

Use and Benefits of Radiotherapy in Locally Advanced Cancer

Shilpen Patel MD, FACRO
Departments of Radiation Oncology
and Global Health
University of Washington

Roadmap – Locally advanced

- XRT Alone
- Risk Factors
- Surgery then XRT? (no chemo)
- Surgery then Chemo and then XRT?
- Chemo->Surgery->XRT?
- Breast Conservation after neoadj Chemo and surgery

TABLE 49–5 Locally Advanced Breast Cancer: Surgery Alone

Study	<i>n</i>	Locoregional Recurrence (%)	5-Yr Survival (%)
Arnold and Lesnick ²⁷	50	57 (local and distant)	40.0
Baker et al ²⁸	67	22	48.0
Butcher ²⁹	48	—	48.0
Donegan ³⁰	130	35	52.0
Fracchia et al ³¹	207	25	43.0
Haagensen and Cooley ^{4, 32}	120	49	2.3
		29 Columbia stage C	37.0
Schottenfeld et al ³³	62	6	53.0

TABLE 49–1 Locally Advanced Breast Cancer: Radiation Therapy Alone

Study	<i>n</i>	Radiation Dose (Gy)	Locoregional Control (%)	5-Yr Survival (%)
Zucali et al ⁵	321	45–70	—	21
Bruckman et al ⁶	116	40–85	64	25
Amalric et al ⁷	341	75–80	59	37 (disease free)
Bedwinek et al ⁸	83		39	—
Fletcher and Montague ⁹	273	80–100	68	28
Chu et al ¹⁰	147	60–70	49	24

Can we identify risk factors for
local-regional recurrence after
mastectomy alone?

Risk Factors for LRR after Mastectomy Alone

TABLE 49-12 Incidence of Locoregional Recurrence Postmastectomy Related to Tumor Size in Patients Not Receiving Adjuvant Therapy

Study	Surgery	Locoregional Recurrence (%)			Follow-Up (Yr)
		T1	T2	T3	
Dao and Nemoto ¹⁹	RM	6	6	24	1.3-3+
Donegan et al ¹	RM	7	16	30	5
Rosenman et al ¹⁷	MRM-RM	8	18	32	2-14
Baker et al ¹⁵	RM	—	—	9	5
	MRM	—	—	39	
Maddox et al ¹⁴	RM	—	—	6	3.5
	MRM	—	—	20	

RM, radical mastectomy; MRM, modified radical mastectomy.

■ Tumors > 5cm

25-30% LRR

■ Tumors 2-5cm

15% LRR

■ Tumors < 2cm

<10% LRR

Risk Factors for LRR after Mastectomy Alone

TABLE 49-13 Incidence of Locoregional Recurrence Postmastectomy Related to Axillary Nodal Status in Patients Not Receiving Adjuvant Therapy

Study	Surgery	Axillary Node Negative	Axillary Node Positive			Follow-Up (Yr)
			All	1-3	≥4	
Haagensen ¹⁸²	RM	3	—	4	22	10-37
Donegan et al ¹	RM	6	27	12	38	5
Fisher et al ²⁹	RM	8	24	24	31	5
Valagussa et al ¹⁸³	RM-MRM	6	—	11	37	10
Rosenman et al ¹⁷	RM-MRM	4	—	17	22	2-14
Lee ³⁷	RM-MRM	6	—	11	37	4.4 (median)
Dao and Nemoto ¹⁹	RM	0	16	—	—	1.3-3 +

RM, radical mastectomy; MRM, modified radical mastectomy.

■ ≥ 4 nodes

25-30% LRR

■ 1-3 nodes

15% LRR

■ No nodes

<10% LRR

Risk Factors for LRR after Mastectomy Alone

■ Extent of Axillary Dissection

TABLE III.—RELATION OF NUMBER OF NODES EXAMINED TO DEGREE OF NODAL INVOLVEMENT IN PATIENTS HAVING A RADICAL MASTECTOMY

		Clinical node negative					Clinical node positive		
		Histologic positive nodes, per cent					Histologic positive nodes, per cent		
No. of nodes examined-removed	No. of pts.	≥1	1-3	≥4	No. of pts.	≥1	1-3	≥4	
3-5	11	36	36	0	9	67	67	0	
6-10	54	35	24	11	38	61	42	18	
11-15	106	35	18	17	82	73	30	43	
16-20	85	35	18	18	73	73	23	49	
21-25	48	56	37	19	38	71	24	47	
≥26	51	39	14	24	46	85	28	57	
Per cent of all patients..	355	38.6	21.4	17.2	286	72.7	30.0	42.7	
Per cent of all patients with positive node ..	137	100	55.5	44.5	208	100	41.3	58.7	

Nodes removed	Axillary recurrence
0	21%
< 5	11%
6-10	5%
> 10	<1%

Risk Factors for LRR after Mastectomy Alone

■ Age

≤ 40yo 46% LRR

> 40yo 12% LRR Donegan, *Surg Gynecol Obstet*, 122: 529, 1966.

■ High histologic grade

■ Involvement of pectoralis fascia

■ Margin Status

Sites of LRR after Mastectomy Alone

TABLE 49-14 Sites of Locoregional Recurrence After Mastectomy

Study	Single Site (% recurrence)				Multiple Sites (% recurrence)	
	<i>Chest Wall</i>	<i>Axilla</i>	<i>Supraclavicular</i>	<i>IMN</i>	<i>Chest Wall and Nodes</i>	<i>Regional Nodes</i>
Aberizk et al ¹⁸⁴	50					
Schwaibold et al ⁴²	67	4	8	3	17	
Bedwinek et al ¹⁸⁵	46	8	19	8	12	4
Halverson et al ¹⁸⁶	60	8	13	6	10	4
Danoff et al ⁸⁵	69	3	0	3	22	
Rutqvist et al ¹⁰⁹	60	11	22	—		

IMN, internal mammary node.

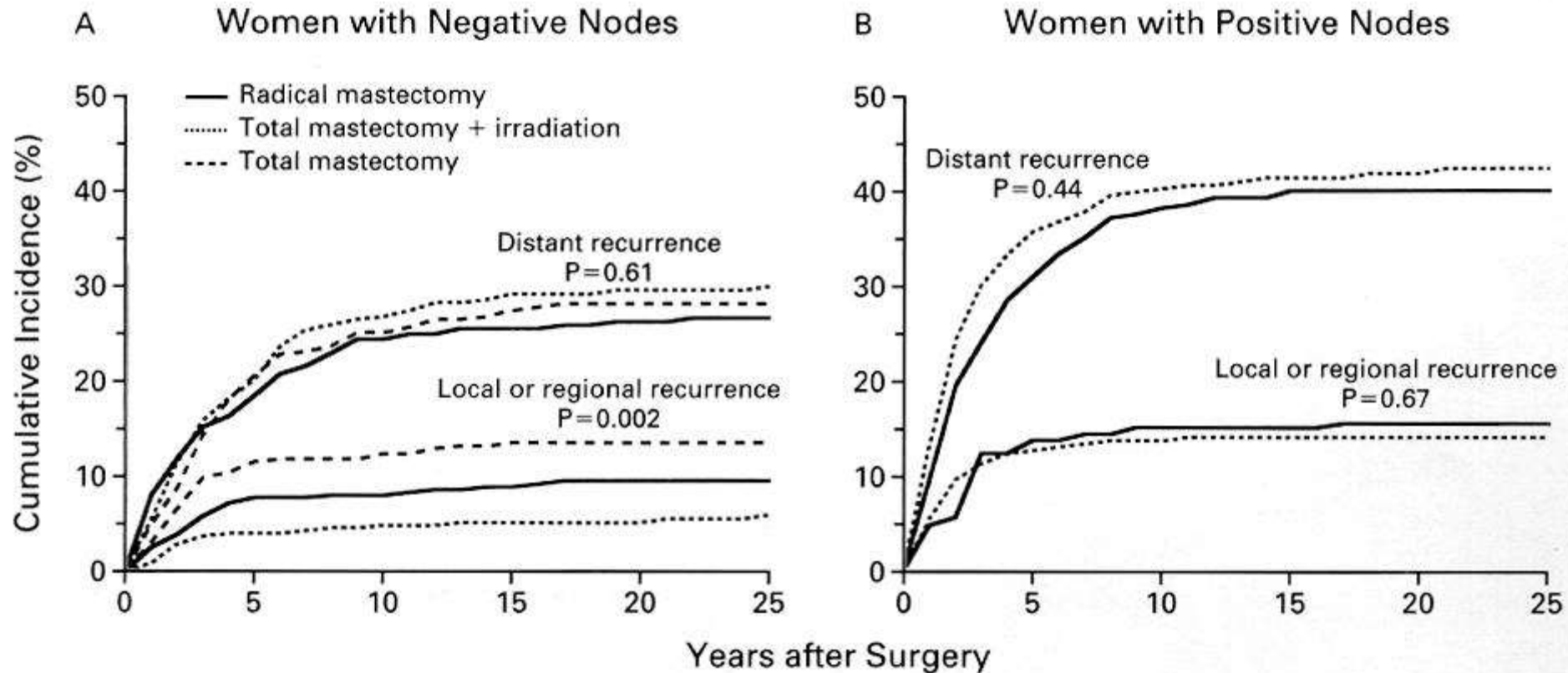
- Chest wall is by far the most common site of recurrence in patients treated with mastectomy alone, followed by supraclavicular nodes.

Is there a role for PMRT in patients who *do not* receive adjuvant chemotherapy?

Fisher, et al. "Postoperative Radiotherapy in the Treatment of Breast Cancer: Results of the NSABP Clinical Trial." Ann Surg; 172: 711-731, 1970.

- Local regional recurrence (CW, scar) was 8% in PMRT group vs 19% in control.
- Marked reduction in proportion of supraclavicular nodal involvement in PMRT group
- In these early trials, survival within each arm related to number of +nodes.
- No difference in survival between groups.

NSABP B-04: results



Cuzick, et al. "Cause-Specific Mortality in Long-Term Survivors of Breast Cancer who Participated in Trials of Radiotherapy." JCO, 12: 447-453, 1994.

- Meta-analysis involving all large studies commencing before 1975 in which surgery was the same for both arms.
 - The only difference in treatment was the random allocation of radiotherapy.
- Initial results first published in 1987 showed:
 - No difference in overall survival
 - In pts surviving > 10yrs, the use of PMRT was associated with significant increase in mortality.
 - Reports from the individual trials revealed increased mortality was related to cardiovascular disease.
- This update includes cause-specific mortality data from 7 of 8 trials (data from NSABP B-04 data unavailable).

Since PMRT seemed associated
w/ excess cardiac mortality, we
rethought how to approach locally
advanced breast cancer.

Recurrence Patterns with Mastectomy and Adjuvant Chemo

- MDACC retrospective review of 1031 patients treated on 5 trials using mastectomy and doxorubicin-based chemo *without RT*

Table 2. Sites of LRR

Site	Median Interval (months)	Isolated LRR		Total LRR	
		No.	%	No.	%
Chest wall	27	122	98	122	68
Supraclavicular	35	41	33	71	40
Axilla	40	21	17	25	14
Infraclavicular	63	10	8	12	7
Internal mammary	39	—	—	15	8
Any site	29	124	100	179	100

NOTE. Percentages represent fraction of LRRs including the specific site as a component of failure. Individual patients may have experienced more than one site of failure, so percentages do not total 100%.

- 42% of LRR occurred after 3yrs, and 21% occurred after 5yrs.
- 10yr isolated LRR: 14%
- 10yr total LRR: 19%
- On multivariate analysis, T-stage, # +LN, ENE remained significant positive predictors for LRR

ECOG Experience

■ Results:

- 55% experienced disease recurrence:
 - Isolated LRF: 13%
 - LRF + DF: 8%
 - DF only: 34%
- 1-3+ nodes 12.9% LRF alone at 10yrs
- ≥ 4 nodes 28.7% LRF alone at 10yrs
- On multivariate analysis, tumor size, ER+, # involved nodes, remained significant prognostic variables for LRF \pm DF.
 - Note: # LNs sampled not predictive (79% had > 10sampled)

ECOG Experience

Table 5. Ten-Year Cumulative Incidence of Isolated LRF, LRF With or Without Simultaneous DF, DF Only, and Specific Sites of LRF in Relation to Conventional Groupings of Tumor Size and Number of Involved Nodes

Tumor Size, No. of Nodes	No. of Patients	Isolated LRF		LRF \pm DF		DF Only		Local		Supraclavicular- Intraclavicular		Axillary	
		%	SE	%	SE	%	SE	%	SE	%	SE	%	SE
T1, 1-3	407	9.1	1.5	12.4	1.7	23.2	2.2	8.5	1.4	3.9	1.0	2.0	0.7
T2, 1-3	576	7.0	1.1	12.1	1.4	28.0	1.9	7.5	1.1	4.1	0.8	1.1	0.4
T3, 1-3	35	22.9	7.2	31.4	8.0	37.4	8.5	25.7	7.5	2.9	2.9	2.9	2.9
T1, 4-7	180	11.1	2.4	19.9	3.1	34.0	3.6	12.3	2.5	7.7	2.1	2.4	1.2
T2, 4-7	349	16.9	2.1	26.7	2.5	34.1	2.7	15.0	2.0	9.5	1.6	6.8	1.4
T3, 4-7	33	28.7	8.3	44.8	9.2	29.0	8.4	25.7	8.1	15.9	6.7	6.2	4.4
T1, \geq 8	110	19.6	3.9	32.7	4.6	39.3	4.8	15.9	3.6	14.9	3.5	11.3	3.1
T2, \geq 8	297	19.6	2.4	32.7	2.8	45.8	3.0	15.9	2.2	15.7	2.2	6.8	1.5
T3, \geq 8	29	7.3	5.1	33.2	9.5	46.8	10.0	18.5	7.9	18.2	7.7	4.0	4.1

Table 10. Specific Sites of LRF for the Study Population

Site	Without Simultaneous DF		With Simultaneous DF		Total	
	No.	%	No.	%	No.	%
Local	131	6.5	67	3.3	198	9.8
Supraclavicular-intraclavicular nodes	64	3.2	49	2.4	113	5.6
Axillary nodes/axillary soft tissue	30	1.5	15	0.7	45	2.2
Internal mammary nodes	1	0.05	1	0.05	2	0.1
Local + axilla	11	0.5	5	0.2	16	0.8
Local + supraclavicular- intraclavicular	8	0.4	15	0.7	23	1.1
Local + internal mammary	0		1	0.05	1	0.05
Local + axilla + supraclavicular- intraclavicular	2	0.1	3	0.1	5	0.2
Local + supraclavicular- intraclavicular + internal mammary	0		1	0.05	1	0.05
Axilla + supraclavicular- intraclavicular	7	0.3	9	0.4	16	0.8

- As # of nodes involved increased, the risk of isolated LRF, LRF \pm DF, and DF increased.
- Majority of failures were local (chest wall, scar), and SCLV.

Can the addition of RT to
adjuvant chemotherapy improve
locoregional control, thereby
improving survival?

British Columbia

■ Median f/u: 150 months

	RT + chemo	Chemo	p-value
10yr LRR	13%	25%	<0.001
15yr LRR	13%	33%	
10yr DFS	56%	41%	<0.001
15yr DFS	50%	33%	
10yr OS	64%	54%	<0.001
15yr OS	54%	46%	

■ Local Regional Recurrence based on LN status (Median #nodes removed: 11)

	RT+chemo	Chemo	p-value
1-3+ nodes			
10yr LRR	10%	16%	1.17
15yr LRR	10%	33%	
≥4+ nodes			
10yr LRR	79%	41%	0.04
15yr LRR	79%	46%	

← Trending towards
significance at 15yrs

Danish 82b

■ Median f/u: 114 months

	RT + chemo	Chemo alone	p-value
10yr LRR	9%	32%	<0.001
1-3+ LN	7%	30%	
≥4+LN	14%	42%	
10yr DFS	48%	34%	<0.001
1-3+ LN	54%	39%	
≥4+LN	27%	14%	
10yr OS	54%	45%	<0.001
1-3+ LN	62%	54%	
≥4+LN	32%	20%	

■ On multivariate analysis, size of primary, frequency and # nodes, grade, use of RT and age were significant predictors of outcome.

Danish 82b: results

■ Criticisms:

- Only 7 nodes on average removed.
 - In ECOG and MDACC experiences, 15 and 17 were removed on average.
- Axillary dissection was limited compared to our standards today
 - 40% of LRRs were in axilla as opposed to most studies where CW/scar are most common sites of LRR.
- This may explain why benefit existed and was so large in pts with 1-3 nodes positive.

	10yr LRR	
	1-3+ nodes	> 3+ nodes
ECOG	13%	29%
MDACC	10%	21%
BC control arm	16%	41%
BC RT/chemo	10%	21%
Danish 82b control arm	30%	42%
Danish 82b RT/chemo	7%	14%

Danish 82c: Results

- Median f/u: 119 months

	RT+T	T alone	p-value
10yr LRR	8%	35%	<0.001
10yr DFS	36%	24%	<0.001
10yr OS	45%	36%	<0.001

	RT+T	T alone
10yr LRR	8%	35%
1-3+LN	6%	31%
≥4+LN	11%	46%
10yr DFS	36%	24%
1-3+LN	44%	31%
≥4+LN	18%	6%
10yr OS	45%	36%
1-3+LN	55%	44%
≥4+LN	24%	17%

- #nodes removed (< 8 or ≥ 8) did not influence 10yr OS in either arm, but #involved nodes did.
- Again, limited axillary dissection would contribute higher LRR in pts with 1-3+ LNs.

What about PMRT
after neoadjuvant
chemotherapy?

PMRT after neoadjuvant chemotherapy

- Huang et al. J Clin Oncol 2004;22:4691-4699
 - Neoadj. Chemo + mastectomy +/- PMRT
 - Imbalances in prognostic factors
 - RT offered to pts with more extensive disease
 - PMRT decreased 10 yr LRR (8% vs 22%)

Subgroup	Treatment	LRR (%)	CSS (%)
T4 disease	PMRT	15	45
	No PMRT	46	24
N2-N3 disease	PMRT	12	49
	No PMRT	40	27
Stage IIIB/IIIC	PMRT	15	44
	No PMRT	51	22

Favorable responders to neoadj chemo still benefited from PMRT

PMRT after neoadjuvant chemotherapy

- PMRT in pts with pCR following neoadj chemo
 - McGuired et al. IJROBP 2007;68(4):1004-1009
 - 10 yr LRR in clinical Stage I/II: No benefit of PMRT
 - 10 yr LRR in clinical stage III
 - Significant improvement with PMRT
 - 7.3 +/- 3.5% with PMRT vs 33.3% +/- 15.7% w/o PMRT (P=0.040)

Breast Conservation after Neoadjuvant Chemotherapy

- Rates of BC higher (Stage II/III) with neoadjuvant vs adjuvant (Fisher et al. J Clin Oncol 1997;15:2483-2493 (NSABP B-18) and van der Hage et al. J Clin Oncol 2001;19:4224-4237 (EORTC 10902))
 - No significant difference in DFS, DM-free survival or OS
 - But higher rates of local recurrence
 - NSABP B-18
 - 10.7% (BCT) vs 7.6% (Mastectomy)
 - If planned mastectomy changed to BCT
 - LR 15.7% vs 9.6% (pre-planned BCT)

Breast Conservation after Neoadjuvant Chemotherapy

- MDACC (Chen et al. J Clin Oncol 2004;22:2303-2312)
 - Careful pts selections for BCT following neoadj. Chemo
 - No post op residual malignant calc
 - No residual T4 skin abnormality
 - Negative surgical margins
 - No multicentric disease
 - Willingness to undergo surgery and XRT
 - 5/10 yr LR → 5%/10% (72% of pts with Stage IIB/III)

Breast Conservation after Neoadjuvant Chemotherapy

- 4 factors associated with inc LRR (Chen et al. Cancer 2005;103:689-695)
 - Clinical N2-N3 disease
 - LVSI
 - Multifocal pattern of residual disease
 - 20% of LRR
 - Residual disease greater than 2 cm
 - 84% of patients with 0 or 1 of these factors
 - LRR=4% at 10 yrs
 - Three of these factors
 - LRR~ 45%
- Pt selection important.
 - Multidisciplinary approach

ASTRO Consensus

Patients:

1. Patients with ≥ 4 +LN
2. Tumors > 5cm

Technique:

1. CW should always be treated
2. IMN inclusion is uncertain
3. Following Level I/II dissection, use of third field to treat axillary apex and SCLV is appropriate for node+ patients (especially ≥ 4 nodes+)
4. Addition of posterior axillary field may be appropriate
5. PRMT has potential to cause late cardiac mortality.
6. The optimal sequencing of chemo and PRMT is uncertain

ASCO Consensus

Patients:

1. Patients with ≥ 4 + LN
2. T3 or Stage III

Technique:

1. CW irradiation is mandatory
2. Insufficient evidence regarding IMN
3. Axillary RT should not be given after complete level I/II dissection. There is insufficient evidence to make recs on some subgroups.
4. SCLV should be treated in all patients with ≥ 4 + LN (insufficient evidence for 1-3+ LN).
5. The risk of serious toxicity of PMRT when using modern techniques is low enough that such considerations should not limit its use when otherwise indicated. There is insufficient data to r/o possibility of very late cardiac toxicities.
6. Doxorubicin should not be administered concurrently with PMRT.

■ QUESTIONS?