risk factors. It has only been validated for women over the age of 35 (Constantino, 1999). The Gail risk assessment tool can be accessed via the National Cancer Institute (NCI) https://bcrisktool.cancer.gov/.
2. What should you look for on physical exam in a patient presenting with concerns for a breast mass?

A careful clinical breast examination (CBE), including visual and manual evaluation, is essential when assessing breast masses. The only factor that correlates with increased sensitivity of the CBE is duration of the exam of at least three minutes per breast (Salzman, 2019). Breast tissue tends to be most nodular at the end of the menstrual cycle; the best time to perform a clinical breast exam is approximately one week after the end of menses. The CBE is composed of visual inspection, palpation of breast tissue, and assessment for lymphadenopathy (Pearlman, 2011):

- Visual inspection should be conducted with the patient sitting both upright and leaning forward with hands on waist, and includes assessment of breast size and symmetry, as well as presence of skin changes such as erythema, dimpling, nipple inversion, or edema (\textit{p\'eau d\'orange}).

- Palpation of the breast should be conducted with the patient supine, with the ipsilateral arm extended, hand behind her head. While no one technique of palpation has been proven superior to another in terms of cancer detection rates, JAMA Rational Clinical Exam recommends using the vertical strip (lawnmower) method for more thorough coverage of breast tissue compared to circular or radial methods. Palpation of the superficial, intermediate, and deep tissues should be performed using the pads of the fingertips in a circular motion (Barton, 1999). If a palpable area of concern is detected, the examiner should note the size, tissue consistency, and mobility of the mass, as well as any associated pain or nipple discharge on palpation.

- The examiner should conduct a careful assessment for axillary, supraclavicular, or infraclavicular lymphadenopathy.

In general, benign masses tend to be small in size (< 2cm), mobile, with smooth, well demarcated borders. Masses with ill-demarcated borders, those that are hard, immobile, associated with skin dimpling, nipple discharge, or new nipple retraction should increase suspicion for malignancy (Pearlman, 2011).

While history and exam can help suggest benign versus malignant etiologies of breast masses, keep in mind that history and CBE alone have poor predictive value for breast cancer - CBE has a sensitivity of 49-69% and specificity of 86-99% (Salzman, 2019). Young age, absence of breast cancer risk factors, and probable “benign” characterization of breast masses should not end your evaluation.
CASE ONE CONTINUED:

Ms. B does not recall any changes in the appearance of her breasts associated with the mass, and the mass does not seem to fluctuate with her menses. She has no prior history of breast lesions or prior breast imaging. Menarche occurred at age 13. She has never been pregnant. She has no family history of breast cancer. On physical exam, she has a 1cm, well circumscribed, firm, mobile mass at the 2 o’clock position, 3cm from the areolar rim in the right breast without any skin changes or expressed nipple discharge.

3. What is the differential diagnosis for a palpable breast mass?

The differential diagnosis of a palpable breast mass can be categorized into benign or malignant etiologies (Pearlman, 2011; Sabel, 2017).

Benign Lesions – The three most common etiologies of benign breast masses are cysts, fibroadenomas, and fibrocystic changes.

- Cyst – A cyst is a fluid-filled mass that originates from the terminal duct lobule unit. Cysts range from microscopic in size to clinically palpable masses. Simple cysts have no internal septations and are almost always benign (Pearlman, 2011).
- Fibroadenoma – Fibroadenomas arise from terminal duct-lobular unit epithelial and stromal tissue. They are the most common etiology of breast masses in adolescents and young women. Median age of onset is around 25-30 years of age. Fibroadenomas are solid masses typically located in the upper outer quadrants of the breast, and are described as 1-2 cm round, firm, well-circumscribed, mobile, non-tender masses. Fibroadenomas may be clinically difficult to discern from cysts based upon exam alone (Pearlman 2011; Pruthi, 2001).
- Fibrocystic changes – Common in women in their 20s-30s, fibrocystic change is described as glandular, often non-discrete thickened tissue in the upper outer quadrants of the breasts. They can be associated with breast pain or tenderness that fluctuates with the menstrual cycle (Pearlman, 2011). Breast involvement is often bilateral, but can be asymmetrical or unilateral (Pruthi, 2001).
- Phyllodes tumors – Uncommon breast masses that typically present in women between 30-50 years of age as a single rapidly enlarging breast mass with consistency like fibroadenomas. Due to their rapid growth, they can sometimes cause stretching of the overlying skin (Pearlman, 2011).
- Breast abscess – Abscesses typically present in women who are nursing. These masses can be associated with erythema, pain, and purulent drainage (Sabel, 2017).
- Galactoceles – These masses are typically found in women who are nursing. They are caused by milk-filled cysts that form as a result of occluded milk ducts (Sabel, 2017).
- Fat necrosis – Rare etiology of breast mass, typically associated with trauma (Sabel, 2017).
**Malignant lesions** – Infiltrating ductal breast carcinoma is the most common breast cancer, accounting for up to 80% of invasive breast cancers. Other malignant etiologies of breast masses include infiltrating lobular carcinoma. Non-invasive cancers such as ductal carcinoma in situ can also present as a palpable breast mass (Sable, 2017).

4. **What imaging tests are available for the evaluation of a palpable breast mass and which would you pursue in this patient?**

Any patient with an identified dominant breast mass or area of concern on breast exam should be referred for breast imaging. Breast imaging reports are accompanied by a Breast Imaging Reporting and Data System (BI-RADS) categorization: BI-RADS 0 = Incomplete study with additional imaging needed; BI-RADS 1 = Negative findings; BI-RADS 2 = Benign findings; BI-RADS 3 = Probably benign (<2% risk of cancer); BI-RADS 4 = Suspicious abnormality (23-34% risk of cancer); BI-RADS 5 = Highly suggestive of malignancy (> 95% risk) (Salzman, 2019).

**Mammogram**: Diagnostic mammography ($218 for bilateral imaging, Healthcare Bluebook) is the first-line imaging choice for women over age 30 presenting with palpable breast masses. Diagnostic mammography should also be ordered for women of ANY age with history or physical exam findings highly suspicious for breast malignancy. Mammograms can identify soft tissue masses, as well as micro calcifications. Mammography has diagnostic accuracy of up to 78% (Salzman, 2019), with sensitivity around 86-91% (ACR, 2017). Of note, 10-15% of breast masses are NOT seen on mammogram alone (Wood, 2016), reinforcing the importance of performing a thorough clinical exam and additional imaging, like ultrasound.

**Ultrasound**: Breast ultrasound ($162, Healthcare Bluebook) is recommended as first-line imaging for women under age 30 presenting with breast masses, due to higher prevalence of dense breast tissue in younger women that decreases the sensitivity of mammograms (Salzman, 2019). Ultrasound effectively discriminates cystic versus solid masses and is superior in detecting benign palpable masses when compared to mammography (97% accuracy in the U.S. versus 87% for mammography) (Klein, 2005). Ultrasound can also identify lesions that are not detected on mammogram. In women over age 30 with palpable breast masses, ultrasound is performed for palpable breast masses with an incomplete or negative mammogram (Bi-Rads 0-1), and mammogram findings equivocal for benign process (BI-RADS 3). Therefore, ultrasound is typically ordered concurrently with diagnostic mammograms (Salzman 2019; ACR, 2017).

**Breast MRI**: Due to higher cost ($1,490 for bilateral imaging, Healthcare Bluebook) and lower specificity (40-70% based upon studies) compared to mammography, breast MRI is not recommended for evaluation of palpable breast masses in most women. Indications for MRI may include prior lumpectomy where MRI can differentiate between malignancy or prior procedural scarring, or in women who have received thoracic radiation when they were between the ages of 10-30 (ACR, 2017).
Women over the age of 30 should start with a bilateral diagnostic mammogram. Depending on mammogram results, she may also benefit from concurrent breast ultrasound to further characterize any focal lesions. Women with mammograms within the last three to six months may start with ultrasound of the breast (Salzman, 2019).

Our patient is under 30 years of age with benign findings on exam. Therefore, she should start with bilateral breast ultrasound.

CASE ONE CONTINUED:

| Breast ultrasonography shows a BI-RADS 2 lesion: a well-circumscribed hypodensity without septations corresponding to the area of the palpated mass, consistent with a simple cyst. |

5. **What is the next step in management for this patient?**

Simple breast cysts do not require further management as they are almost always benign in nature. Patients may elect for aspiration if they find the cyst symptomatic or bothersome. Aspirated cyst fluid that is clear, serous, or green is not concerning for malignancy. Aspirated fluid that is bloody is concerning for malignancy, and the patient should be referred for further tissue sampling (Pearlman, 2011).

CASE TWO:

| Ms. C is a 36-year-old Caucasian woman presenting to establish care in your office. Her main concern is a left-sided breast lump. She first noticed the lump incidentally while showering about eight months ago and is concerned as it seems to have increased in size in the ensuing months. The size of the lump does not seem to fluctuate with menses and it is not tender or painful. She has no significant past medical history. She takes no medications. She does not smoke or drink alcohol. She is of Ashkenazi Jewish decent. Her mother had breast cancer diagnosed at age 60, and one sister with breast cancer diagnosed at age 40. Her family members have not been tested for BRCA mutations. Ms. C reports no prior history of breast lesions or prior breast imaging. Menarche occurred at age 13. She has never been pregnant. On physical exam, the breasts are symmetrical. She has a firm, 3cm discrete, non-tender, mobile mass that is palpated in the outer, upper quadrant of the left breast at ~10 o’clock, 2cm from the areolar edge. There is a small area of skin dimpling over the mass. She has no nipple drainage. No cervical, supraclavicular, or axillary lymph nodes are appreciated. Ms. C undergoes bilateral diagnostic mammogram which shows a BI-RADS 3 lesion in her left breast. Ultrasonography is performed and is consistent with a BI-RADS 3 lesion. |
6. **What are the indications and options for breast tissue sampling? What would you recommend for our patient?**

Tissue sampling should be obtained if findings suspicious for malignancy are noted at ANY stage in the breast mass evaluation. Benign imaging findings should not preclude biopsy if the patient has highly suspicious findings on exam; any patient with BI-RADS 4 or 5 findings on imaging should undergo biopsy regardless of benign findings on exam (Salzman, 2019). Because biopsies cause changes in the breast tissue that can distort imaging findings, the American College of Radiology recommends obtaining breast imaging prior to biopsy (ACR, 2017).

There are three main sampling approaches to suspicious findings on exam or imaging:

**Fine needle aspiration (FNA) biopsy** – FNA biopsies ($266, Healthcare Bluebook) are minimally invasive using a small-bore needle. FNA can be performed in the office and is helpful in differentiating between cystic or solid masses. However, the diagnostic accuracy of FNA biopsies is heavily operator dependent and requires a cytopathologist with expertise in breast cytology. Furthermore, FNA cannot differentiate between in-situ versus invasive breast lesions, necessitating further biopsies if FNA is positive (Pearlman, 2011).

The combination of FNA with clinical breast exam and imaging studies is referred to as “the triple test.” Each component is given a score of 1-3 (1 = benign, 2 = suspicious, 3 = malignant). The clinical breast exam is scored 1 for a soft or firm, freely mobile mass; 2 for a mass with doubtful fixity to skin or breast tissue; and 3 for a hard, immobile mass adherent to breast tissue. If all three components of the triple test are consistent with benign breast disease, the diagnostic accuracy that the breast mass is benign is nearly 100%, and no further evaluation is needed (Morris, 2001).

**Core needle biopsy (CNB)** – Minimally invasive biopsy using a large-bore needle, typically performed with image guidance ($1,800 Healthcare Bluebook). CNB has been shown to have superior sensitivity and specificity compared with FNA (Salzman, 2019) and also preserves the architecture of breast tissue during pathology review. Core biopsies have low complication rates, cause less scarring, require shorter recovery time, and are less costly compared to surgical excision. As a result, CNB is the biopsy procedure of choice for most breast masses (ACR, 2017).

**Excisional biopsy** – Resection of the breast mass in its entirety ($3,068 Healthcare Bluebook). Due to larger surgical changes associated with excisional biopsies, these are reserved for lesions that are not amenable to core biopsies (e.g., location or presence of breast implants); lesions on core biopsy that require additional tissue to confirm benign etiology; if the core needle biopsy is non-diagnostic; or if the core needle biopsy shows normal tissue in a patient with clinical exam or imaging highly suspicious for malignancy (Pearlman, 2011).
Based upon the algorithm in Figure 1 of the Salzman article, with a BI-RADS 3 result on both mammogram and ultrasound, based upon imaging alone, Ms. C’s palpable breast mass has a less than 2% chance of being malignant. In patients with otherwise low clinical risk of breast cancer on history and exams, patients with BI-RADS 1 and 3 masses can be monitored with repeat imaging every six months for two years. Patients with otherwise low clinical risk of breast cancer and BI-RADS 2 results on imaging only require routine clinical follow-up.

However, Ms. C has several features in her history and exam that increase her risk of malignancy, including early menarche, nulliparity, two first degree relatives with breast cancer (conferring a 33.6% lifetime risk of breast cancer by the Gail model compared to 12.5% for an average 36-year-old woman). She also has skin dimpling on exam, a concerning finding for malignancy. Due to higher clinical concern for malignancy, the clinician should discuss with Ms. C the discordant findings on history and exam compared to her mammogram, and if she agrees, Ms. C should be referred for core needle biopsy.

**BONUS QUESTION:**

7. **Does Ms. C meet criteria for BRCA gene mutation testing?**

The USPSTF issued recommendations in 2019 that primary care clinicians screen women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer with a brief familial risk assessment tool, and if positive, refer patients for genetic counseling to discuss BRCA mutation testing. There are multiple validated risk assessment tools, including the Ontario Family History Assessment Tool, Pedigree Assessment Tool, International Breast Cancer Intervention Study – scoring systems can be found in the 2019 *JAMA* article by the USPSTF. Risk factors included in these tools include:

- Breast cancer diagnosis (personal or in a first-degree relative) before age 50 years
- Bilateral breast cancer
- Presence of both breast and ovarian cancer in one individual
- Male family members with breast cancer
- Multiple cases of breast cancer in the family
- One or more family members with two primary types of *BRCA*-related cancer (such as ovarian cancer)
- being of Ashkenazi Jewish decent

(Each risk factor is assigned a set of points, a total of more than 10 points yields a recommendation for referral to genetic counseling). Ms. C is of Ashkenazi Jewish decent, has multiple cases of breast cancer in first-degree relatives, one before age 50. She would meet criteria for referral to genetic counseling.
Primary References:

   https://www.aafp.org/afp/2019/0415/p505.html
   https://dx.doi.org/10.1097/AOG.0b013e3181ee9fc7

Additional References:

   https://bcrisktool.cancer.gov/
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Knowledge Questions:

1. Ms. A is a 28-year-old African-American woman presenting with an enlarging palpable right breast mass for the last year. Menarche was at age 13. She has no children. She takes no medications. She is adopted and unsure of her family history. Her breast exam is notable for a hard, 4 cm right breast mass at 10’clock that is somewhat mobile but associated with right axillary lymphadenopathy. What is the next best step in management?
   
   a. Fine needle aspiration
   b. Bilateral breast ultrasound
   c. Bilateral diagnostic mammogram and breast ultrasound
   d. Right diagnostic mammogram

2. Ms. W is a 40-year-old woman who recently had a diagnostic mammogram and ultrasound performed for a palpable mass in her left breast, with imaging most consistent with a simple cyst. Due to some discomfort, Ms. W chooses to have the cyst aspirated. The evacuated fluid is bloody. What is the next best step in management?
   
   a. No further interventions
   b. Repeat imaging every six months for two years
   c. Excisional biopsy
   d. Image-guided core needle biopsy

3. Which of the following clinical scenarios might warrant an MRI of the breast for evaluation of a palpable breast mass?
   
   a. Dense breast tissue
   b. History of lumpectomy
   c. Prior history of simple breast cyst
   d. Presence of breast implants
Answers:

1. c  Although the patient is younger than 30, she has findings on exam that are concerning for malignancy. Therefore, she should undergo both breast ultrasound and bilateral diagnostic mammography. Women younger than 30 with palpable breast mass should be evaluated with ultrasound due to higher prevalence of dense breasts. As discussed above, women of ANY age with a palpable breast mass and high risk of malignancy by history or exam should undergo diagnostic mammography.

2. d  Bloody fluid aspirated from a cyst is concerning and warrants further biopsy. When biopsy is required for a suspicious breast mass, image-guided core needle biopsy is first-line and preferred over excisional biopsy as it is less invasive and less costly.

3. b  MRI of the breast is typically not the first-line imaging modality in palpable breast mass evaluation but can be helpful in discerning between mass versus scar tissue in women with prior lumpectomy.