Breast Cancer: Innovation and Interdisciplinary Care
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Objectives

• Understand the work up of a new breast abnormality
• Understanding the principles of staging and treatment
• An overview of innovation
• Understanding surgical treatment of breast cancer
Hypotheses of breast cancer

William Stewart Halsted, M.D. (September 23, 1852 – September 7, 1922) Hopkins
Concentric circles of spread
• By Bernard Fisher: Chairman (1967-1994) and Scientific Director- U Pittsburgh
  Systemic disease at outset
• Current thinking:
  Multiple distinct diseases
Tumor Formation by Human Breast Cancer “Stem Cells”

20,000
CD44- CD24+ Cells

200
CD44+ CD24- Cells

Al Hajj et al PNAS 2003
Models of Cancer Development

**Stochastic model**

Cancer cells are heterogeneous, but most cells can proliferate extensively and form new tumors.

**Cancer stem cell model**

Cancer cells are heterogeneous, and only rare cancer stem cells have the ability to proliferate extensively and form new tumors.
Breast Cancer is Multiple Diseases

2012 Stage IV ER pos/Her2 neg: Hormonal Rx

2015 same Rx
Stage IIIA  Er 60%, PR 40%, Her2 1+. Feb 2015 started preoperative chemotherapy
JM Locally Advanced Breast Cancer

• Preop chemotherapy tolerated: 2/2015
• Response borderline
• PET/CT: Significant response to Rx: 4/2015
• Radical mastectomy: 7/2015
JM Post Chemo and Mastectomy Pathology

- 3.6 CM IDC
- 3 Positive LNs
- Margins widely negative.
- Swelling increases 6 weeks after surgery
- Evaluation and biopsy: Metaplastic Carcinoma
Prior to treatment

3 months following preoperative chemotherapy, radical resection with negative margins
Staging and Other Disease Characteristics: Evaluating the **severity** of Breast Cancer

**Staging**

- Staging Types
- TNM Staging
- Stage 0
- Stage 1
- Stage 2
- Stage 3
- Stage 4

**Genotypes and Phenotypes**

- Estrogen/Progesterone
- Her 2 receptor
- Ki 67
- Tumor profiling
- Intrinsic subtypes
Oncotype DX® Recurrence Score
Calculated from 21 Different Genes

16 CANCER RELATED GENES

- ER
- PR
- Bcl2
- SCUBE2
- Ki-67
- STK15
- Survivin
- Cyclin B1
- MYBL2
- GRB7
- HER2
- Stromelysin 3
- Cathepsin L2
- CD68
- GSTM1
- BAG1

5 REFERENCE GENES

- Beta-actin
- GAPDH
- RPLPO
- GUS
- TFRC
NSABP B-20 Results: Tam vs. Tam + Chemo

28% absolute benefit from tam + chemo

HER2 The Target: HER Family of Receptors

HER = human epidermal growth factor receptor; EGF=epidermal growth factor, TGF=transforming growth factor, HB-EGF=heparin binding EGF

HER2 The Therapeutic Target: Trastuzumab

**Mechanism of Action (MOA)**

- Humanized monoclonal antibody specific for HER2
- Targets HER2 protein-overexpressing cells
- Proposed mechanism of action based on preclinical studies
  - Extracellular
  - Intracellular

Extracellular

Trastuzumab binds to subdomain IV of HER2 receptors on tumor cells, flagging them for destruction by the immune system.

Intracellular

Trastuzumab blocks HER2 signaling to inhibit proliferation of tumor cells.

Dimerized HER2 receptors signal tumor cells to proliferate.


Herceptin® (trastuzumab) [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2010.
Early Detection and Screening

- Screening Mammography
- Screening MRI
- Screening Ultrasound
Diagnostic Studies

- Screening Mammogram
- Diagnostic mammogram
- Ultrasound
- Breast MRI
- PEM/ Nuclear imaging

- BIRADS:
  0- Needs additional imaging
  1- Negative
  2- Benign finding
  3- Probably benign
  4- Suspicious
  5- Highly suspicious
  6- Known cancer
Mammography
Biopsy instruments
Principles of treatment: Individualized Treatment Plans

- Local-Regional: Breast and axillae
- Systemic or the potential for systemic disease
- The person: Physical and emotional well-being
Treatment Principles

• Stage 0, 1 and 2: A large majority are amenable to lumpectomy and radiation therapy
• Stage 3 and many stage 2 patients may benefit from preop chemotherapy
• Stage IV treatment is palliative: Prolong life, control or prevent symptoms and improve the quality of life
Lumpectomy, SLN biopsy and Radiation Therapy

• Most common breast surgery operation
• Designing our surgery reduces reoperation rate
• Post lumpectomy radiation:
  Standard WBI: 5-6 weeks
  Hyperfractionation: 3 week Canadian fractionation
  APBI: 5 days, 2x daily 1-3 weeks postop
  IORT: 10 minutes during surgery
Lessons learned from application of IORT (Intra-Operative Radiation Therapy) as a treatment modality for DCIS and early stage breast cancer

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Introduction
Partial breast radiation has replaced whole breast radiation for many patients with early breast cancer. Intra-operative radiation therapy (IORT) is one form of partial breast radiation that offers selected patients great convenience. One of its theoretical benefits is being able to deliver the radiation specifically to the bed of the resected tumor. We have set out to review our initial experience and extracting lessons from the first 30 consecutive intraoperative radiation therapy cases using the Xoft eBX system after lumpectomy for DCIS and early stage breast. The radiation source used in Xoft eBX is a miniaturized 50 kV X-ray tube located at the tip of the source delivers a brachytherapy radiation through applicator. The dosimetry characteristic of the source is similar to Iridium-192 dosimetry and it has been designed to deliver a high dose rate of radiation into the tissue surrounding the applicator that has been inserted into the treatment cavity. IORT was successfully completed in all of first 30 patients. We reviewed indications, complications, technical factors and outcomes. We are developing a tool to classify patients who are being considered for IORT into the various favorable or unfavorable categories according to currently published partial breast radiation guidelines.

Methods
Our breast service initiated an intra-operative electronic brachytherapy (IORT) program in October 2013. We have maintained a prospective database of all our patients and are reporting on the first 30 consecutive cases that were offered and treated with IORT at the time of their lumpectomy. The information was recorded prospectively or obtained from the patients' medical record. Institutional IRB approval was obtained for this study.

Our patients were discussed in our multidisciplinary tumor board and then evaluated concomitantly by breast surgery, medical and radiation oncology. Patients were selected that:
1- Have favorable disease that is suitable for accelerated partial breast radiation (APBI) by ASTRO or ASBS guidelines
2- Patients who would not be able to perform whole breast radiation or
3- When compliance with treatment is highly questionable

Surgical planning and needle localization plans were developed in collaboration with our breast imaging team. The ultrasound was used intraoperatively to:
1- Design our incision and the lumpectomy taking into consideration tumor location and its distance from the skin and the chest wall.
2- Evaluate margins when a tumor is visible by ultrasound and
3- Radiation balloon to skin distance and cavity conformation with the radiation balloon

All lumpectomy specimen were sent for gross evaluation in pathology. Additional margins were obtained if needed prior to balloon placement.

Results
IORT was offered and completed successfully for the 30 consecutive patients with an age range of 50-96.

Stage distribution and tumor size: Stage 0: 8/30, Stage I 15/30, Stage II 6/30, Stage III 1/30.

Tumor size ranged from no residual in 1 patient to 37 mm. All margins were negative except one patient with focal DCIS involvement. The patient is elderly and was offered hormonal therapy only.

Additional radiation:
Three patients needed whole breast radiation without a boost to the tumor bed.

Receptor Status:
Two of these 3 patients had ER positive, Her2 negative sub-centimeter primaries with a positive lymph node. One patient was found to have 9 positive lymph nodes despite a negative axillary ultrasound. That is the same patient who had a 37 mm ILC who was offered the treatment because of serious concern about the patient’s compliance with whole breast radiation.

Skin Spacing:
It is required to have at least 10 mm distance between the brachytherapy balloon to the skin in order to deliver the radiation safely. Skin spacing in our patients was 9.8-20.9 mm. We injected saline to increase the balloon to skin distance in the 1 patient with 9.8mm skin distance.

Balloon Size and seroma formation:
Twenty one of 30 patients required a 3-4 cm spherical balloon. 4-5 cm spherical balloons were used in the rest. We experienced three seromas with one suspected infection early in this experience. That problem was eliminated with the use of JP drains based on the surgeon's clinical judgement.

Follow up:
We have not experienced any local recurrences thus far with a median follow up of 1 year

Conclusions
1- IORT can be safely and successfully implemented with low complication and re-operation rates. The successful implementation of such a program depends on patient selection, collaboration with other specialties, designing surgery utilizing intraoperative ultrasound and skin excision when tumor proximity to the skin is noted on imaging.
2- Intra-operative ultrasound use and gross pathology consultation may decrease re-operative rates.
3- Selective drains should be considered to reduce seroma formation.
Indidualized Rx: Bilateral Favorable Breast Cancers
2006
Individualized Rx: Locally Advanced
Locally Advanced Triple Negative Cancer JT
Triple Negative After 3 Cycles of Chemotherapy
Individualized Rx: Massive Sarcoma in a 55 Y/O School Teacher
Individualized Rx: Massive Sarcoma in a 55 Y/O School Teacher

Post Surgery

- Chemotherapy
- Chest wall radiation

Alive and well 5.5 years later
Individualized Rx: Local Recurrence 15 Years Later
NSM with immediate reconstruction
Hallmarks of Our Program: Multidisciplinary Clinic and Care

• Multi D clinic started 2 years ago
• MultiD conference: Surgery, medical and radiation oncology, radiology, pathology, social work, genetic counselor, rehab….
• Patients evaluated and individual plan developed
• Survivorship
• Multi D conference

• Dedicated Team

MedStar Franklin Square Medical Center
The Harry and Jeanette Weinberg Cancer Institute

Focused on You
Conclusions

• Lumpectomy and XRT have largely replaced mastectomy
• IORT may replace over 1/3 of WBI cases
• The multi disciplinary approach and adjuvant therapies have extended patient survival
• Breast cancer is a host of different syndromes which will be treated differently in the future
• Radical surgical procedures are still indicated in some patients