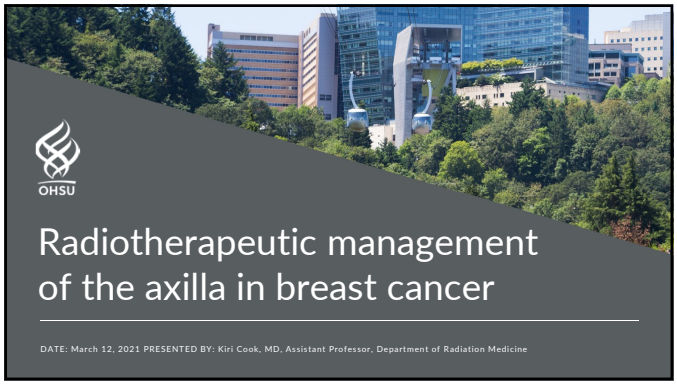
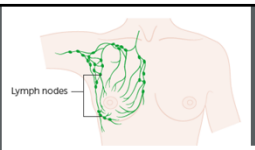


Radiotherapeutic management of the axilla in breast cancer

DATE: March 12, 2021 PRESENTED BY: Kiri Cook, MD, Assistant Professor, Department of Radiation Medicine

Learning Objectives

- Review the data for axillary radiation in the management of breast cancer
- Discuss the controversies surrounding radiation field design in women with low volume axillary disease
- Review the available data to help guide radiation decision making in controversial areas
- Address some unanswered questions in axillary management



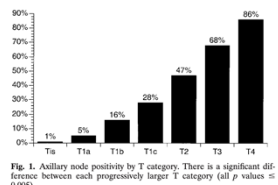


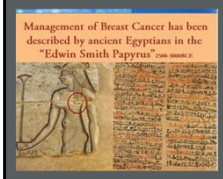
Fig. 1. Axillary node positivity by T category. There is a significant difference between each progressively larger T category (all p values $\leq$ 0.005).

Table 1. T category predicts nodal positivity.

T category	Positive dissections/patients (no.)	p
Tis	3/391 (0.8%)	0.005
T1a	5/110 (5%)	0.002
T1b	47/291 (16%)	0.0001
T1c	195/689 (28%)	<0.00001
T2	276/585 (47%)	<0.00001
T3	106/157 (68%)	0.006
T4	51/59 (86%)	
Total	683/2282 (30%)	

Silverstein et al., World J Surg 2001

Historical Perspective



- 1800s: William Halsted and the radical mastectomy
- 1930s: Radiation therapy as an alternative to surgery
- 1948: Radiation used adjuvantly post-mastectomy
- 1980s: NSABP B-04
- 1994: Sentinel lymph node biopsy

cN0 patients – ACOSOG Z0011

- cT1-T2 N0, post lumpectomy with 1-2 positive sentinel nodes
- Median age 55
- Majority ER/PR+
- Randomization: completion ALND vs no completion ALND
- All received adjuvant whole breast radiation (no RNI)
- 97% had systemic therapy (chemo or endocrine)
- DFS at 10 years 78% ALND vs 80% SNB
- OS at 10 years 84% vs 86%

Giuliano, JAMA 2011 and 2017

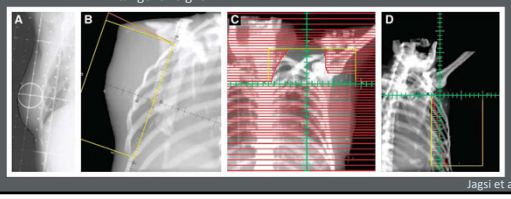
ACOSOG Z0011

	ALND	RT
Lymph node metastases		
0	4 (1.2)	29 (7.0)
1	199 (58.0)	295 (71.1)
2	68 (19.8)	76 (18.3)
3	25 (7.3)	11 (2.7)
≥4	47 (13.7)	4 (1.0)
Missing	77	21

- 27% in ALND group had additional positive nodes
- Median nodes removed = 17
- Radiation can sterilize microscopic nodal disease
- Radiation was tangent only; targeted axilla/3rd field was prohibited

Radiation in Z0011

- 856 women enrolled
  - 605 case report forms obtained
  - 228 detailed RT records
  - 142 with sufficient records to evaluate tangent height
- 50% of patients in each group received high tangents
- 19% received a 3rd field
  - Those receiving a 3rd field had more nodal involvement



Jagsi et al., JCO 2014

AMAROS

- cT1-2 N0 with a positive sentinel node
- Median age 55
- 80% post lumpectomy, majority had 1-2 positive sentinel nodes
  - 60% macromet vs 30% micromet
- 90% received adjuvant systemic treatment
- Randomization: ALND vs adjuvant radiation
- 10 year LRR equivalent (~4%)
- 33% had additional positive nodes on ALND

Donker et al., Lancet 2014 and Rutgers et al., SABCS 2018

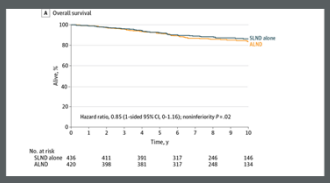
Radiation in AMAROS

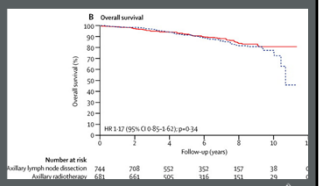
- Axillary RT included all 3 axillary levels and the medial supraclavicular fossa
- Axillary RT allowed after ALND if ≥ 4 positive nodes

	ALND	RT
Lymph node metastases		
0	4 (1.2)	29 (7.0)
1	199 (58.0)	295 (71.1)
2	68 (19.8)	76 (18.3)
3	25 (7.3)	11 (2.7)
≥4	47 (13.7)	4 (1.0)
Missing	77	21

# positive	ALND	Axillary RT
SN	78%	75%
1	17%	20%
2	4%	4%
3	1%	1%
>=4		

Z11 and AMAROS





Toxicity

- Z0011
  - ALND group had higher:
    - Surgical complications
    - Lymphedema
    - Axillary parasthesias
- AMAROS
  - ALND group had higher:
    - Lymphedema
    - Difficulty moving the arm (post hoc analysis)
  - No difference in QoL

- Radiation is standard of care for cT1-2N0 with 1-2 SN+
- RNI or no?

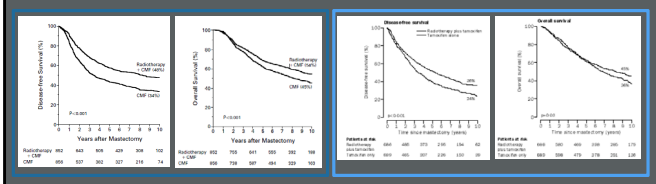
High Risk Breast Cancer

- 82b: Premenopausal women
- LN+, tumor > 5cm, or invasion of skin or pec fascia
- Surgery: total mastectomy and ALND
  - Median LN removed: 7
- Chemo: Cyclophosphamide, MTX, fluorourocil
- Randomized to adjuvant chemo +/- radiation

- 82c: Postmenopausal women randomized to tamoxifen +/- radiation

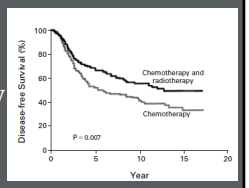
Overgaard et al., NEJM 1997 and Lancet 1999

Danish 82b/82C



British Columbia

- Pre-menopausal women
- LN+
- Surgery: Modified radical mastectomy
  - Median LN removed = 11
- Chemo: CMF
- Randomized to chemo +/- radiation
- OS: 54% vs 46% at 15 years (p = .07)



Ragaz et al., JNCI 2005

Field design in PMRT Trials

- Danish 82b/82c: Chest wall, axilla, supraclav, infraclav, IMN
  - 50 Gy in 25 fx or 48 Gy in 22 fx
- British Columbia: Chest wall, axilla, supraclav, infraclav, bilateral IMN
  - 37.5 Gy in 16 fx

Controversy

- Axillary RT well established alternative to ALND for early stage N+ breast cancer
  - AMAROS: RNI covered
  - Z11: ?? covered
- Survival benefit to PMRT with RNI in high risk patients
- = RNI for everyone!

MA.20

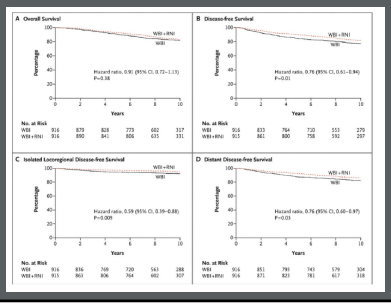
- S/p lumpectomy and SNB or ALND
- Positive nodes or node negative with "high risk features"
  - T3
  - T2 with <10 nodes removed and at least one of: grade 3, ER-, LVSI
- ALND required if SNB+
- Majority received adjuvant chemo
- Median nodes removed: 13
- Randomization: WBRT +/- RNI

Whelan et al., NEJM 2015

Radiation in MA.20

- 50 Gy in 25 fractions, boost allowed
- RNI group: included supraclavicular, infraclavicular and internal mammary nodes
  - If <10 axillary nodes removed or >3 positive nodes, included level I/II axilla.

MA.20 Results



- Improved locoregional recurrence, distant DFS, and DFS, but not OS

EORTC 22922

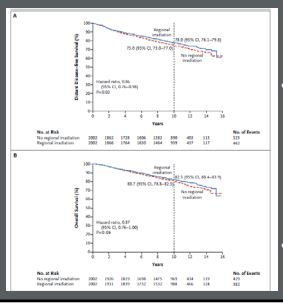
- S/p lumpectomy (76%) or mastectomy + SNB or ALND
- Centrally or medially located N+/-
- Externally located N+
- Majority (85%) had either no involved nodes or 1-3 involved nodes
- Most received systemic therapy
- Median nodes removed: 15
- Randomization: whole breast/chest wall RT +/- RNI

Poortmans et al., NEJM 2015

Radiation in EORTC 22922

- 50 Gy in 25 fractions, most with boost
- RNI group: medial supraclavicular (to AC joint or apical axillary clips or both) + IMN in first 3 intercostal spaces (or first 5 if LIQ primary)
- Axilla not intentionally targeted in majority of cases

EORTC 22922 results



- Improved rate of any first recurrence, distant DFS, and breast cancer mortality, with a marginal effect on OS
- RNI for everyone?!

Toxicity

MA.20

- Acute dermatitis 49% vs 40% (S)
- Pneumonitis/fibrosis: 0.4% vs 0.3% (NS)
- Cardiac disease: 0.9% vs 0.4% (NS)
- Lymphedema: 8.4% vs 4.5% (S)

EORTC

- Pulmonary fibrosis: 4.4% vs. 1.7% (S)
- Cardiac fibrosis: 1.2% vs. 0.6% (NS)
- Cardiac disease: 6.5% vs 5.6% (NS)
- Lymphedema: 12% vs. 10.5% (NS)

Lymphedema

- Prospective screening trial
- 1815 patients from 2005-2018
- Median follow up: 52 months
- Lymphedema: ≥10% relative increase in arm volume >3 months postop

	SNB	SNB+RNI	ALND	ALND+RNI
Lymphedema	8%	10.7%	24.9%	30.1%
LRR	2.3%	0%	3.8%	2.8%

Naoum et al., JCO 2020

Controversy?

- MA.20 and EORTC: DFS benefit seen even in low nodal burden/high risk node negative patients
- The classic PMRT trials (Danish 82b/82c and British Columbia) used RNI and demonstrated a survival benefit in any number of positive nodes
  - Criticisms: high rates of locoregional recurrence; inadequate axillary dissection and outdated systemic therapy
- Higher skin, lung toxicity, slightly increased lymphedema risk
- Modern retrospective series show low rates of regional failure in 1-3N+ patients

OHSU

Supraclavicular failure

Study	N (1-3 N+)	Type of surgery	Median f/u	S'clav failure
Livi 2010	1107	BCS	6.8 yrs	2.1%
Yu 2010	448	BCS (144) Mastectomy (302)	88 mths	1.8%
Wo JY 2010	218	BCS	77 mths	2.1%
Truong 2009	1255	BCS	8.6 yrs	2.2%
MacDonald 2009	165	mastectomy	80 mths	1.8%
Reddy 2007	202	BCS	72 mths	2%
DBCCG 2006	1545 (any N+)	mastectomy	18 yrs	2%
Strom 2005	465	mastectomy	116 mths	5%
Taghian 2004	2957	mastectomy	11.1 yrs	2.3-3.5% (Regional failure)
Stranzl 2004	183	BCS (146) Mastectomy (37)	44.4 mths	1.6%
Chen 2002	2658	BCS (307) Mastectomy (2351)	39 mths	4.3%
Galper 1999	691 (0-3LN+)	BCS	125 mths	1.3%

OHSU

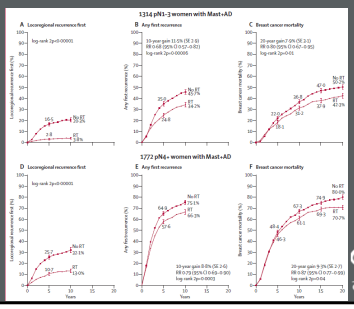
Predicting Supraclavicular Failure

Risk Factor
Age <50
Grade 3
ER-
LVSI
2-3 positive axillary nodes
Level II or III nodes pos
ECE
>20% nodes pos (only applies to ALND)
<10 nodes removed
Largest axillary node >2cm

OHSU

EBCTCG Meta-analysis

- 22 trials, 3786 women
- Post-mastectomy
- Radiation included chest wall, supraclavicular or axillary fossa (or both) and IMN



Lancet 2014

A note on IMN

- DBCG-IMN
- 3089 patients, early stage node positive breast cancer
- All received RT to breast/chest wall, supraclav, axilla II-III, and level I if 6 or more nodes involved
- Right sided: received IMN radiation
- Left sided: no IMN radiation
- Breast cancer mortality: 20.9% vs 23.4% (p = .03)
- Overall survival 72.2% vs 75.9% (p = .005)
- Cardiac disease equivalent

Thorsen et al., JCO 2016

What to treat?

	Breast/CW	Sclav/iclav	Axilla	IMN
1-3 LN+	yes	Z0011-no MA20-yes EORTC-yes 3 RCTs of post mast RT-yes Retro reviews-select cases	Yes if inadequate nodal dissection	Z0011-no MA20-yes EORTC-yes DBCG-yes 3 RCTs of post mast RT-yes
>=4 LN+	yes	3 RCTs of post mast RT-yes	Yes if inadequate nodal dissection or >50% LN+	DBCG-yes 3 RCTs of post mast RT-yes

What to Treat

- For 1-3 nodes, no high risk features: default to covering regional nodes but can consider sacrificing some coverage if normal tissue constraints hard to treat
- For 4+ nodes, high risk features: cover regional nodes, only sacrifice coverage if all options have been exhausted

Unanswered Questions

- Low volume axillary disease
  - MA.39/Tailor RT: ER+, Her2-, LN 1-3+, Oncotype < 18
    - Randomization: RNI vs no RNI (OPEN AT OHSU)
- Neoadjuvant chemotherapy
  - NSABP B51: cT1-3N1, s/p NACT, nodal pCR
    - Randomization: RNI vs no RNI
  - Alliance A011202: cT1-3N1, s/p NACT, positive SNB
    - Randomization: ALND +/- RNI
- Fractionation
  - Standard: 50 Gy in 25 fractions, Hypo: 42.56 Gy in 16 fractions (or similar)
  - RT-CHARM: Hypofractionated vs standard PMRT, in patients planned for breast reconstruction (OPEN AT OHSU)

Thank You!