

## **Excerpts from the American College of Surgeons Educational Courses about Breast Disease:**

### **Gynecomastia**

Gynecomastia is a benign enlargement of the male breast that can be unilateral or bilateral. It typically presents as a retroareolar, rubbery, discoid-shaped mass which is in contrast to male breast cancer which usually presents as a firm, irregular, retroareolar mass that may be associated with some overlying nipple distortion or inversion. Cimetidine, marijuana, heroin, excessive alcohol, thiazide diuretics, HIV medication and benign prostatic hypertrophy medications such as Finasteride, can lead to gynecomastia. Anabolic steroid use can also lead to gynecomastia. Imaging studies aid in the diagnosis and a mammogram will demonstrate the classical flame sign associated with gynecomastia. Other causes are steroid use, Klinefelter syndrome, hydrochlorothiazide diuretics and liver disease. Definitive diagnosis can be made only cytologically or pathologically.

### **Nipple Sparing Mastectomy**

Breast cancer surgery has evolved from radical mastectomy to the viable option of preserving the entire skin envelope, including the nipple-areolar complex, in appropriate clinical scenarios. Nipple involvement can be found in up to 20% of mastectomy specimens. Yet multiple studies have now documented the appropriateness, viability, and the safety of the procedure.

Nipple sparing mastectomy is done in young, non-smoking, non-obese, non-diabetic, small breast size, minimal co-morbidities, small tumor more than 2-cm from the nipple, after neoadjuvant therapy, if above criteria are met. BRCA mutation carriers are candidates for nipple sparing mastectomy. Incising more than 30% of the nipple areola complex leads to a higher nipple necrosis rate. Nipple sparing mastectomy has superior cosmetic outcome to skin sparing mastectomy.

### **Fibroadenoma**

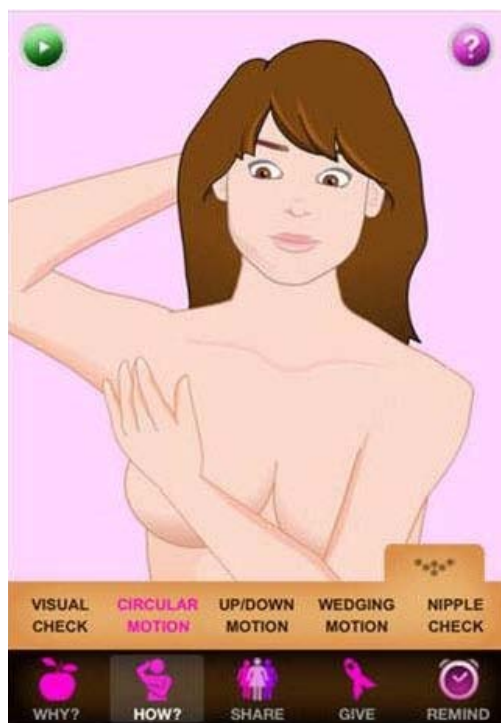
Fibroadenoma is the most common cause of a breast mass in young women. Fibroadenomas are benign and typically do not harbor cancer. Options for management of fibroadenomas, first and foremost, involve proving that it is a fibroadenoma (and not a malignancy), and this can only be done through a biopsy. A biopsy can be performed via fine needle aspiration, under palpation, core needle biopsy under ultrasound guidance, or excision. Excision is warranted if the mass increases in size, regardless of what the biopsy shows. Strong consideration of excision should be given to women of child-bearing age or those who cannot be compliant with follow-up surveillance. Core biopsy is the most accurate and appropriate way to evaluate new or changed findings on imaging that is suspicious. Pathology results from core biopsy dictate the need for further intervention. With some pathology entities, excision is warranted. Radial scar, papilloma and lesions containing atypical cells all warrant excision, because there is an approximately 10-15% upgrade rate to malignancy. Ductal hyperplasia without atypia does not require excision. Pseudoangiomatous stromal hyperplasia (PASH) is one of the most common benign causes of breast masses. The only reason for subsequent excision when pathology yields benign results would be if results were determined to be discordant with imaging findings.

### Atypical Ductal Hyperplasia (ADH)

Atypical Ductal Hyperplasia is a benign lesion of the breast that indicates an increased risk for breast cancer. It is characterized by cellular proliferation with architectural abnormalities.

If ADH is found on a core (needle) biopsy, it mandates a wider excision ( breast lumpectomy or surgical excisional biopsy) to exclude the presence of breast cancer. The conversion of an ADH on core biopsy to breast cancer on surgical excision, is approximately 30%.

Tamoxifen should be offered to patients with atypical ductal hyperplasia. It decreases the risk of breast cancer by 50%.



### Nipple Discharge

The most common cause of a new onset of nipple discharge is a papilloma which is responsible for approximately 85% of all cases. In 10-15% of patients, nipple discharge is a symptom of a new malignancy whether or not it is bloody. Duct excision is the single most reliable diagnostic test. An MRI can identify abnormalities causing nipple discharge, but it does not rule out malignancy or eliminate the need for surgery. A ductogram can provide a road map to the source of the discharge, identify filling defects, and determine concordance with other imaging findings, but it does not establish a pathology diagnosis or eliminate the need for surgery. Compared with cytological examination of nipple discharge fluid, duct lavage yields a more cellular specimen, but the reproducibility of duct lavage is poor and sensitivity for the detection is low. Interval follow-up is appropriate for patients with multiple duct nipple discharge who have no localized abnormality on physical examination or imaging or those with a history of nipple discharge that had either resolved or could not be confirmed. Nipple discharge is suspicious if spontaneous, recurrent, bloody or postmenopausal.

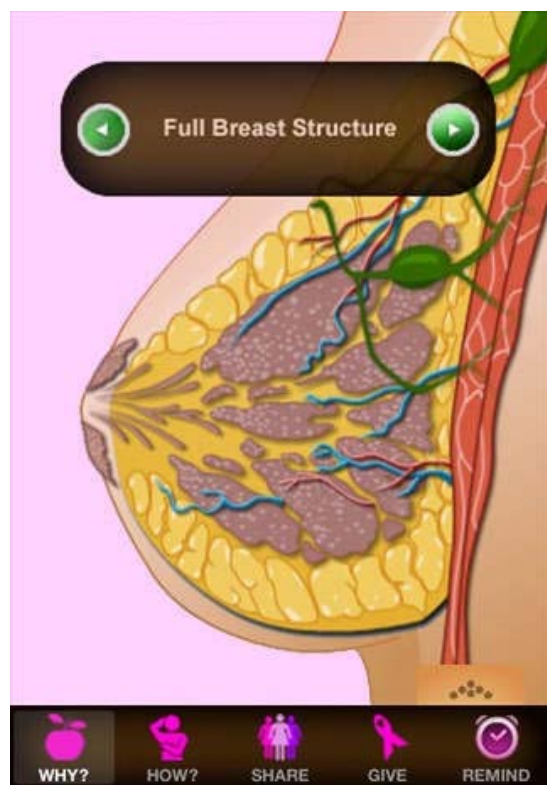
### Indications for Mastectomy

Mastectomy is indicated for large tumor to breast ratio, large area of ductal carcinoma in-situ, multi-centric\* breast cancer, inflammatory breast cancer, patients in first trimester of pregnancy and when radiation therapy is contraindicated or refused.

\*Multi-focal means 2 or more lesions within the same quadrant. Multi-centric means 2 or more lesions in different quadrants.

### Breast Pain

The source of breast pain is usually difficult to discern and can be multifactorial related to diet, medications or referred from other areas. Although most breast cancers are not associated with pain, it is important to rule out malignancy with new onset of symptoms. Mammogram (depending on age) and ultrasound evaluation along with history and physical examination should be performed. For most women with breast pain, reassurance alone is provided once appropriate imaging and examination reveals no suspicious findings. Dietary factors such as caffeine intake are associated with breast pain, and cessation of caffeine intake may reduce symptoms. Therefore, querying dietary habits is important. In older women chest pain of cardiac origin should be ruled out especially for women complaining of left breast pain. Excisional biopsy of a painful area is almost never appropriate with no suspicious findings on exam or imaging, because pain from healing and scars can exacerbate symptoms and the precise source of pain usually cannot be specifically identified.



### **Test Positive for BRCA Mutation**

Patients with BRCA mutations are at highest identifiable risk for developing breast cancer (60-80%). They are also at significantly higher risk of developing ovarian cancer (20-40%). For BRCA1 carriers, breast care options include surveillance with mammogram and MRI, with or without sonogram, versus bilateral risk reducing mastectomy. Nipple sparing mastectomy can be performed in appropriately selected patients because BRCA1 mutation carriers have an approximately 20-40% risk of ovarian cancer. Bilateral salpingo-oophorectomy (BSO) should be strongly considered by the age of 40. Ovarian cancer screening with pelvic sonogram and CA-125 is not reliable for early detection of malignancy, but is frequently performed with women before BSO. Tamoxifen is not appropriate for BRCA1 carriers because most cancers, approximately 75%, are triple negative. Tamoxifen can be considered for BRCA2 mutation carriers and can reduce the risk of breast cancer by 40-50%.

### **Indications for Breast MRI**

A breast MRI cancer screening is recommended in the following cases: known deleterious BRCA mutation carrier, BRCA1, BRCA2, first degree family member of BRCA mutation carrier who has not yet been tested, life-time risk of breast cancer at least 20% as determined by risk models such as BRCAPRO or other models (Gail, Tyler-Cuzick), radiation to the chest wall between the ages of 30 – 40 years, dense breasts, occult breast cancer in axilla, invasive lobular carcinoma because of the need to evaluate the contralateral breast, locally advanced breast cancer before and after neoadjuvant treatment and lobular carcinoma in-situ. MRI has shown to be of greatest value in those patients who present with axillary metastasis in an unknown primary tumor. Also, breast MRI is to be considered in some high risk situations to screen the contralateral breast.

### **Sentinel Node Biopsy**

Sentinel lymph node biopsy has replaced routine axillary node dissection as a standard of care in patients presenting with clinically negative axillary examination. Initially reserved for T1 and small T2 tumors, it is now widely applied with few exceptions, although important racial and social disparities persist in its use. For ductal carcinoma in-situ, sentinel lymph node biopsy is generally reserved for patients with extensive high grade disease in whom there is a greater risk of upstaging to invasive cancer, a mass is present, as well as those patients undergoing mastectomy where subsequent sentinel lymph node biopsy, if needed, may be compromised. Sentinel lymph node biopsy is reliable after neoadjuvant chemotherapy in women presenting with clinically lymph node negative disease. Sentinel lymph node biopsy is indicated in male breast cancer, multicentric multifocal disease, ductal carcinoma in-situ with invasion, mass or waiting for mastectomy. Sentinel lymph node biopsy is to be avoided in ductal carcinoma in-situ without invasion, in locally advanced breast cancer, inflammatory breast cancers and pregnant patients.

### Contraindications to Breast Conservation

Breast conservation surgery is absolutely contraindicated in women who present with inflammatory breast cancer because inflammatory breast cancer usually involves the breasts diffusely and the lymphatics, mastectomy (modified radical mastectomy) along with axillary dissection is recommended. Aside from inflammatory breast cancer, the primary setting in which lumpectomy is not recommended is patient preference. Otherwise, breast conservation can be considered regardless of tumor size, node status, presence of ductal carcinoma in-situ and bilateral disease, provided that negative margins can be obtained and good cosmesis can be achieved. These competing goals often make breast conservation surgery more difficult to accomplish in patients with larger tumors or extensive intraductal component, both of which may require removal of significant volume of breast tissue to achieve negative margins. Generally, multifocal disease is not a contraindication to breast conservation, although most surgeons favor mastectomy for involvement of more than one quadrant or for more than two sites of the disease. An absolute contraindication to radiation is known collagen vascular disease, and this may affect breast conservation surgery as an option.

### Guidelines for BRCA Testing

1. Two first degree relatives with breast cancer, one diagnosed younger than 50;
2. Three or more first and second degree relatives with breast cancer;
3. Combination of ovarian plus breast cancer in first and second degree relatives;
4. First degree relative with bilateral breast cancer;
5. Two or more first or second degree relatives with ovarian cancer;
6. History of breast cancer in male relative;
7. Women who are Ashkenazi Jewish plus one or second degree relative with breast or ovarian cancer.



### **Indications for Post Mastectomy Radiation Therapy (PMRT)**

- More than four positive lymph nodes
- Tumor larger than 5-cm
- T4 tumor
- Positive surgical margins
- Chest wall invasion
- Inflammatory breast cancer

### **21-Gene Recurrence Score(RS)**

It is a reverse transcription polymerase chain reaction assay that has both prognostic and predictive value for hormone receptor positive breast cancer. It has now been included in the National Comprehensive Cancer Network guidelines for determining treatment recommendations for hormone receptor positive node negative breast cancers. Although hormonal therapy confers a greater risk reduction than chemotherapy for all hormonally sensitive tumors, the benefit of chemotherapy is lowest in patients with low 21-Gene Recurrence Score. In NSABP B-20 which randomized women in early stage node negative hormone positive disease to Tamoxifen or Tamoxifen plus chemotherapy, there was a 28% absolute benefit from the addition of chemotherapy in women in the highest 21-Gene recurrence Score group (score equal or above 31) with little benefit seen in the low or intermediate score groups. Currently the most wide spread use of the recurrent score is in ER positive node negative patients to determine magnitude of chemotherapy benefit.

### **Breast Cancer in Pregnancy**

Breast cancer in pregnancy is uncommon. Treatment requires a complex multi-disciplinary approach that addresses many facets of healthcare to optimize outcomes for both mother and fetus. General principles of treatment should follow those of care for the non-pregnant patient. The care team must consist of higher risk obstetrics and psychological support staff as well as surgery, radiation oncology and medical oncology. Surgery, including the use of general anesthesia, is safe during all three trimesters. Sentinel node biopsy can be performed during pregnancy with radiotracer which has been shown to have low uterine exposure in dosimetry studies. As in the non-pregnant patient, sentinel node biopsy should not be performed in the setting of node positive disease. Use of vital blue dye is discouraged because of the small but serious risk of anaphylactic reactions. Lumpectomy is not contraindicated, although radiation must be delayed until after delivery to minimize the side effects of treatment to the fetus. Chemotherapy has also been used without increased morbidity to fetus after third trimester, although it is recommended to avoid Herceptin (Trastuzumab) and Methotrexate. Pregnancy associated breast cancer is associated with a higher risk of mortality thus treatment should not be withheld, but rather sequenced to best accommodate the pregnancy.

### **Male Breast Cancer**

Male breast cancer is rare with approximately 1,500 cases diagnosed in the United States each year. It accounts for less than 1% of all breast cancers, less than 1% of all newly diagnosed male cancers, and 0.2% of male cancer deaths. The incidence of male breast cancer is increasing with a 26% increase in the

United States between 1973 and 1998. Owing to the low incidence, treatment of breast cancer in men has been extrapolated from experience with women with breast cancer.

Breast cancer in men occurs at an older age than breast cancer in women. At diagnosis, men have a more advanced disease than women possibly owing to the lack of awareness. Men have a higher stage disease, larger tumor and more lymph node positive disease. The most common surgical treatment is mastectomy. Mastectomy remains the preferred treatment for male breast cancer given the central location of tumor, the size of the tumors in relation to breast size, and the paucity of breast tissue. Sentinel lymph node surgery is feasible and accurate in male breast cancer. The incidence of SLN positivity is higher in men than women. In men with a positive sentinel lymph node, the rate of additional positive non-sentinel lymph node is higher than women and the size of the largest lymph node metastasis is greater in men than in women. Pathologic status of the axillary node remains the strongest prognostic factor in male and female breast cancer. Post mastectomy radiotherapy has an important role in reducing the risk of local recurrence in cases with large tumor, positive lymph node and muscle involvement. Tamoxifen is the most widely used adjuvant therapy because it improves survival. Men have a higher rate of oxygen receptor positivity. Chemotherapy may be useful in node positive and locally advanced disease. The male breast contain only ductal tissue hence most male breast cancers are of the ductal type. No lobules in men. The remaining 10% are ductal carcinoma in-situ. Given the absence of terminal lobules in normal male breast, lobular carcinoma, invasive and in-situ is rarely seen. Approximately 80% are ER positive, 75% are progesterone receptor positive and 35% are HER-2/neu. The prevalence of male breast cancer increased with age with a mean age of 60-65 years at diagnosis. Risk factors include increasing age, radiation exposure and factors related to abnormality in estrogen and androgen imbalance including testicular disease, infertility, obesity and cirrhosis. Gynecomastia is not a risk factor. Risk factors related to a genetic predisposition include Klinefelter syndrome, family history and BRCA gene mutation, particularly BRCA2 mutation. Men with BRCA2 mutation and breast cancer are recommended not to pursue contralateral prophylactic mastectomy because contralateral breast cancer risk is low. Prognostic factors in male breast cancer are the same as in female breast cancer and include nodal involvement, tumor size, histologic grade and hormonal receptor status. When matched for age and stage, survival is similar to that in women. A poor prognosis is attributed to old age, axillary lymph node metastasis and negative hormonal receptors.

### **Neoadjuvant Chemotherapy for Breast Cancer**

Neoadjuvant chemotherapy is increasingly being used for patients with operable breast cancer. Ideally, neoadjuvant chemotherapy would be given to patients who have the highest likelihood for good response to neoadjuvant therapy. Patients who are most likely to have good clinical response to neoadjuvant chemotherapy are patients with ER negative disease, HER-2 positive disease, grade III disease, younger than 50 years and node positive disease. In addition, monitoring the clinical response of patients receiving neoadjuvant chemotherapy has shown that patients, who have initial good response to chemotherapy in the first one or two cycle, generally have a sustained response. Molecular genetic assays such as oncotypedX and MammoPrint, are genomic predictive essays. Oncotype DX is a 21 multi-gene essay used in patients with ER positive breast cancer and has been shown to predict response to neoadjuvant chemotherapy and benefit from chemotherapy. Sentinel lymph node surgery to stage the axilla can be performed after completion of neoadjuvant chemotherapy in patients with clinically negative axilla at presentation and has similar accuracy in the upfront setting. Patients undergoing neoadjuvant chemotherapy should have a clip placed in their tumor prior to the therapy. After the completion of neoadjuvant chemotherapy, if the patient is interested in breast conservation,

the surgical resection is focused around the residual disease and does not require resection of the whole initial tumor bed. Pathological complete response (pCR) means eradication of disease from breast and lymph nodes. Patients who achieve complete pathologic response have better survival than those with residual disease.

### **Accelerated Partial Breast Irradiation (APBI)**

The majority of breast tumor recurrences for women undergoing lumpectomy with whole breast radiation occur within the region of the lumpectomy bed and the surrounding 1-cm of tissue. Recurrences elsewhere in the breast are not common. Although breast conservation surgery remains a good option for many women with early stage breast cancer, many women are deterred from breast conservation due to limited access or availability of whole breast radiation. While breast radiation generally takes 3-6 weeks and affects patients in terms of time off from work, inconvenience, and cost of travel to and from a radiation facility. These effects have been shown to decrease patient compliance with adjuvant radiation recommendations.

Partial breast radiation involves treatment to the lumpectomy bed only and requires fewer treatments with higher dose of radiation, resulting in a decrease in the length of time committed to adjuvant radiation therapy. Patients who are currently suitable for partial breast radiation are patients who meet all of the following criteria:

- Older than 60 years with a tumor < 2-cm
- Margins negative by at least 2-mm
- Absence of lymphovascular invasion
- ER-positive tumor
- Unicentric invasive ductal breast cancer
- Node-negative disease.
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Patients with BRCA mutations and patients receiving neoadjuvant chemotherapy are not recommended for partial-breast-radiation.

### **Inflammatory Breast Cancer (IBC)**

Inflammatory breast cancer (IBC) is a rare but especially aggressive form of locally advanced breast cancer. IBC manifests with an erythematous, warm, edematous breast with peau d'orange. The clinical picture is often confused with cellulitis or mastitis and often may be treated initially with antibiotics, which leads to a delay to diagnosis. The presentation is due to involvement of the subdermal lymphatics with tumor emboli. The onset is clinically rapid with early distant dissemination. IBC is staged as T4c. Patients frequently have axillary node involvement at the time of the initial examination. However, nearly 7-% of patients with IBC will have disease localized to the breast and the axilla at the time of initial examination. Biopsy of the involved skin can help in the diagnosis. The first line of treatment is chemotherapy. If adequate response is seen, surgery is the next line of treatment, followed by comprehensive chest wall and nodal radiation. Patients without adequate response to chemotherapy receive an alternative chemotherapy regimen, and if still not candidate for surgical resection, preoperative radiation is considered. Surgical treatment for IBC is modified radical mastectomy. Surgery is contemplated only when it is anticipated that negative surgical margins can be achieved. There is no



role for attempted breast conservation or sentinel node in these cases because the subdermal lymphatics are partially obstructed, contain tumor emboli, and are functionally abnormal. The false-negative rate for sentinel lymph node biopsy for patient with IBC may be unacceptably high. Patients with IBC therefore require axillary lymph node dissection. Post mastectomy radiation is an important part of treatment and broad margins on the chest wall flaps are treated. Because survival of patients with IBC has improved with the addition and routine use of chemotherapy, local management has emerged as a critical component of curative management.