

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

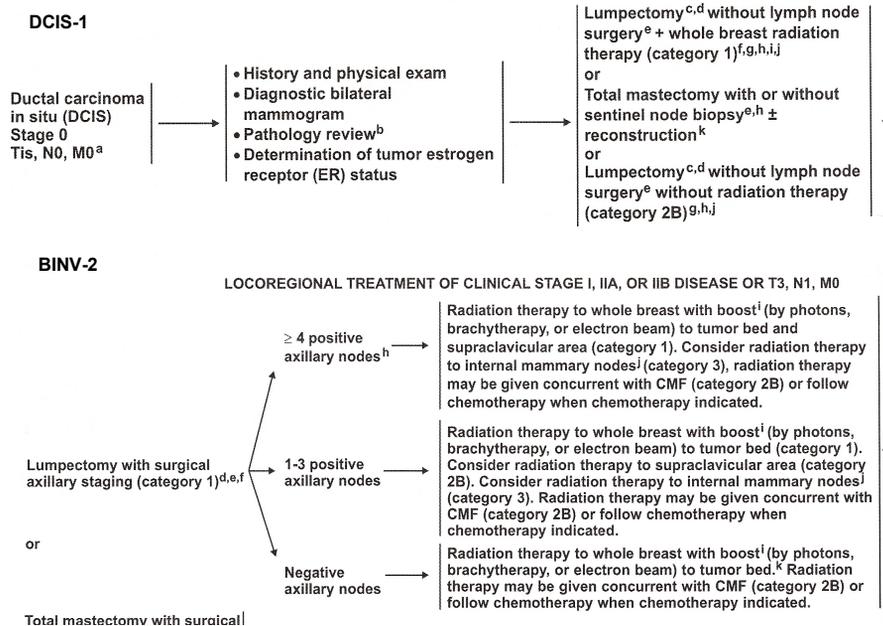
Outline

- 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?

Current NCCN Breast Guidelines (2.2008)



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)

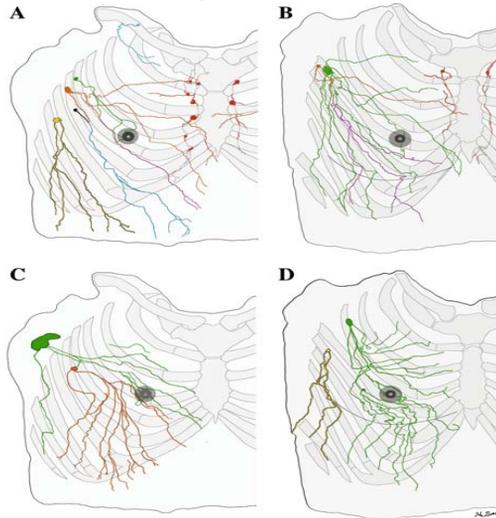
h. Staging for invasive disease after mastectomy or re-excision

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, include[ing] 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, T1 tumors who receive adjuvant endocrine therapy (category 1).”

Breast Lymphatic Draining into the Axillary Nodal Basin



Sappey MPC: "Anatomie, Physiologie, Pathologie des vaisseaux Lymphatiques consideres chez L'homme at les Vertebres Paris: A. Delahaye and E. Lecrosnier, 1874.

Suami H, Pan W-R, Mann B, & Taylor GI: "The Lymphatic Anatomy of the Breast and its Implications for Sentinel Lymph Node Biopsy: A Human Cadaver Study" *Annals of Surgical Oncology* 2008;15(3):863-71.

Suami 2008: Suami H, Pan W-R, Mann B, & Taylor GI: "The Lymphatic Anatomy of the Breast and its Implications for Sentinel Lymph Node Biopsy: A Human Cadaver Study" *Annals of Surgical Oncology* 2008;15(3):863-71

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
 - Lymphedema [Beadle 1984, Fehlaue 2003, Lawenda 2008]
 - Infection (Cellulitis, inflammation, ulceration) [Fehlaue 2003]
 - Telangiectasia [Huang 2002]
 - Radiation fibrosis [Borger 1994, Böhler 1992 Delanian 2004, Gothard 2004]
 - Induration, atrophy, retraction [Fehlaue 2003]
 - Pain [Tasmuth 1995, Fehlaue 2003]
 - Angiosarcoma, genetically-independent carcinoma [Sachs 2005, Brenner 2007, Majeski 2000]
- CONTRALATERAL BREAST
 - Carcinoma [Boice 1992, Gao 2003]

Beadle 1984: *Cancer* 1984;54(1):2911-8.

Böhler 1992: *Strahlenther Onkol.* 1992;168(6):344-9.

Boice 1992: *N Engl J Med.* 1992 Mar 19;326(12):781-5.

Borger 1994: *Int J Radiat Oncol Biol Phys.* 1994;30:1073-81.

Brenner 2007: *J Clin Oncol.* 2007;25(31):4868-72.

Delanian 2004: *Radiother Oncol.* 2004;73:119-31.

*Fehlaue 2003: *Int J Radiat Oncol Biol Phys.* 2003;55(3):651-8.

Gao 2003: *Int J Radiat Oncol Biol Phys.* 2003;56:1038-45.

Gothard 2004: *Radiother Oncol.* 2004;70:217-24.

Huang 2002: *Br J Radiol.* 2002;75:444-7.

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

Majeski 2000: *J Surg Oncol.* 74(3):208-12.

Sachs 2005: *Proc Nat Acad Sci USA.* 2005;102:13040-5.

Tasmuth 1995: *Ann Oncol.* 337:956-62.

*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]

Delay E, Gosset J, Toussoun G, Delaporte T & Delbaere M: “Séquelles thérapeutiques du sein après traitement conservateur du cancer du sein” [Post-treatment sequelae after breast cancer conservative surgery] in French, *Ann Chir Plast Esthét* Apr, 2008;53(2):135-52. “Breast lymphedema is also a common incapacitating after-effect that is believed to be largely under-diagnosed in clinical practice.”

Andreasson CH, Overgaard J, et. al.: “ATM sequence variants and risk of radiation-induced subcutaneous fibrosis after postmastectomy radiotherapy” *I J Radiol Oncol Biol Phys.* 64(3):776-83.

Böhler FK, Rhomberg W & Doring W: [Hypertension as a risk factor for increased rate of side effects in the framework of breast carcinoma irradiation] in German, *Strahlenther Onkol.* 1992;168(6):344-9.

Incidence of Breast Lymphedema

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

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

Clarke D, Martinez A, Cox RS & Goffinet DR: "Breast edema following staging axillary node dissection in patient with breast carcinoma treated by radical radiotherapy" *Cancer* Jun 1, 1982;49(11): 2295-9.

Beadle GF, Silver B, Botnick L, Hellman S & Harris JR: "Cosmetic results following primary radiation therapy for early breast cancer" *Cancer* Dec 15,1984;54(12):2911-8.

Senofsky GM, Moffat FL, Davis K, Masri MM, Clark KC, Robinson DS, Sabates B & Ketcham AS: "Total axillary lymphadenectomy in the management of breast cancer" *Arch Surg* Nov 1991;126(11):1336-41, discussion 1341-2.

Meek AG: "Breast Radiotherapy and Lymphedema", *Cancer* Dec 15, 1998;83(12 Supplement): 2788-97, American Cancer Society Workshop on Breast Cancer Treatment-Related Lymphedema, New York, NY, February 20-22, 1997.

Bosompra K, Ashikaga T, O'Brien PJ, et. al.: "Knowledge about preventing and managing lymphedema: a survey of recently diagnosed and treated cancer patients" *Patient Educ Counsel*. 2002;47:155-63.

Goffman TE, Laronga C, Wilson L & Elkins D: *The Breast J*. 2004;10(5):405-11.

Rönkä RH, Pamilo MS, von Smitten KAJ & Leidenius MHK: "Breast lymphedema after breast conserving treatment" *Acta Oncolog*. 2004;43(6):551-7.

Rönkä R, von Smitten K, Tasmuth T & Leidenius M: "One-year morbidity after sentinel node biopsy and breast surgery" *Breast* Feb 2005;14(1):28-36.

Leidenius M, Leivonen M, Vironen J & von Smitten K: "The consequences of long-time arm morbidity in node-negative breast cancer patients with sentinel node biopsy or axillary clearance" *J Surg Oncol*. 2005 Oct 1;92(1):23-31.

Mellor RH, Bush NL, Stanton AWB, Bamber JC, Levick JR & Mortimer PS: "Dual-frequency ultrasound examination of skin and subcutis thickness in breast cancer-related lymphedema" *Breast J* Nov 6, 2004;10(6):496-503.

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

Kroshinsky D, Grossman ME and Fox LP: “Approach to the Patient With Presumed Cellulitis” in *Seminars in Cutaneous Medicine and Surgery* September 2007;26(3):168-78.

Degnim AC, Boughey JC, et. al.: “Breast lymphedema after breast surgery: signs and symptoms” Poster F-3 presented at 32nd Annual Symposium, American Society of Breast Disease, April 10-12, 2008, San Diego.

Measurement of Breast Lymphedema

- Clinical observation [Fehlauer 2003]
- Ultrasonic skin thickness measurement [Shukla 1984, Warszawski 1998, Mellor 2004, Rönkä 2004]
- 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]

Clodius L, Deak L & Piller NB: "A new instrument for evaluation of tissue tonicity in lymphedema" *Lymphology* 1976;9:1-5.

Cluzan RV, Pecking A, Ruiz JC, Alliot F, Ghabboun S, Pascot M, Gachon-Lameyre V. Biphotonic absorptiometry of the secondary upper limb lymphedema. *Lymphology* (Suppl) 1998;31:296-8.

Cornish BH, Chapman M, Hirst C et. al.: "Early diagnosis of lymphedema using multiple frequency bioimpedance" *Lymphology* 2001;34:2-11.

Gorodetsky R, Lotan C, et. al.: "Late effects of dose fractionation on the mechanical properties of breast skin following post-mastectomy radiotherapy" *Int J Radiat Oncol Biol Phys.* 1999;45:893-900.

Idy-Paretti I, Bittoun J, Alliot FA et. al.: "Lymphedematous skin and subcutis: *In vivo* high resolution magnetic resonance imaging evaluation" *J Invest Dermatol.* 1998;110:782-7.

Lahtinen T, Nuutinen J & Mayrovitz HN: "A new water-specific technique for local measurement of edema and lymphedema induced by cancer therapy" *ESTRO Newsletter* Winter 2006;61:23-4.

Mellor RH, Bush NL, Stanton AWB, et. al.: "Dual-frequency ultrasound examination of skin and subcutis thickness in breast cancer-related lymphedema" *The Breast J.* Nov 2004;10(6):496.

Mikes DM, Cha BA, et.al.: "Bioelectrical impedance analysis revisited" *Lymphology* 1999;32:157-65.

Rönkä RH, Pamilo MS, von Smitten KAJ & Leidenius MHK: "Breast lymphedema after breast conserving treatment" *Acta Oncolog.* 2004;43(6):551-7.

Russell NS, Knoken H, et. al.: "Quantification of patient-to-patient variations of skin erythema developing as a response to radiotherapy" *Radiother Oncol.* 1994;30:213-21.

Shukla HS, Gravelle IH, et. al.: "Mammary skin oedema: a new prognostic indicator for breast cancer" *Br Med J (Clin Res Ed).* 1984;288(6427):1338-41.

Szuba A, Shin WS, Strauss HW & Rockson S: "The third circulation: Radionuclide lymphoscintigraphy in the evaluation of lymphedema" *J Nucl Med.* 2003;44(1):43-57.

Warszawski A, Rottinger EM, et. al.: "20-MHz ultrasonic imaging for quantitative assessment and documentation of early and late postradiation skin reactions in breast cancer patients" *Radiother Oncol.* 1998;47:241-7.

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

Baddour LM: “Breast cellulitis complicating breast conservation therapy” *J Intern Med.* 1999 Jan;245(1):5-9.

Brewer VH, Hahn KA, Rohrbach BW, Bell JL & Baddour LM: “Risk factor analysis for breast cellulitis complicating breast conservation therapy” *Clin Infect Dis.* Sep;3, 2000(3):654-9. Epub 2000 Sep 21.

Indelicato DJ, Grobmyer SR, et al.: “Delayed breast cellulitis: an evolving complication of breast conservation” *Int J Oncol Biol Phys.* Dec 1, 2006;66(5):1339-46.

Miller SR, Mondry T, Reed JS, Findley A & Johnstone PAS: “Delayed cellulitis associated with conservative therapy for breast cancer” *J Surg Oncol.* 1998;67(4):242-5.

Zippel D, Siegelmann-Danieli N, Ayalon S, Kaufman B, Pfeffer R, Zvi Papa M: “Delayed breast cellulitis following breast conserving operation” *Eur J Surg Oncol.* 2003 May;29(4):327-30.



“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.

Clarke M, Collins R Darby S, et. al.; Early Breast Cancer Trialists’ Collaborative Group (EBCTCG): “Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomized trials” *Lancet* Dec 17, **2005**;366(9503):2087-106.

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]

EBCTCG: "Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomized trials" *Lancet* Dec 17, 2005;366(9503):2087-106.

Fisher B, Anderson S, et. al.: "Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy with irradiation for the treatment of invasive breast cancer" *N Engl J Med.* Oct 17, 2002;347(16):1233-1241.

Hughes KS, Schnaper LA, Berry D, et. al. "Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer" *N Eng J Med.* 2004;351:971-7.

Overgaard M, Jensen MB, et. al.: "Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomized trial" *Lancet* 1999;353:1641-8.

Van der Leest M, Evers L, et.al.: "the safety of breast-conserving therapy in patients with breast cancer aged <40 years" *Cancer* 2007;109:1957-64.

Viani G, Stefano EJ, et. al. "Breast-conserving surgery with or without radiotherapy in women with ductal carcinoma in situ: A meta-analysis of randomized trials" *Radiat Oncol.* 2007;2:28

Vinh-Hung V & Verschraegen C: "Breast-conserving surgery with or without radiotherapy: Pooled-Analysis for risks of ipsilateral breast tumor recurrence and mortality" *J Nat Cancer Inst.* Jan 21, 2004;96(2):115-21.

Vujovic O, Yu E, et. al.: "Eleven-year follow-up results in the delay of breast irradiation after conservative breast surgery in node-negative breast cancer patients" *Int J Radiat Oncol Biol Phys.* Mar 1, 2006;64(3):760-4.

Yarnold J: "Minimizing oncological treatment of early breast cancer" *Breast Cancer Res.* 2008;10(Suppl 3):P6.

20-Year Follow-Up NSABP B-06 Trial

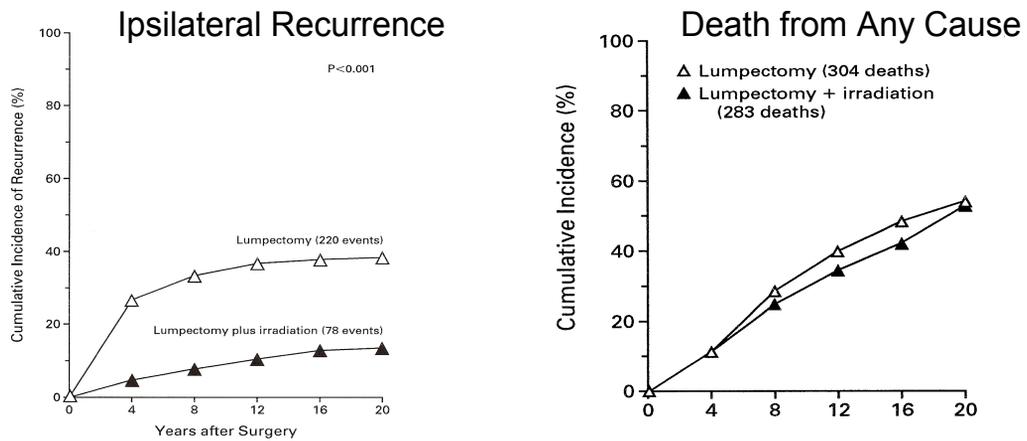


Figure 1 Cumulative Incidence of a First Recurrence of Cancer

- Fisher: *N Engl J Med.* 2002;347:1233-41
- 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.

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.

Rutqvist LE, Rose C, Cavallin-Ståhl E: "A systematic overview of radiation therapy effects in breast cancer" *Acta Oncol.* 2003;42(5-6):532-45.

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 potential for use of gene-expression profiles [Chang 2004, Nuyten 2006, Niméus-Malmström 2007, Tamimi 2008]
 - 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]

Brenner DJ, Shuryak I, et. al.: “Reducing second breast cancers: a potential role for prophylactic mammary irradiation” *J Clin Oncol.* 2007;25(31)4868-72.

Chang HY, Sneddon JB, et. al.: “Gene expression signature of fibroblast serum response predicts human cancer progression: similarities between tumors and wounds” *PLoS Biology* 2004;2:E7.

Dewar J & Graylow: “Hypofractionation for early breast cancer: First results of the UK standardisation of breast radiotherapy (START) trials” *J Clin Oncol.* 2007;25(18S)7s.

Hannoun-Levi: *Breast Cancer Res Treat.* 2003;81(8):243-51.

Hughes L, Wang M, ECOG, NOCTG: “5-year results of intergroup study E5194: Local excision alone (without radiation therapy) for selected patients with DCIS” SABCS Poster 2006:29.

Jobsen JJ, van der Palen J, et. al.: “Timing of radiotherapy and survival benefit in breast cancer” *Breast Cancer Res Treat.* Oct 2006;99(3):289-94.

Lawenda BD, Taghian AG, Kachnic LA, et. al.: “Dose-volume analysis of radiotherapy for T1N0 invasive breast cancer treated by local excision and partial breast irradiation by low-dose interstitial implant” *Int J Radiat Oncol Biol Phys.* 2003;56(3):671-80.

Niméus-Malmström E, Krogh M et. al.: “Gene expression profiling in primary breast cancer distinguishes patients developing local recurrence after breast conservation surgery, with or without postoperative radiotherapy” *Breast Cancer Res.* 2008;10:R34.

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

Tamimi RM, Baer HJ, et. al.: “Comparison of molecular phenotypes of ductal carcinoma in situ and invasive breast cancer” *Breast Cancer Research* 2008, 10:R67