Evolving Practices in Breast Cancer Management

The Georgia Tumor Registrars Association
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Objectives
1. understand newer indications for neoadjuvant treatment
2. understand the decision making process in surgical decisions for breast cancer
3. understand why less is often more in the surgical treatment of breast cancer

1894 William Halsted

• Theory: cancer spreads through local tissues and LN to rest of body (not hematogenous)
• Goal: remove every last cancer cell
• Procedure – Halsted radical mastectomy – removing whole breast, chest muscles and axillary nodes.
1894 Halsted radical mastectomy

- Improved cure rates and local recurrence rates
- But cosmetically a problem
- Lots of side effects — pain, lymphedema, decreased shoulder motility

1940-1960 - role of estrogen

- Found that breast cancers are responsive to lowering estrogen levels
- Methods of decreasing estrogen levels
  - XRT to ovaries
  - removing ovaries
  - removing adrenal glands
- Improved overall survival and recurrence

1970s - Changing the Halstedian view of cancer

- Breast cancer not just a local disease; but a systemic disease - hematogenous metastases
- Invasive cancer (broken outside ducts or lobules) can get into either lymphatic or blood vessels
- Lymphatic spread becomes hematogenous
1971 – Modified Radical Mastectomy

- remove breast tissue and axillary nodes
- without removing chest wall muscles
- just as good as radical mastectomy

1974 – Chemotherapy for advanced disease

- World War II – mustard gas found to affect rapidly dividing cells.
- Nitrogen mustard developed as treatment for hematologic malignancies
- Led to more research for other agents
- 1974 - doxorubicin (Adriamycin) – found to shrink advanced tumors

1975 – Adjuvant chemotherapy

"Adjuvant" - something that assists or helps
- In medicine: a treatment that enhances an existing medical regime
- In breast cancer – surgery was the basic treatment
  - Adjuvant chemotherapy – chemo after surgery
  - Adjuvant radiation therapy – radiation after surgery
- Adjuvant chemotherapy showed improved overall survival in early breast cancer
- But chemo has many side effects and toxicities, so there was long discussion about benefits vs. risks.
- Discussion continues today re how to balance these
1977 – Lumpectomy/partial mastectomy

- Lumpectomy + XRT was found to be as effective as mastectomy in early stage breast cancer
- Essentially same survival
- Axillary node dissection was still routine as part of treatment

Late 1970s – Screening mammography

Screening mammography promoted
- finds cancers at earlier stage;

(Early detection has contributed to a >25% decrease in breast cancer mortality since 1975)

1977 – testing for Estrogen Receptors

- ER+ tumors grow in response to estrogen
  - This is why reducing body levels of estrogen improves outcome in many women.
  - But only ~ 80% breast cancers are ER+
- Found that patients with ER+ tumors have a lower recurrence rate than those with ER negative tumors.
- ER status was the first objective tool to help stratify which patients needed more aggressive treatment
Tamoxifen
(a SERM – Selective Estrogen Receptor Modulator)

• 1977 approved for advanced ER+ breast cancer.
• 1986 approved for adjuvant use
  ▪ 5 years of tamoxifen decreased recurrence; improves survival
• 1990s approved for risk reduction in high risk patients.
  NOT helpful in ER-negative patients.

Mid 1990s - BRCA1 and BRCA2 discovered

• BRCA 1&2: genes that produce proteins that repair damaged DNA.
  ▪ Mutations in these genes lead to accumulation of defects and development of cancer.
• BRCA 1&2 mutations – 50-85% increased risk of breast/ovarian cancer
  ▪ Present in ~5-10% of all breast cancers
  ▪ Present in ~ 25% of hereditary breast cancers
• Initial recommendations: increased screening or preventive surgery
  ▪ later tamoxifen/raloxifene

Mid-1990s – development of other chemotherapy

• Individual drugs paclitaxel (Taxol)
• Combinations:
  ▪ CAF (cyclophosphamide, Adriamycin, fluorouracil)
  ▪ CMF (cyclophosphamide, methotrexate, fluorouracil)
  ▪ FEC (fluorouracil, epirubicin, cyclophosphamide)
  ▪ TAC (Taxotere, Adriamycin, cyclophosphamide)
1998 – Neoadjuvant chemotherapy

Lumpectomy now standard treatment for most breast cancers

But some women not candidates for lumpectomy because of size of tumor.

Neoadjuvant chemotherapy – used to shrink large tumors to allow lumpectomy
Successful in downsizing tumor in 2/3 patients

1998 – trastuzumab (Herceptin)

- Mid 1980s – discovery of human epidermal growth factor receptor (Her2)
- Breast cancers that overexpress this receptor are more aggressive – grow faster, spread more quickly, less likely to respond to standard therapy (~20% breast cancers)
- Late 1980s – 1990s – development of an antibody that blocked Her2 action
- 1998 – Trastuzumab (Herceptin) approved for advanced breast cancer
  - Improved survival in Her2+ tumors

Comparison of chemotherapy and trastuzumab

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Trastuzumab</th>
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<tbody>
<tr>
<td>Cytotoxic – kills cells</td>
<td>Prevents growth/division of cells</td>
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<tr>
<td>Indiscriminate – affects all fast-growing cells</td>
<td>Targeted – attaches to cells over-expressing Her2</td>
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<tr>
<td>Many toxicities</td>
<td>Minimal side effects</td>
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<tr>
<td></td>
<td>Only works in Her2+ cancers</td>
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2000 – Bone marrow transplants NOT effective

1990s - High dose chemotherapy to try to obliterate all cancer cells.
But this also wiped out patient’s bone marrow.
• Had to be rescued with stem cell transplant (bone marrow transplant)
Gained popularity without having definitive clinical trials.
These were finally done and showed that BMT did NOT improve survival in either early stage or advanced breast cancer

2000 – Sentinel Lymph Node biopsy

In development and studies for several years.
Found that negative SLNB accurately predicts axillary status

2000 – Genetic sequencing

Development of ability to do gene sequencing
Genetic sequencing of tumors identifies breast cancer subtypes
This gives rise to the idea that there is the potential to individualize treatment for each patient
2002-2004 – commercially available genetic tests

Oncotype Dx – 21 gene test
Can be done on paraffin imbedded tissue – no need for fresh tissue
Validated in large tumor banks
Categorizes early (Stage 1 and 2) ER+ Her2 neg patients by risk of distant recurrence in next 10 years
Predicated on receiving tamoxifen
Can help identify patients at high risk who need more treatment and at low risk who may be able to avoid toxicity of chemotherapy

Mammaprint - 70 gene recurrence score
Initially required fresh tissue (so did not get popular in USA)
Now can be done on paraffin blocks

2002 – Partial breast radiation
For small tumors, low grade tumors, negative nodes, older women
Post lumpectomy radiation to area of cancer only
<1 week treatment
Good results in appropriately selected patients.
Some cosmetic issues – improved with multi-lumen devices
2003  Dose dense chemotherapy

Dose dense chemo
  giving chemotherapy every 2 instead of every 3 weeks

Benefits:
  shorter course
  improves survival
  no significant increase in side effects

2004 – Aromatase inhibitors

Aromatase inhibitors – block formation of estrogen

Postmenopausal women
  Initially used for adjuvant treatment;
  Later found to improve survival and quality of life in advanced disease

2005 – digital mammograms

Digital mammograms
  better resolution
  ability to manipulate images for better diagnosis
  easier to store, send, review

Improves diagnosis especially in women <50

Now in standard use almost everywhere
2006 – Adjuvant Herceptin

Herceptin approved for adjuvant treatment (in conjunction with chemotherapy)

Reduces risk of recurrence by >50% in Her2 + patients.

2006 – Raloxifene for risk reduction

Raloxifene (Evista) – a SERM (like tamoxifen)

• Developed to prevent osteoporosis in postmenopausal women
• Found that patients on raloxifene developed fewer breast cancers.
• Comparative study – raloxifene and tamoxifen essentially equivalent to reduce risk of invasive ductal carcinoma in high risk patients
• Avoids risk of endometrial cancer associated with tamoxifen

2007 – Hypofractionated radiation therapy

Usual whole breast radiation – takes about 6 ½ weeks
Hypofractionated XRT – larger doses/fewer doses - about 4 weeks

  as effective as standard XRT
  more convenient and less expensive
  easier to complete – better compliance
  no increase in side effects (10-year f/u)

Not well studied in ALL patient groups
2010 – Intraoperative radiation therapy
At time of lumpectomy, radiation is given to tumor bed in the OR

Benefits:
• Cheaper
• One time dosing
• Seems to have similar outcomes to standard radiation

Downsides
• Awaiting longer term studies
• Do not have final pathology report (margins, nodes) at time of procedure
• Special OR and OR equipment

2010 – Z0011 study
Patients all received lumpectomy and whole breast radiation
All patients had sentinel node biopsy (SLNB)

If 1 or 2 SLN positive – randomized to axillary node dissection or no further surgery

No difference in overall survival, disease free survival, or local recurrence

2012 – Pertuzumab (Perjeta)
Pertuzumab – like trastuzumab
an antibody interfering with Her2 function

2012 - chemotherapy+trastuzumab + pertuzumab produced improved response in Her2+ advanced cancer

2013 – approved for neoadjuvant therapy for Stage 2 or above (tumor >2 cm, + lymph nodes)
2012 – genetic test for DCIS

Prognostic - stratifies risk for local recurrence (DCIS or invasive)
• Implication that low risk patients may forgo XRT
At this time no predictive value for benefit of XRT
Not yet included in ASCO or NCCN guidelines

2013 - antibody-chemotherapy conjugate

T-DM1 – Trastuzumab emtanzine
A very toxic chemotherapy agent attached to trastuzumab
Antibody attaches to cancer cell – chemo drug enters the cancer cell
Fewer side effects
Approved for Her2+ metastatic breast cancer that failed with standard chemo-trastuzumab

2013 – Extended hormonal therapy

Gene test:
PROGNOSTIC: assesses risk of late distant recurrence for ER+
PREDICTIVE: assesses benefit of extended hormonal therapy

10 year risk of distant recurrence
Two studies
2014 – lumpectomy margins

Years of discussion

Now: no ink on tumor - fewer returns to surgery for margins

2016 – DCIS -2 mm better, but individualize repeat excision for narrower margins

2014-15 – Broader genetic panels

BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, TP53 and others

Surgical changes

Radical mastectomy
Modified radical mastectomy
Lumpectomy/ Axillary node dissection/XRT
Lumpectomy/ SLNB + AxND if + node/XRT
Lumpectomy/ SLND/ XRT – AxND only if >2 nodes +
Necessary margins

Gradual recognition that more is not better in every patient
Chemotherapy changes

Chemotherapy in advanced disease
Adjuvant chemotherapy for tumors > 2 cm
Adjuvant chemotherapy for tumors >1 cm
Genetic profiling – stratifies need/benefit
Neoadjuvant chemotherapy
Trastuzumab - adjuvant/neoadjuvant
Pertuzumab
T-DM1 – antibody–drug conjugate
Many other chemotherapy changes going on too!

Hormonal therapy

Ovariectomy/ adrenalectomy
Testing for ER/PR
Tamoxifen
Aromatase inhibitors
Neoadjuvant hormonal
Extended hormonal treatment

Radiation therapy

Whole breast radiation
Hypofractionated radiation
Partial breast radiation
Intraoperative radiation
Genetic profiling for risk of recurrence in DCIS
So how do I decide what to do?

Need to know:

- ER/PR/Her2 status
- Clinical axillary status
- Clinical size of tumor
- Likelihood of BRCA or other genetic predisposition

ER/PR/Her2 status help determine role for chemotherapy

If patient is definitely going to need chemo – consider neoadjuvant
- Her2 positive
- Triple negative

Benefits of neoadjuvant:
- Chemo most important part of treatment - impacts distant recurrence
- Allows evaluation of effectiveness of chemotherapy
- May allow less surgery
- Pertuzumab only approved for neoadjuvant (not adjuvant)
- (If neoadjuvant planned, make sure tumor has a marker in it.)

Clinical node status

- If palpable axillary node – need US and NCB with marker
- If no palpable nodes - should US of axilla be done?
- ? Routine US of axilla
- ? SLNB before or after neoadjuvant chemo
  - Currently felt if no palpable nodes, do SLNB after chemotherapy
Clinical size of tumor

- Actual size less important than size relative to breast
- If lumpectomy planned, consider cosmetic result
- If too large for good cosmesis with lumpectomy – consider neoadjuvant treatment – either chemo or hormonal
- If chemo may be recommended because of size of tumor (>2 cm), consider Medical Oncology consult prior to surgery for consideration of neoadjuvant treatment.

Likelihood of genetic mutation

If deleterious mutation present, mastectomy (? bilateral) may be recommended. Consider testing if:

- Triple Negative Cancer < age 60
- Diagnosis < 50 yo
- Bilateral or second primary breast cancer
- FH ovarian cancer or male breast cancer
- If age >50 but with
  - FH two other cancers – breast/ovarian/pancreatic/prostatic/other

Patient preferences

Lumpectomy or mastectomy
Ok with radiation, or prefer to avoid it
Need for chemotherapy/hormonal is NOT affected by surgical procedure
Most women do VERY well

Five year survival rates:
• Stage 0 or stage I - close to 100%.
• Stage II - ~ 93%.
• Stage III - ~ 72%.
• Stage IV - ~ 22%. Often many treatment options available for women with this stage of breast cancer.

Thank you for all you do for facilitating progress in treating our patients.