Fertility Preservation in Breast Cancer
Challenges for the Surgeon

Carol S. Connor, MD
Associate Professor of Surgery
University of Kansas Medical Center
Breast Cancer: Overall Incidence and Mortality

- Most common cancer in women (excluding skin cancer)
  » ~ 230,000 new invasive breast cancers per year

- 2nd most common cause of cancer death in women and the leading cause of cancer death in young women
  » ~ 40,000 deaths per year

- Over 2 million women are alive in the US with a history of breast cancer (over half diagnosed less than 10 years ago)
  » Importance of survivorship issues!

American Cancer Society Facts and Figures, 2011-2012
BREAST CANCER IN YOUNG WOMEN (Age < 35-40)

• YOUNG WOMEN ACCOUNT FOR A SMALL PERCENTAGE OF BREAST CANCER PATIENTS

  » ONLY 5% OF NEW BREAST CANCER PATIENTS ARE < AGE 40
    • ONLY 3% OF BREAST CANCER DEATHS OCCUR IN WOMEN < AGE 40

  » BUT…. THIS EQUALS ~ 11,000 YOUNG BREAST CANCER PATIENTS EACH YEAR
    • ~ 1100 BREAST CANCER DEATHS

American Cancer Society Facts and Figures, 2011-2012
SEER Program Public use CD-ROM. NCI, 2000
• “As part of education and informed consent before cancer therapy, oncologists should address the possibility of infertility with patients treated during their reproductive years.”

» BUT… LESS THAN 50% OF MEDICAL ONCOLOGISTS FOLLOW THESE GUIDELINES

» There is clearly room for improvement in the identification and referral of patients who may desire fertility preservation
WHAT IS THE ROLE OF THE SURGEON IN FERTILITY PRESERVATION?

- A SURGEON IS USUALLY THE FIRST CANCER SPECIALIST TO SEE A NEWLY DIAGNOSED BREAST CANCER PATIENT

- THIS INITIAL SURGICAL EVALUATION PROVIDES AN OPPORTUNITY FOR EARLY REFERRAL

- HOWEVER, THERE ARE MANY CHALLENGES TO SUCCESSFUL RECRUITMENT OF SURGEONS INTO THIS PROCESS
Fertility Preservation: Challenges for Surgeon

• Challenge #1:
  » Surgeon’s primary focus is treatment of the recently diagnosed breast cancer

• Challenge #2:
  » Surgeon already faces a complex treatment and referral algorithm at the initial visit

• Challenge #3:
  » Surgeon usually has a very limited understanding of fertility preservation

• Challenge #4:
  » Surgeon may lack an established referral system to facilitate a fertility consultation
CHALLENGE #1
SURGEON IS FOCUSED ON TREATMENT

• TREATMENT OF YOUNG WOMEN WITH BREAST CANCER OFTEN HAS A REAL SENSE OF URGENCY
  » YOUNG WOMEN WITH BREAST CANCER HAVE A LOWER SURVIVAL RATE THAN OLDER WOMEN
  » ATTRIBUTED IN PART TO PRESENTATION AT A LATER STAGE
    » 70% present with a palpable mass
    » 50% present with a mass greater than 2 cm (versus 35% in older women)
    » 40% node positive (versus 25% in older women)

• LARGER TUMORS AND POSITIVE AXILLARY NODES ARE ASSOCIATED WITH DECREASED SURVIVAL

American Cancer Society Facts and Figures 2011-2012
TUMOR BIOMARKERS: BREAST CANCER SUBTYPES

- BREAST CANCER SUBTYPES HAVE BEEN IDENTIFIED BASED UPON TUMOR MARKERS (ER, PR and Her2 neu or epidermal growth factor receptor 2)

- Hormone positive subtypes
  - **ER positive, Luminal A (~40%)**: Strongly ER and PR positive. Has the best prognosis
  - **ER positive, Luminal B (~20%)**: ER positive with unfavorable features--PR poor, Her2 positive or high Ki67. Remaining are hormone negative (worse prognosis than Luminal A)

- Hormone negative subtypes
  - **Her2 positive (~10-20%)**: ER negative, Her2 positive. Unfavorable prognosis, but significantly improved with targeted Herceptin therapy
  - **Basal Type or “triple negative” (~15-20%). Least favorable**

CHALLENGE #1
SURGEON IS FOCUSED ON TREATMENT

• YOUNG WOMEN MORE LIKELY TO HAVE UNFAVORABLE TUMOR BIOLOGY

  • Estrogen Receptor negative
  • Her 2 positive
  • Triple negative (negative ER, PR, and Her2)
  • Even if ER positive, more likely to have unfavorable features

• THESE UNFAVORABLE MARKERS ARE ALL ASSOCIATED WITH DECREASED SURVIVAL
CHALLENGE #1
SURGEON IS FOCUSED ON TREATMENT

• YOUNG WOMEN WITH BREAST CANCER ARE MORE LIKELY TO HAVE A BRCA MUTATION

  » Increases the risk of future breast cancer
    • Impacts surgical treatment: bilateral mastectomy often advised

  » Increases the risk of ovarian cancer
    • Prophylactic oophorectomy is advised as soon as childbearing is complete
CHALLENGE #1
SURGEON IS FOCUSED ON TREATMENT

• DUE TO LOCALLY ADVANCED TUMOR AND/OR AGGRESSIVE BIOLOGY
  » Most women under age 40 with invasive breast cancer will be advised to undergo chemotherapy
  » If hormone positive may also be advised to undergo extended antihormonal therapy

• SYSTEMIC THERAPY REDUCES BREAST CANCER RECURRENCE AND DEATH BY ~ 50%
  » BUT, CHEMOTHERAPY MAY REDUCE FERTILITY
    • Influenced by age of the patient and type chemotherapeutic agent
CHALLENGE #2: SURGEON IS FACED WITH COMPLEX MULTIDISCIPLINARY DECISION TREE

IDENTIFY MULTICENTRIC OR CONTRALATERAL DISEASE/POSSIBLE ADDITIONAL IMAGING/BIOPSIES

CONSULT FOR GENETIC TESTING

DETERMINE EXTENT OF LOCAL/REGIONAL DISEASE--CLINICAL EXAM; REVIEW OF IMAGING CONSULT RADIOLOGY

DETERMINE TUMOR BIOLOGY; Review pathology, tumor markers (hormone receptor status, Her2), grade, Ki67

Locally advanced disease (large tumor or positive axilla) or unfavorable biology

NO

DETERMINE AND PERFORM SURGICAL THERAPY

IF BCT, RADIATION ONCOLOGY CONSULT

IF MASTECTOMY: PLASTIC SURGERY CONSULT

PATIENT EDUCATION REGARDING DIAGNOSIS AND TREATMENT OPTIONS

Urgent Medical Oncology Consult

YES

Neoadjuvant therapy not advised

Neoadjuvant chemotherapy advised and completed
CHALLENGE #3: LIMITED UNDERSTANDING OF FERTILITY PRESERVATION

- The addition of fertility preservation to this initial surgical algorithm is complicated by the surgeon’s lack of knowledge regarding basic fertility issues. These include:
  
  » The options for Fertility Preservation in breast cancer patients
  » The impact of tumor biology and the timing of therapy on fertility preservation
  » The safety of ovarian stimulation in breast cancer patients
  » The safety of ovarian tissue harvest and transplantation
  » The safety of pregnancy after breast cancer
FERTILITY PRESERVATION OPTIONS IN BREAST CANCER

- **IVF with Embryo Cryopreservation**
  - Most established method and has the highest pregnancy rate
  - Requires ovarian stimulation followed by egg retrieval
  - Requires a partner or donor sperm

- **Oocyte Cryopreservation**
  - Also requires time for ovarian stimulation and egg retrieval, but does not require a partner

- **Ovarian tissue harvest**
  - May be only option if patient unable to undergo ovarian stimulation
  - Laparoscopic oophorectomy is done prior to initiation of chemotherapy and the ovarian tissue cryopreserved
  - Ovarian tissue later transplanted if needed
  - Pregnancy rates lower than embryo or oocyte freezing

- **Gonadotropin releasing hormone (GnRH) agonists during chemotherapy may be utilized to provide ovarian protection**
IMPACT OF TUMOR BIOLOGY AND TIMING OF THERAPY ON FERTILITY PRESERVATION?

» FAVORABLE HORMONE POSITIVE TUMOR, NO CHEMOTHERAPY
  
  • Fertility may still be impacted due to delayed pregnancy while on antihormonal therapy
  
  • Fertility Preservation Option: Controlled ovarian stimulation with embryo or oocyte cryopreservation after surgery and before initiation of antihormonal therapy

» CHEMOTHERAPY ADVISED: ADJUVANT
  
  • Fertility Preservation Option: Controlled ovarian stimulation in the interval between surgery and chemotherapy
    
    » With newer protocols, may be used in either ER negative or ER positive patients
    
    » Planning before surgery to allow timing of the COS is helpful
IMPACT OF TUMOR BIOLOGY AND TIMING OF THERAPY ON FERTILITY PRESERVATION?

- **CHEMOTHERAPY ADVISED: NEOADJUVANT**
  - Patients typically have locally advanced tumors and/or unfavorable biology
  - Fertility Preservation Options influenced by urgency of initiating chemotherapy. There may not be time for controlled ovarian stimulation
    - ...in Her 2 positive patients, medical oncologist may consider the use of Herceptin as a “bridge”, during controlled ovarian stimulation
    - Laparoscopic oophorectomy with ovarian tissue freezing may be the only option in these patients
WHAT IS THE SAFETY OF OVARIAN STIMULATION IN BREAST CANCER PATIENTS?

• Conventional ovarian stimulation protocols are contraindicated in breast cancer patients due to significant elevations in estradiol levels which could stimulate tumor growth.

• More recent ovarian stimulation protocols using letrozole provide endogenous estrogen levels comparable to a natural cycle with no known adverse impact on recurrence or survival.

• Reservations may still exist regarding ovarian stimulation in neoadjuvant patients with large intact hormone positive tumors.

J Clin Oncol 26; 2008
WHAT IS THE SAFETY OF OVARIAN TISSUE REIMPLANTATION?

» In the absence of systemic disease, occult ovarian metastases is rare in breast cancer patients
  • Ovarian metastases from breast cancer is most commonly associated with invasive lobular carcinoma, which is more common in older post-menopausal patients
  • Currently, no cancer has been reported secondary to transplanted ovarian grafts

» In BRCA patients, there is an additional concern of introducing ovarian cancer via the re-implanted tissue
  • Removal of the transplanted ovarian tissue is advised at the time of prophylactic oophorectomy.

Am, J Surg Pathol.33;2009
J Clin Oncol 26;2008
WHAT IS THE SAFETY OF PREGNANCY AFTER BREAST CANCER?

Available data supports the safety of pregnancy following breast cancer, but…

• Pregnancy is not advised until completion of antihormonal therapy (which may take 5-10 years)

• Even if the patient has a hormone negative tumor (and does not require antihormonal therapy) a two year delay before pregnancy is typically advised
Case presentation

- 29 yo female presented with a right breast mass on SBE
- The tumor involved the majority of the right breast (locally advanced)
- Core needle biopsy revealed a grade 3, hormone positive, Her 2 positive invasive ductal carcinoma with a high proliferation rate (biologically unfavorable)

- **Surgical consult first**
  - Referred by the surgeon to Medical Oncology for neoadjuvant therapy due to locally advanced, unfavorable disease
  - Referred by the surgeon to Reproductive Endocrinology for a fertility consult

- BRCA Testing done and positive for BRCA2 mutation
Case presentation

• Urgent initiation of chemotherapy was advised

• Oophorectomy with ovarian tissue cryopreservation advised by the reproductive endocrinologist
  » Laparoscopic oophorectomy with cryopreservation of one ovary performed prior to initiation of chemotherapy

• Neoadjuvant chemotherapy completed followed by Bilateral mastectomy/Right SLNB/radiation therapy/reconstruction.

• Pathologic complete response
Case presentation

- Tamoxifen for at least 5 years advised
- She is currently without evidence of disease 3 years following her diagnosis
- …She wants to discontinue her Tamoxifen and attempt pregnancy. Not advised by her medical oncologist…

- Multidisciplinary care may be required for years to complete fertility preservation process
CHALLENGE #4
Surgeon may lack an established referral pattern for fertility consultation

» The surgeon may be unaware of resources for fertility preservation in their community

» If the patient desires a fertility consultation, it may be unclear to the surgeon how this can be accomplished during the complex initial office visit
OPTIONS FOR RESOURCES: INTEGRATION WITH SURVIVORSHIP PROGRAMS

• At the University of Kansas Cancer Center newly diagnosed young breast cancer patient are offered “real time” genetic counseling during the initial medical/surgical consultation
  » KU Breast Cancer Survivorship Center’s dedicated, full-time navigator provides this counseling
  » Navigator is trained to ask the patient if they are interested in fertility preservation
  » Navigator coordinates referrals from the surgeon to medical oncology and reproductive endocrinology
INTEGRATION INTO EXISTING OUTREACH PROGRAMS:

Example: Midwest Cancer Alliance

Established by KU Cancer Center:
A network of oncology practices and practitioners in Kansas and Western Missouri that provides access to evidence based clinical care and clinical trials

Telemedicine services at all sites
Dedicated Nurse Manager
Opportunity for communication/referrals regarding fertility preservation in young breast cancer patients
Web-based Resources

• Oncofertility.northwestern.edu
  » Includes a health care professionals site with information on how to make a fertility referral

• Fertilehope.org
  » National LIVESTRONG initiative
  » Sharing Hope program for financial assistance
Conclusion

• Surgeons are frequently the first cancer specialist to encounter a young patient with breast cancer.

• The initial surgical consultation provides an opportunity to identify young women with breast cancer who are interested in fertility preservation.

• Education of surgeons regarding the option of fertility preservation, coupled with a clearly defined fertility consultation process would facilitate successful early referral of these patients.
University of Kansas