Do Early Stage Breast Cancer Patients Receive Adequate Information With Which to Make Informed Decisions?

(How Knowledge of the Risk of Breast Lymphedema May Change a Patient’s Breast Cancer Treatment)

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Glossary

- ALND = axillary lymph node dissection
- AST = adjuvant systemic treatment (chemo/hormonal therapy)
- BC = breast cancer
- BCS/BCT = breast conserving surgery/therapy (lumpectomy, quadrantectomy)
- BrLE = breast lymphedema
- DCIS/LCIS = ductal/lobular carcinoma in situ
- DFS = disease-free survival
- DHHS = (United States) Department of Health and Human Services
- DHS = (California) Department of Health Services
- DSS = disease-specific survival
- Dx = dissection
- EBCTCG = Early Breast Cancer Trialists’ Collaborative Group
- IBC = invasive breast cancer
- IBCR/IBTR/IBR = ipsilateral breast tumor/carcinoma recurrence
- LE = lymphedema
- LR = local recurrence
- LRR/LRF = loco-regional recurrence/loco-regional failure/local recurrence rate
- NCCN = National Comprehensive Cancer Network
- OS = overall survival
- PMRT = post mastectomy radiation therapy
- QoL = quality of life
- RTx = radiotherapy, radiation therapy
- SLNB = sentinel lymph node biopsy
Outline

• NCCN breast cancer treatment guidelines
• Lymphatic drainage of the breast and upper limb
• Radiotherapy morbidities
• Breast lymphedema, breast cellulitis
• Weighing benefits and risks to make an *informed* decision
• Recommendations
What is the Problem?

- **Assumptions**
  - Patient Rights include *Informed* Consent
  - Informed Consent requires complete benefit/risk information
  - Treatment Decision is shared between patient and physician

- **Treatment Guidelines**
  - Based on evolving treatment protocols
  - Based on recurrence and mortality statistics
  - Decision must incorporate patient preferences and quality of life

- **Questions**
  - How does Breast Lymphedema influence the Risk-Benefit trade?
  - Is there a reasonable No-Radiotherapy Option?
In 2001 Radiation was added: Carlson RW, Edge SB, Theriault RL, et. al.: “NCCN: Breast Cancer” Cancer Control 2001;8(6 Suppl. 2):54-61. Radiation to be used as a component of breast conservation therapy for all patients with invasive breast cancer.

In 2008 a “no-radiation” path was added to DCIS Treatment Guideline: “Changes in the 2.2008 version of the Breast Guidelines: Primary treatment of DCIS now includes 3 options: lumpectomy without lymph node surgery plus whole breast radiation (category 1); total mastectomy with or without sentinel node biopsy with or without reconstruction (category 2A); lumpectomy without lymph node surgery without radiation (category 2B).”

**DCIS-1**

g. Documentation of complete resection (margins)
h. Staging for invasive disease after mastectomy or re-excision
j. “Whole breast radiation therapy following lumpectomy reduces recurrence rates in DCIS by about 50%. Approximately half of the recurrences are invasive and half DCIS. A number of factors determine that local recurrence risk, including size, tumor grade, margin status and patient age. Some patients may be treated by excision alone, if the patient and physician view the individual risks as “low”. All data evaluating the three local treatments show no differences in patient survival.”

**BINV-2 (Lumpectomy)**
k. “Breast irradiation may be omitted in those 70 y[ears] of age or older with estrogen-receptor positive, clinically node negative, Ti tumors who receive adjuvant endocrine therapy (category 1).”
Breast Lymphatic Draining into the Axillary Nodal Basin

FIG. 4. Tracing distally of lymphatics of both hemi upper torsos (male: A and C, female: B and D) from each first-tier lymph node colour coded; pectoral node (green, orange, black and yellow), subclavicular node (light blue), and internal mammary node (red). Note (i) that the lymph collecting vessels from the nipple and areolar region on each specimen drain into the green-colored lymph node; (ii) the similar pattern of chest and breast drainage between the male and female studies; (iii) that the breast lies in the pathway of collecting lymphatics that start peripherally and (iv) that, although the majority of the breast drains to one sentinel node in D, every breast area is drained by more than one first-tier node in each study.

With surgical removal of nodes, the body tends to regenerate and reconnect to existing functional lymphatics. Radiation of the nodes tends to fibrose the node. Radiation of the lymphangion tends to fibrose the surrounding tissue, possibly including the anchoring filaments responsible for autonomous pumping of lymph.

Goyal 2004: Goyal et. al.: Axillary treatment in patients with positive sentinel nodes radiotherapy or dissection. Results of the ALMANAC Trial: No significant differences in upper limb lymphedema and breast edema was found between the RT and ALND groups. Poster #1056 2004 SABCS.

Palesty 2005: “In whole breast radiation, the low axilla receives the full treatment dose.”
Long-Term Morbidities of Breast Irradiation, ALND and SLNB (1)

- **IPSILATERAL BREAST**
  - Infection (Cellulitis, inflammation, ulceration) [Fehlauer 2003]
  - Telangiectasia [Huang 2002]
  - Induration, atrophy, retraction [Fehlauer 2003]
  - Pain [Tasmuth 1995, Fehlauer 2003]

- **CONTRALATERAL BREAST**
  - Carcinoma [Boice 1992, Gao 2003]

Lawenda 2008: *NLN LYMPHLINK* 2008;20(3).

*S*Surveys & Overviews
Breast Lymphedema—New Parameter in the Risk-Benefit Equation?

- Incidence [See page 9] [Delay 2008]
- Measurement methods [No standard. See page 11]
- Treatment [lifelong daily care]
- Cellulitis risk [lifelong elevated risk of recurrent cellulitis]
- Genetic predisposition [Andreasson 2006]
- Hypertension [Böhler 1992]


## Incidence of Breast Lymphedema

<table>
<thead>
<tr>
<th>Researcher</th>
<th>Date</th>
<th>Number</th>
<th>Conditions</th>
<th>Axillary Treatment</th>
<th>Incidence % Mild/Med/Sev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarke</td>
<td>1982</td>
<td>74</td>
<td>Breast Irradiated No Mastectomy</td>
<td>None/SLNB ALND</td>
<td>6/25 79</td>
</tr>
<tr>
<td>Beadle</td>
<td>1984</td>
<td>@6 months @5 years</td>
<td>RT/NoRT ALND</td>
<td></td>
<td>32/3/0 23/0/0</td>
</tr>
<tr>
<td>Senofsky</td>
<td>1991</td>
<td>133</td>
<td></td>
<td>Limited Dx Full Dx</td>
<td>21/5 12</td>
</tr>
<tr>
<td>Meek</td>
<td>1998</td>
<td></td>
<td></td>
<td></td>
<td>8-25 15-80</td>
</tr>
<tr>
<td>Bosompra</td>
<td>2002</td>
<td>148</td>
<td>@2-4 years Patient survey</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Goffman</td>
<td>2004</td>
<td>240</td>
<td>&gt;1.5 years Clinical exam</td>
<td>SLNB ALND 76%</td>
<td>8.3//1.3</td>
</tr>
<tr>
<td>Rönkä</td>
<td>2004</td>
<td>160</td>
<td>@1 year, US skin thickness</td>
<td>SLNB ALND</td>
<td>*28/17 *70/54-59</td>
</tr>
<tr>
<td>Rönkä</td>
<td>2005</td>
<td>109</td>
<td>@1 year Self-reported</td>
<td>SLNB ALND</td>
<td>16/7/0 41/15/2</td>
</tr>
<tr>
<td>Leidenius</td>
<td>2005</td>
<td>139</td>
<td>@3 years Self-reported</td>
<td>SLNB ALND</td>
<td>6/1/0 21/4/0</td>
</tr>
</tbody>
</table>

* Note: Ultrasonic skin thickness measurement = subcutaneous edema/interstitial fluid


Diagnosis of Breast Lymphedema

- Clinical
  - Breast edema
  - Breast erythema
  - Painful to the touch
  - Heightened temperature
- Self-scored breast symptoms
  - Swollen appearance or feel
  - Heaviness
  - Redness
  - Tenderness, discomfort
  - Fullness or numbness
  - Pain


Measurement of Breast Lymphedema

- Clinical observation [Fehlauer 2003]
- Magnetic resonance imaging of skin [Idy-Paretti 1998]
- Bioelectrical impedance measurement [Mikes 1999, Cornish 2001]
- Lymphoscintigraphy [Weissleder 1988, Szuba 2003]
- Dielectric Skin fluid measurement [Lahtinen 2006]
- Tissue tonometry [Clodius 1976]
- Optical skin erythema measurement [Russell 1994]
- Skin visco-elasticity [Gorodetsky 1999, Marcenaro 2004]
- Dual-beam absorptiometry [Cluzan 1998]


Weissleder H & Weissleder R:” Lymphedema: evaluation of qualitative and quantitative lymphoscintigraphy in 238 patients” Radiology, 1988;167:729-35,
Delayed Breast Cellulitis

- “Delayed breast cellulitis, the most severe form of breast lymphedema, may pose problematic diagnostic and management dilemmas.” [Rönkä quoting Zippel 2003]
- Distinct from infection following lumpectomy [Zippel 2003]
- Pathogen usually not identified [Baddour 1999, Zippel 2003]
- Mechanism probably involves lymph stasis [Miller 1998]
- Upper limb lymphedema significant risk factor for breast cellulitis [Brewer 2000]
- Characterized by erythema, edema, tenderness, warmth, pain [Indelicato 2006, Brewer 2000]
- Incidence 3-8%
- Median time to onset 190 days after surgery, 109 days from radiotherapy [Brewer 2000], 226 days [Indelicato 2006]
- 22% had recurrent episodes

Risk-Benefit Considerations
T1N0
Radiotherapy or No Radiotherapy?

Favoring Radiotherapy:
- Lower IBCR risk (1)
- Less fear of Second Surgery (2A)
- Lower Distant metastasis risk (2B)
- Lower Cancer-specific mortality (2A)
- Ipsilateral BC Suppression (2B)

Favoring No Radiotherapy:
- Less onerous Primary treatment (1)
- Lower Upper limb LE risk (1)
- Lower Breast LE risk (1)
- Lower Breast Cellulitis risk (1)
- Lower Contralateral BC risk (2B)

7% 5-Year Local Recurrence* 26%
30.5% 15-Year BC Mortality Risk* 35.9%

*EBCTCG 2005

( ) Categories of Evidence and Consensus Author’s Assessment

“The balance between beneficial and harmful effects of post-mastectomy radiation therapy depends on the risk of local recurrence, the age of the patient, the efficacy of the systemic therapies (especially endocrine agents) and competing causes of morbidity and mortality.” A. Goldhirsch 2005.


Vinh-Hung V, Verschraegen C. Breast-conserving surgery with or without radiotherapy: pooled-analysis for risks of ipsilateral breast tumor recurrence and mortality. J Natl Cancer Inst. 2004;96:115-121. A pooled analysis of randomized clinical trials was conducted to compare radiotherapy vs. no radiotherapy after breast-conserving surgery. The relative risk of ipsilateral breast tumor recurrence after breast-conserving surgery,comparing no radiotherapy or radiotherapy,was 3.00. The relative risk of mortality was 1.086, corresponding to an estimated 8.6% relative excess mortality if radiotherapy was omitted. Omission of radiotherapy is associated with a large increase in risk of ipsilateral breast tumor recurrence and with a small increase in the risk of patient mortality.

Wapnir I, Dignam J, Julian TB, et al.: “Long-term outcomes after invasive breast tumor recurrence (IBTR) in women with DCIS in NSABP B-17 and B-24” J Clin Oncol. 2007 ASCO Annual Meeting Proceedings Part 1 2007;25(18S):520. The 12-year cumulative incidence of all IBTRs was 32.9% for lumpectomy only, 15.8% for lumpectomy plus RTx, and 12.5% with the addition of Tamoxifen. Survival similar across all treatment arms.
Lumpectomy Without Radiotherapy

- Benefits of postoperative RTx for high risk patients in terms of both reduction of LRR and mortality are well established [Overgaard 1997]
- Analyses of the benefits and risks of omitting adjuvant RTx in the treatment of certain DCIS patients resulted in addition of that option in the NCCN DCIS Treatment Guidelines [Viani 2007]
- Guidelines based on populations not all of whom received adjuvant systemic treatment (AST)
- Recent trials show AST reduces risk of LRR and collateral BC by about 50% [van der Leest 2008]. It is not yet clear whether similar risk reduction would obtain among lower risk patients without irradiation
- Analysis of a subset of the randomized trials by the EBCTCG indicated an absolute benefit of 19% in 5-year LRR and 5% in 15-year cancer mortality for adding RTx to breast conserving surgery [EBCTCG 2005]
- Analyses and trials are underway to determine whether there are populations of early breast cancer patients who are candidates for BCS and hormonal therapy without RTx [Fisher 2002, Vin-Hung 2004, Hughes 2004, 2006, Vujovic 2006, Yarnold 2008]

20-Year Follow-Up NSABP B-06 Trial

- RTx was associated with a marginally significant decrease in deaths due to breast cancer. This decrease was partially offset by an increase in deaths from other causes.
- Current administration of systemic therapy after lumpectomy reduces the rates of ipsilateral and contralateral recurrences as well as distant metastases.

![Graphs showing cumulative incidence of recurrence and deaths from any cause.](Image)
A Systematic Overview of Radiation Effects in Breast Cancer [Rutqvist 2008]

- There are conflicting data whether BCS plus RTx is comparable to MRM alone in terms of LRR.
- There is strong evidence that BCS plus RTx is comparable to MRM alone in terms of DFS and OS.
- There is strong evidence that postoperative breast RTx following BCS results in a statistically and clinically significant reduction of IBR followed by diminished need for salvage mastectomies.
- There is strong evidence that the omission of postoperative breast RTx following BCS has no impact on OS. In one meta-analysis including three randomized studies a survival advantage is demonstrated by Bayesian statistics.
- There is strong evidence that the addition of a radiation boost after conventional RTx to the tumour bed after BCS significantly decreases the risk of IBR but has no impact on OS after short follow-up.
- There is strong evidence for the use of postoperative breast RTx following BCS for DCIS. RTx leads to a clinically and statistically significant reduction of both non-invasive and invasive IBRs.
- There is insufficient evidence to define the optimal integration of systemic adjuvant therapy and postoperative RTx.
- There are limited data on RTx-related morbidity in breast cancer. No conclusions can be drawn.

Recommendations (1)

• Physician education
  – Improve understanding of impact of upper limb and breast LE on patient quality of life
  – Improve recognition of adverse effects of radiotherapy

• Patient-Physician shared decision (informed consent)
  – Full discussion of benefits and risks of each viable treatment modality and combination
  – Explain trade between recurrence risk and lymphedema risk

• Breast cancer treatment guidelines
  – Consider option and criteria for omitting adjuvant RTx after BCS
  – Revise patient guidance information and decision charts
Recommendations (2)

- Research
  - Standardize BrLE measurement techniques and definition criteria
  - Investigate other radiotherapeutical options
    - Partial breast irradiation [Lawenda 2003, Hannoun-Levi 2003]
    - Delayed course of radiotherapy [Jobsen 2006, Vujovic 2006]
    - Reduced standard dose [Dewar 2007]
    - Prophylactic low-level mammary irradiation [Brenner 2007]
  - Identify subgroup and criteria for whom RTx can be withheld [Hughes 2006, Vujovic 2006, Yarnold 2008]


Nuyten DS, Kreike B, et. al.: “Predicting a local recurrence after breast-conserving therapy by gene expression profiling” *Breast Cancer Res.* 2006;8:R62