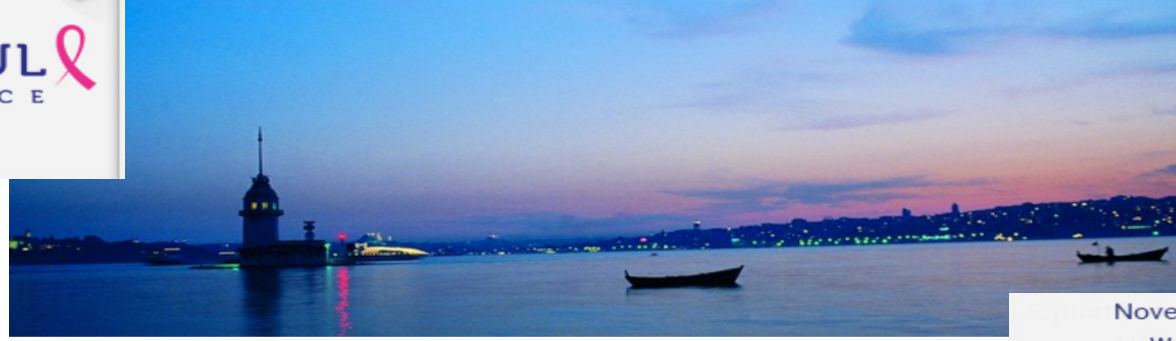


BREASTANBUL
THE CONFERENCE



November 10-12, 2016
Wyndham Grand
Istanbul, Levent

Radiation is an optimal choice for treating axilla in SLN positive mastectomized pts

Merdan Fayda, MD

Istinye University Faculty of Medicine

Dept. of Radiation Oncology

Background

Clinical negative axilla

ALND vs. Axillary RT

N= 658, All BCS, < 3 cm tumor

15-year survival

73,8 % vs 75,5 %

Axillary recurrences

1 % vs. 3 % (p= 0.04)

Louis-Sylvestre, JCO, 2004

Clinical negative axilla

RM vs. TM + axillary RT [no ALND] vs TM + ALND (+ax)

N= 1079

Clinical positive axilla

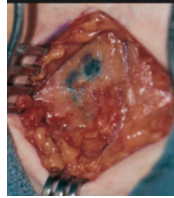
RM vs. TM + axillary RT [no ALND]

N= 589

Removing of occult + nodes and

RT has no surv. Adv.

Fisher, NEJM, 2002



The probability to find additional lymph node at ALND

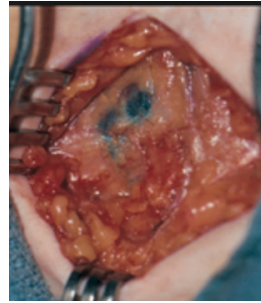
SLN status	ITC	Micro	Macro
	0 %	13 %	27 - 32 %
			<p>ECE vs no ECE 20% vs 3 % had additional ≥ 4 positive nodes at ALND</p> <p>Pts with ECE if the ECE < 2mm vs > 2mm 9 % vs 33 % had additional ≥ 4 positive nodes at ALND</p>

Chu, Ann Surg, 1999

Galimberti,
Lancet Oncol,
2013

Gooch, Ann Surg Oncol, 2014

Giuliano, Ann Surg 2016

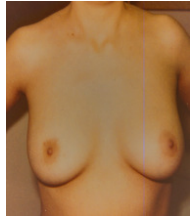


RCT for SLND +

	ITC	Micro	Macro	ECE
Z0011 (all BCS) n=856	included	40 %	60 %	Gross ECE excl.
IBCSG 23-01 n=931 Mastectomy (9%) n=86	included	100%	None	None
AMAROS n= 1425 Mastectomy (17%) n= 248	12 %	29 %	59 %	Unknown

Retrospective studies mastectomy + SLND no PMRT

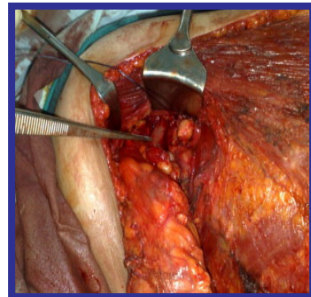
MSKCC n=200 (n=10 PMRT)	54 %	37 %	9 %	?
MD Anderson n=58 (n=12 PMRT)	none	81 % (25 %)	19 % (75%)	5 %



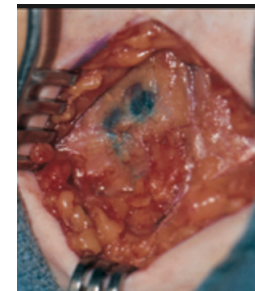
RCT for SLND + Z 0011

- All BCS n=856
- T1-2 clinic N0 pts with 1-2 + sentinel lymph node(s)

[Micro (40%) [ITC+] and Macro mets, Gross ECE excl.]



ALND vs SLND



Med FU 9.25 years

5 y OS
91.8 % vs 92.5 %

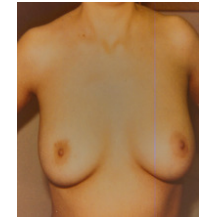
5 y DFS
82.2 % vs 83.9 %

Ten year LRR 6,2 %

Ten year LRR 5,3 %

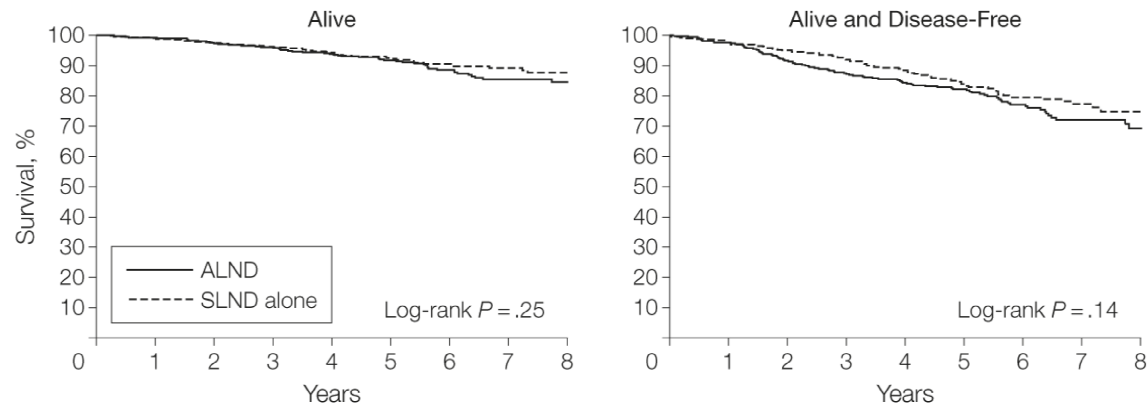
Giuliano, Ann Surg 2016

RCT for SLND + Z 0011



T1-2 clinic N0 pts with 1-2 + sentinel lymph node(s)

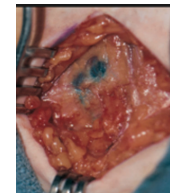
[Micro (40%) ITC+ and Macro mets]



No. at risk		0	1	2	3	4	5	6	7	8	0	1	2	3	4	5	6	7	8
ALND	420	408	398	391	378	313	223	141	74	420	369	335	310	286	226	152	83	37	
SLND alone	436	421	411	403	387	326	226	142	74	436	395	363	337	307	231	147	81	36	



ALND \cong SLND



Giuliano, JAMA 2011

Radiation Field Design in the ACOSOG Z0011 (Alliance) Trial

Reshma Jagsi, Manjeet Chadha, Janaki Moni, Karla Ballman, Fran Laurie, Thomas A. Buchholz, Armando Giuliano, and Bruce G. Haffty

228 patients' detailed RT fields:

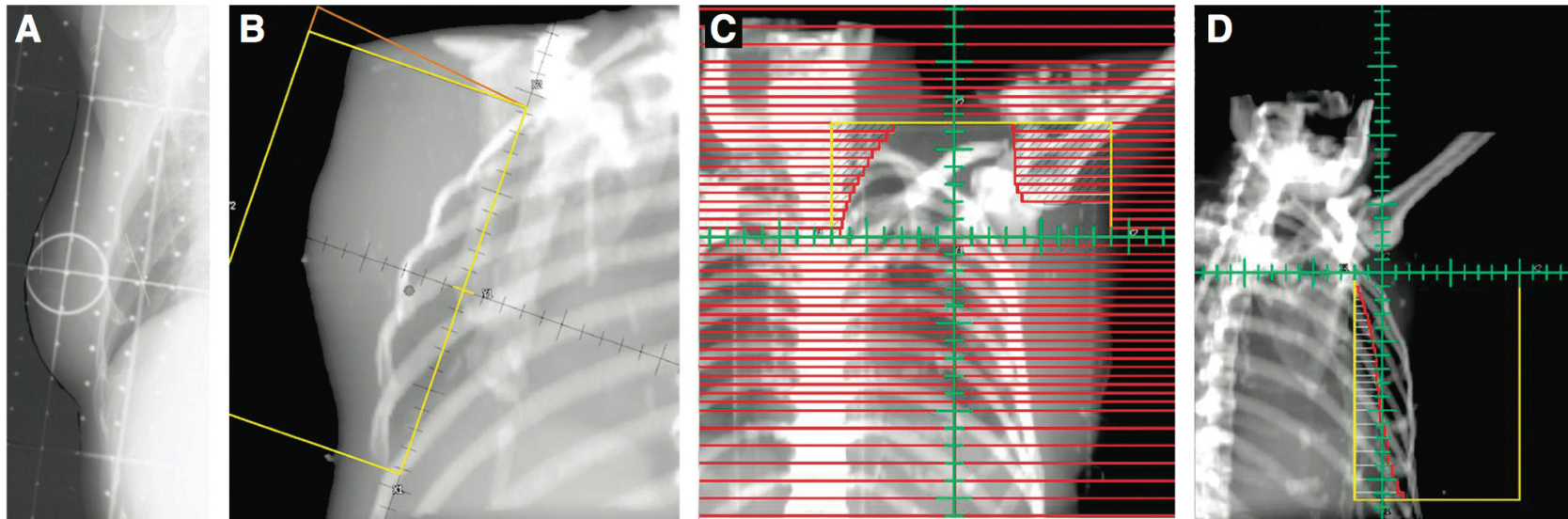
- 104/389 (26.7%) ALND
 - 61 of 104 (59%) received some form of lymphatic RT
 - SCV n=22 (21%)
 - PAB (posterior axillary boost) n=6 (6%)
 - High tangents n=33 (32%)
- 124/404 (30.7%) SLND
 - 73 of 124 (59%) received some form of lymphatic RT
 - SCV n=21 (17%)
 - PAB n=12 (10%)
 - high tangents n=40 (32%)

Major protocol violation

Major protocol violation

Radiation Field Design in the ACOSOG Z0011 (Alliance) Trial

Reshma Jagsi, Manjeet Chadha, Janaki Moni, Karla Ballman, Fran Laurie, Thomas A. Buchholz, Armando Giuliano, and Bruce G. Haffty

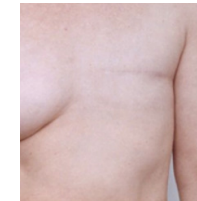
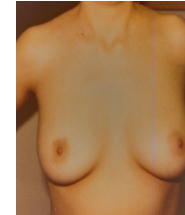


60 % of both arm recieved some form of lymphatic RT

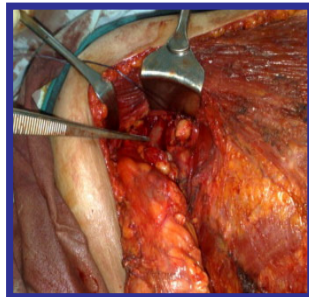
Jagsi, JCO, 2014

RCT for SLND + IBCSG 23-01

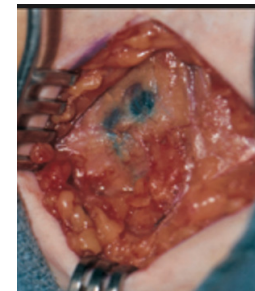
- BCS and mastectomy (9 %) n=931
- T1-2 clinic N0 pts with 1-2 + [95% 1+]sentinel lymph node(s)



[Micro (100%) ITC included, ECE excluded]



ALND vs SLND

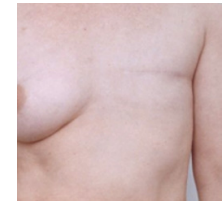


5 y DFS
84.4 % vs 87.8 %

Galimberti, Lancet Oncol, 2013



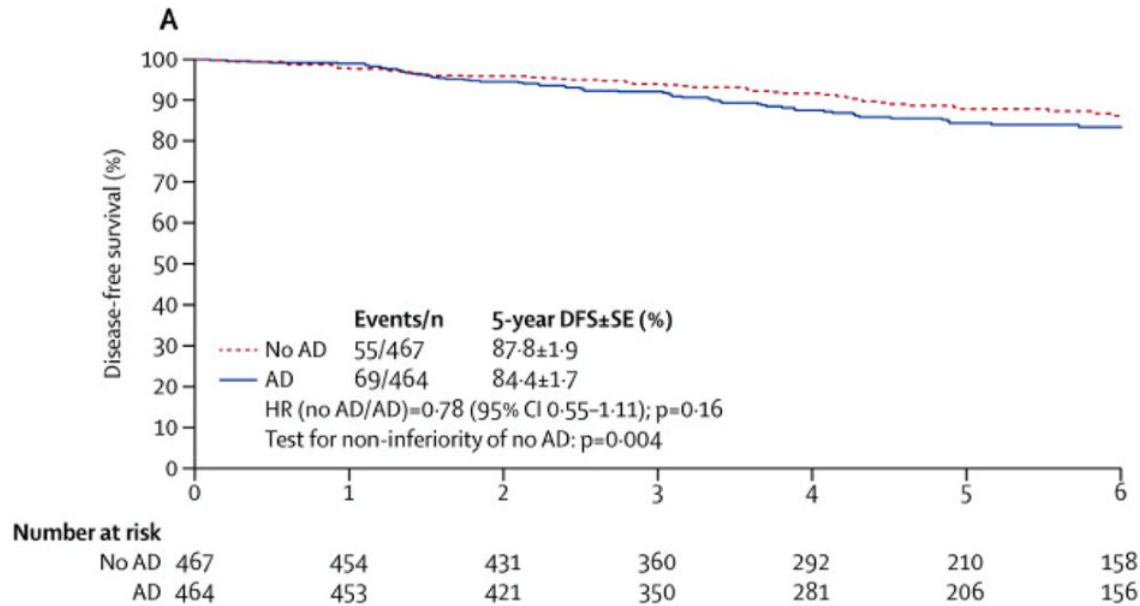
RCT for SLND + IBCSG 23-01



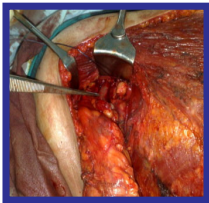
- T1-2 clinic N0 pts with 1-2 + [95% 1+] sentinel lymph node(s)

PMRT details ?

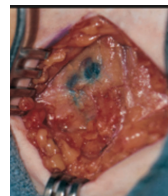
[Micro (100%) ITC , ECE excluded]



Less sensory-motor neuropathy and lymphedema with SLND



ALND \cong SLND

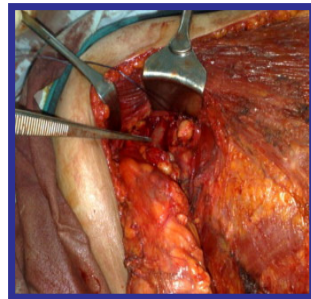
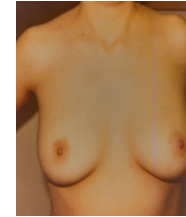


Galimberti, Lancet Oncol, 2013

RCT for SLND + AMAROS

- BCS and mastectomy (17 %) n= 1425
- T1-2 clinic N0 pts with 1-2 + sentinel lymph node(s)

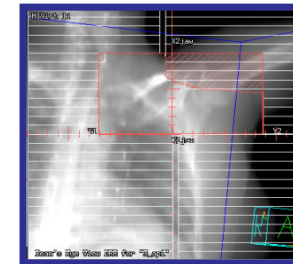
[Micro (29 %), ITC (12%), macro (59%), ECE unknown]



ALND vs Axillary RT

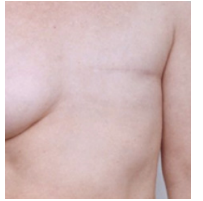
Med FU 6,1 y

5 y axillary recurrence rates
0.54 % vs 1.03 %



Mastectomy
26 % in ALND arm
42 % in Ax RT arm
also recieved CWRT

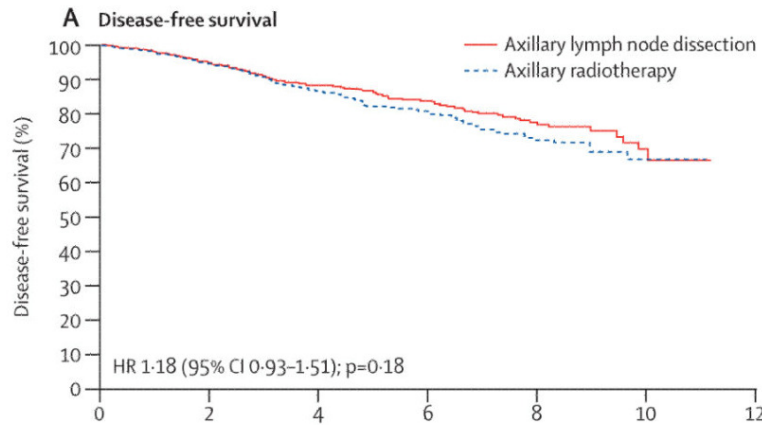
Donker, Lancet Oncol, 2014



RCT for SLND + AMAROS

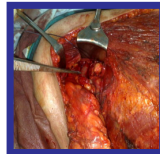
- T1-2 clinic N0 pts with 1-2 + sentinel lymph node(s)

[Micro (29 %), ITC (12%), macro (59%), ECE unknown]

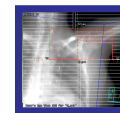


	0	2	4	6	8	10	12
Axillary lymph node dissection	744	686	511	322	140	33	0
Axillary radiotherapy	681	633	468	284	131	24	0

Less lymphedema with Axillary RT

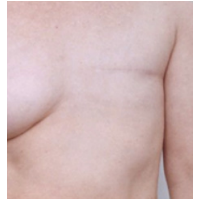


ALND \cong Axillary RT



Donker, Lancet Oncol, 2014

MD Anderson study (retrosp) SLND + mastectomy



- Post mastectomy T1-2 N1 (sn)

n = 58 (no PMRT)

n = 12 (PMRT)

med. Follow-up: 66 months

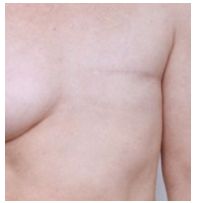
ITC	Micro	Macro	ECE
none	81 % (25 %)	19 % (75%)	5 %

Selected cases could be treated mastectomy + SLNB

TABLE 3 Clinicopathologic characteristics of patients with a positive SLNB treated with mastectomy without axillary treatment who developed a regional recurrence

Age	Histology/ nuclear grade	Tumor(s) size (cm)	Tumor markers (ER/PR/Her2)	# SLN positive/ removed	Size SLN metastasis (mm)	Extranodal extension/lymphovascular invasion	Chemotherapy	Radiation therapy	Hormonal therapy	Recurrence	Predicted probability of positive non-SLN ¹⁰ (%)
58	IDC/3	3.5	±/+	1/6	<1	±	Adjuvant	-	+	Axillary	4
34	IDC/2	1.0, 0.7	+/-±	1/3	0.3	-/-	Adjuvant	-	+	Supra- clavicular	7

MSKCC (retrosp) SLND + mastectomy



- Post mastectomy T1-2 N1 (sn)
n = 200 (no PMRT)
n = 10 (PMRT)
med. Follow-up: 58 months

ITC	Micro	Macro
54 %	37 %	9 %

After ITC excluded
5 y local and regional rec.
1.2% and 2.5%

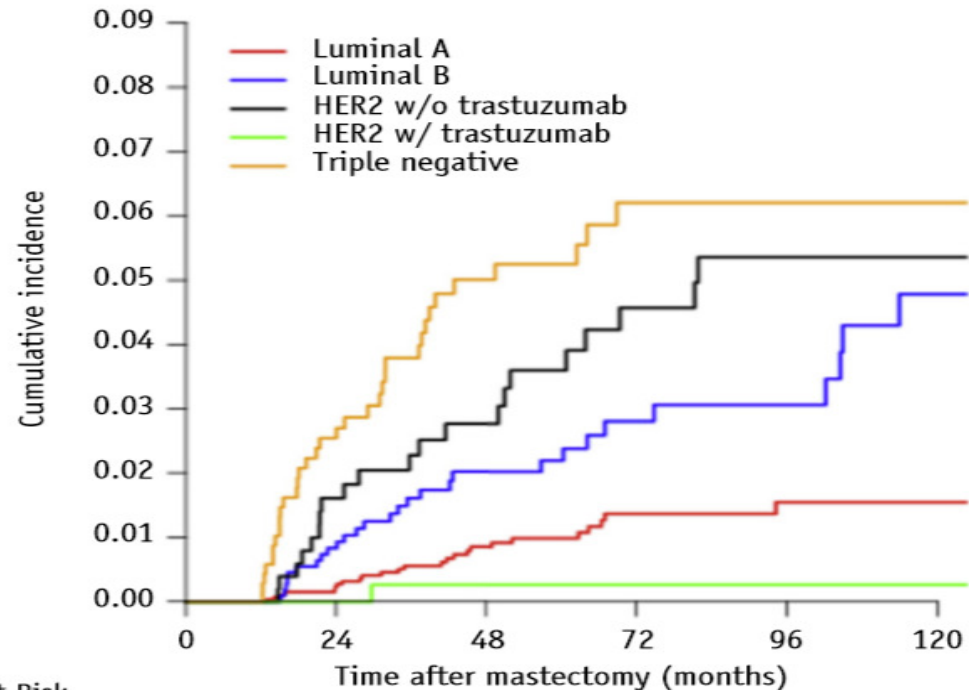
TABLE 3 Clinical and pathologic characteristics of patients with regional recurrence

Age at diagnosis (years)	Surgery type	Histology	T stage	N stage	ER status	PR status	Her2 status	CT	RT	HT	Mo. to recurrence
43	TM	IDC	T2	N1mic	+	+	-	ACT	None	Yes	31.7
43	TM	IDC	T1mic	N1mic	-	-	-	-	None	No	29.8
78	TM	IDC	T1a	N1mic	-	-	+	ACT	None	No	24.9

Milgrom, Ann Surg Oncol, 2012

Biological Subtype Predicts Risk of Locoregional Recurrence After Mastectomy and Impact of Postmastectomy Radiation in a Large National Database

- 2000-2009
- N=5673
- Stage 1-3
- 30 % PMRT
- Med FU: 50,1 months



No. at Risk	0	24	48	72	96	120					
Luminal A	2741	2741	2386	1842	1466	1093	741	517	345	209	90
Luminal B	1147	1147	976	726	555	413	280	184	121	77	43
HER2 w/o trastuzumab	524	524	447	381	317	262	213	174	122	79	46
HER2 w/ trastuzumab	566	566	476	338	250	150	66	36	21	10	4
Triple negative	695	695	549	427	327	244	165	113	81	46	23

Further treatment of axilla postmastectomy pT1-2 N1(sn)

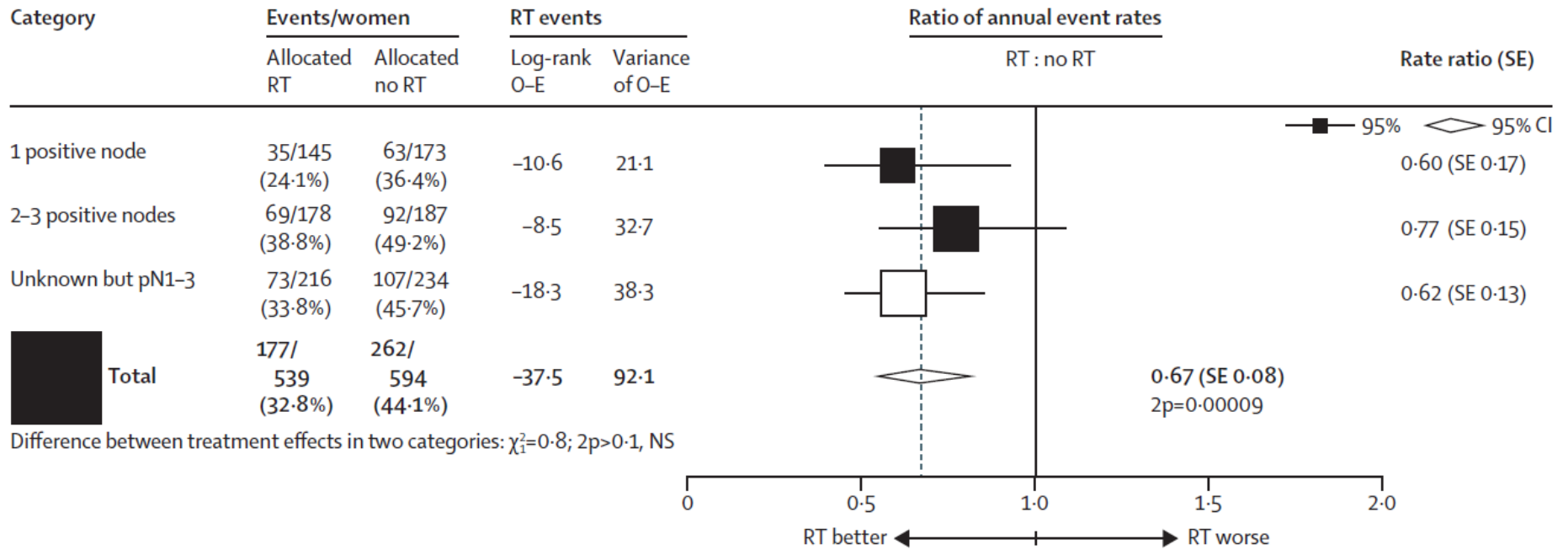
T 1-2	PMRT		Axillary RT		ALND	
SLN status	ER + / cerbB2 -	ER-/cerbb2+	ER + / cerbB2 -	ER-/cerbb2+	ER + / cerbB2 -	ER-/cerbb2+
1 + micro.	-	+	-	+	-	-
2+ micro.	+/-	+	+/-	+	-	-
≥ 3 micro	+ (postALND)	+ (postALND)	+ (postALND)	+ (postALND)	+/-	+
1-2 + macro.	+	+	+	+	-	-
≥ 3 + macro.	+ (postALND)	+ (postALND)	+ (postALND)	+ (postALND)	+	+

Second part

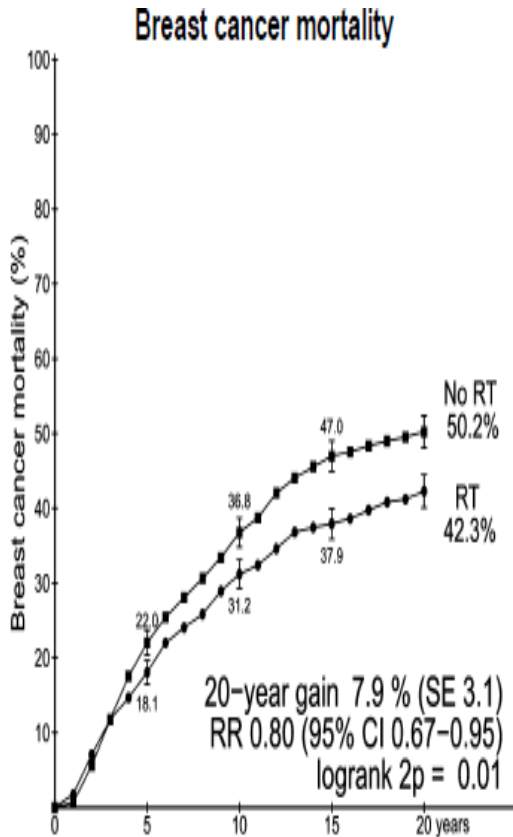
Positive effect of lymphatic RT / PMRT

- EBCTG metaanalysis of PMRT, 2014
- MA-20
- EORTC MI-MS trials

A Any first recurrence (years 0-9)

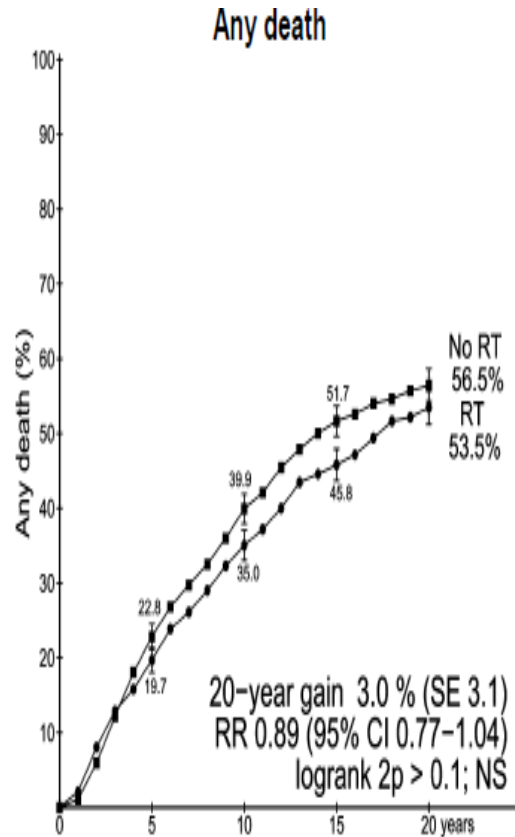


1314 pN1-3 women with Mast+AD



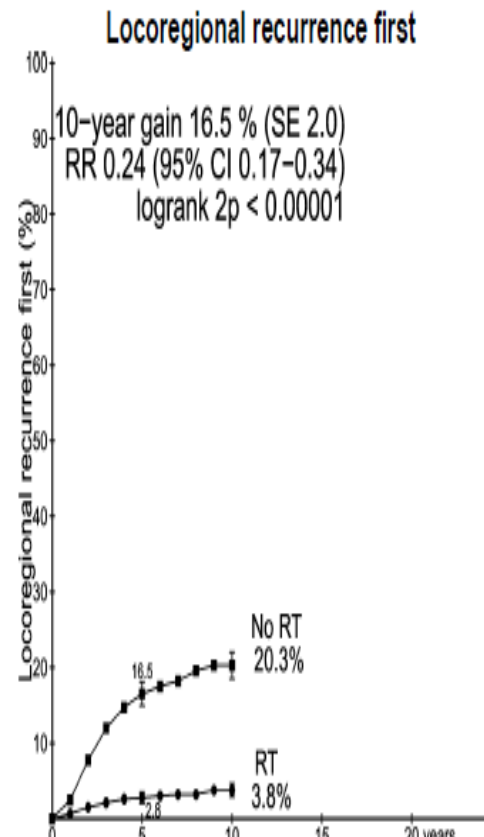
Breast cancer mortality rates (%/year) and logrank analyses

	Years 0-4	Years 5-9	Years 10-14	Years 15-19	Years 20+
RT	3.33 (111/2822)	3.50 (79/2172)	2.12 (35/1646)	1.39 (15/1090)	1.29 (11/859)
No RT	4.83 (148/3064)	4.17 (84/2255)	3.56 (58/1630)	1.32 (13/966)	1.59 (12/757)
Rate ratio, from	0.82 SE 0.12	0.84 SE 0.15	0.59 SE 0.17	1.17 SE 0.44	0.88 SE 0.42
(O-E)/V	-11.2/66.7	-6.5/37.4	-11.0/20.7	0.8/6.1	-0.6/5.0



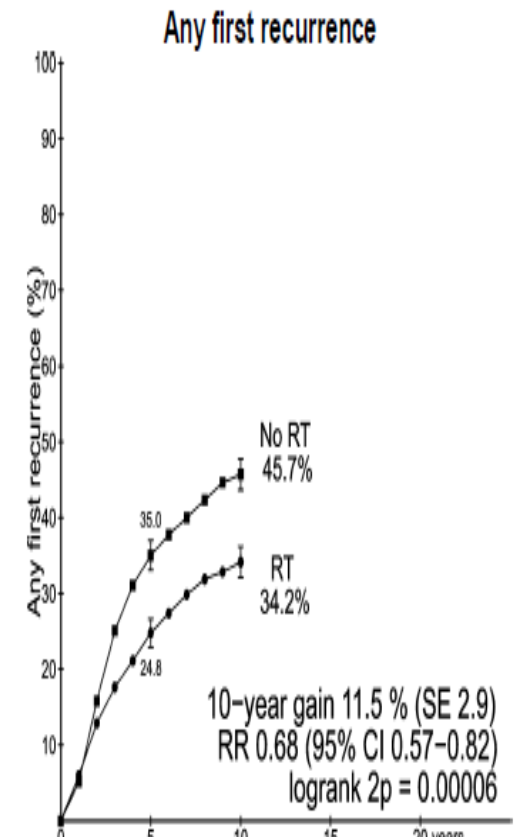
Any death rates (%/year) and logrank analyses

	Years 0-4	Years 5-9	Years 10-14	Years 15-19	Years 20+
RT	4.50 (127/2822)	4.37 (85/2172)	3.76 (62/1646)	3.06 (33/1090)	4.12 (35/859)
No RT	6.22 (160/3064)	5.06 (114/2255)	4.48 (73/1630)	2.64 (26/966)	4.48 (34/757)
Rate ratio, from	0.88 SE 0.12	0.85 SE 0.14	0.83 SE 0.17	1.51 SE 0.36	0.90 SE 0.25
(O-E)/V	-8.2/33.2	-7.5/46.4	-5.6/30.3	5.0/12.1	-1.4/13.9



Locoregional recurrence first rates (%/year) and logrank analyses

	Years 0-4	Years 5-9
RT	0.58 (15/2588)	0.21 (4/1876)
No RT	3.61 (86/2383)	0.97 (17/1745)
Rate ratio, from	0.23 SE 0.10	0.28 SE 0.25
(O-E)/V	-36.1/25.8	-6.5/5.1



Any first recurrence rates (%/year) and logrank analyses

	Years 0-4	Years 5-9
RT	6.00 (157/2616)	2.85 (54/1896)
No RT	8.75 (235/2696)	3.87 (69/1782)
Rate ratio, from	0.67 SE 0.09	0.75 SE 0.17
(O-E)/V	-34.8/44.8	-7.8/26.7

Nodal Status	No. of Patients	10-Year Local Recurrence Risk		20-Year Breast Cancer Mortality			20-Year Any-Cause Mortality		
		RT v no RT (%)	<i>P</i>	RT v no RT (%)	RR	<i>P</i>	RT v no RT (%)	RR	<i>P</i>
Mastectomy plus axillary dissection to \geq level II (14 trials)									
Negative	700	3.0 v 1.6	>.1	28.8 v 26.6	1.18	>.1	47.6 v 41.6	1.23	.03
Positive	3,131	8.1 v 26.0	<.001	58.3 v 66.4	0.84	.001	65.4 v 70.4	0.89	.01
One to three positive	1,314	3.8 v 20.3	<.001	42.3 v 50.2	0.80	.01	53.5 v 56.5	0.89	>.1
One to three positive plus systemic therapy	1,133	4.3 v 21.0	<.001	41.5 v 49.4	0.78	.01	52.6 v 55.5	0.86	.08
\geq Four positive nodes	1,772	13.0 v 32.1	<.001	70.7 v 80.0	0.87	.04	75.1 v 82.7	0.89	.05
\geq Four positive nodes plus systemic therapy	1,677	13.6 v 31.5	<.001	70.0 v 78.0	0.89	.08	74.9 v 82.0	0.90	>.1
Mastectomy plus axillary sampling (nine trials)									
Negative	870	3.7 v 17.8	<.001	32.0 v 35.8	0.97	>.1	46.1 v 49.9	1.00	>.1
Positive	2,541	6.3 v 37.2	<.001	55.6 v 68.2	0.74	<.001	63.1 v 71.8	0.79	<.001
Mastectomy only (four trials)									
Clinically negative	2,896	16.1 v 35.4	<.001	50.8 v 53.1	0.97	>.1	62.8 v 61.8	1.06	>.1
Clinically positive	1,481	18.0 v 45.0	<.001	56.6 v 63.3	0.86	.03	67.1 v 71.5	0.91	>.1

Regional Nodal Irradiation in Early-Stage Breast Cancer

Timothy J. Whelan, B.M., B.Ch., Ivo A. Olivetto, M.D., Wendy R. Parulekar, M.D., Ida Ackerman, M.D., Boon H. Chua, M.B., B.S., Ph.D., Abdenour Nabid, M.D., Katherine A. Vallis, M.B., B.S., Ph.D., Julia R. White, M.D., Pierre Rousseau, M.D., Andre Fortin, M.D., Lori J. Pierce, M.D., Lee Manchul, M.D., Susan Chafe, M.D., Maureen C. Nolan, M.D., Peter Craighead, M.D., Julie Bowen, M.D., David R. McCready, M.D., Kathleen I. Pritchard, M.D., Karen Gelmon, M.D., Yvonne Murray, B.Sc., Judy-Anne W. Chapman, Ph.D., Bingshu E. Chen, Ph.D., and Mark N. Levine, M.D., for the MA.20 Study Investigators*

T 1-2 N +

T3 N0

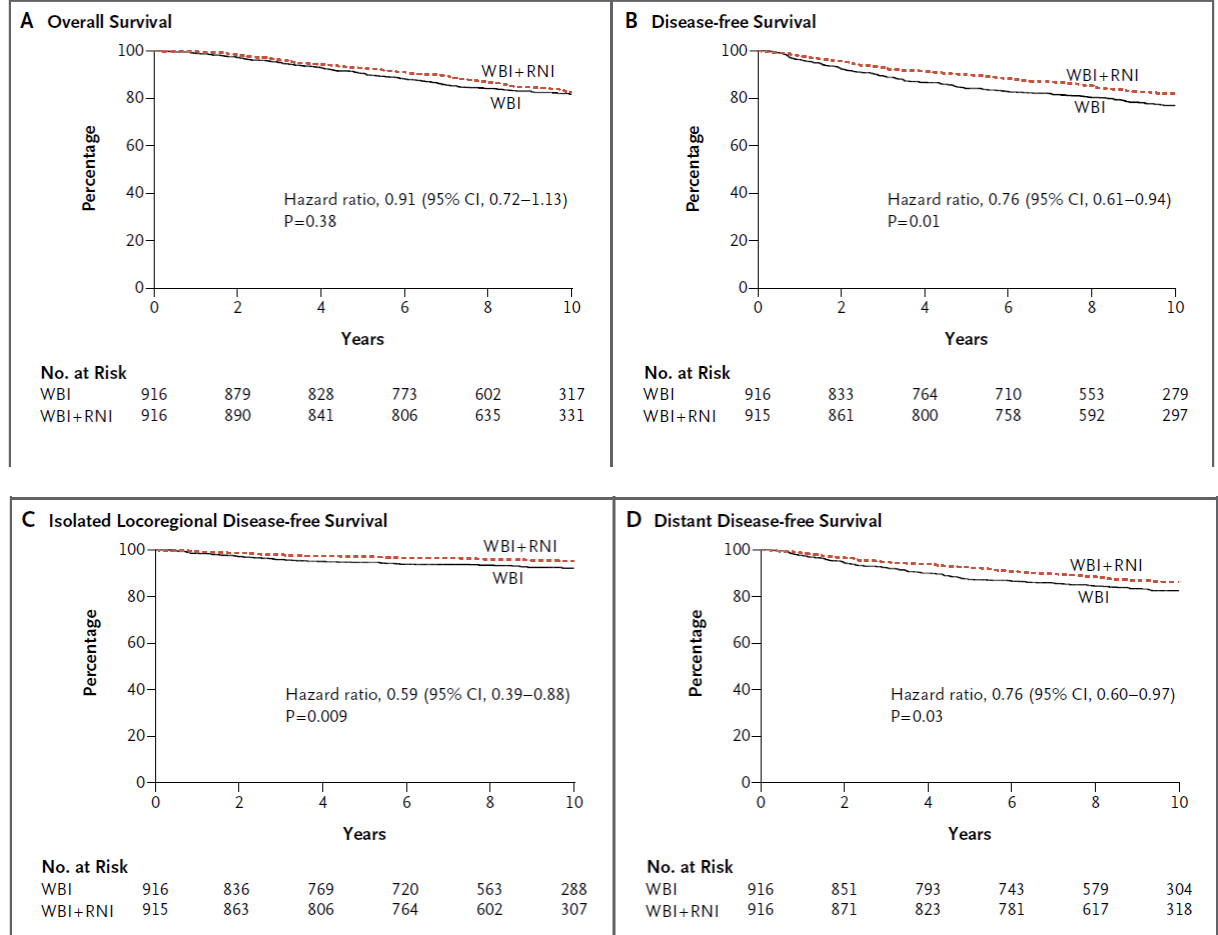
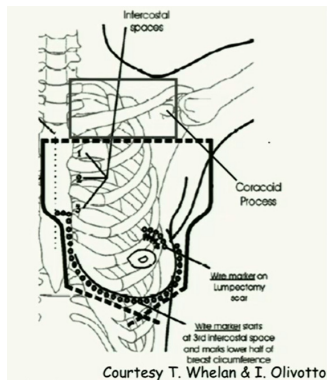
T2N0 but <10 nod dissected

and at least one of them:

grad 3

ER-

LVI



CONCLUSIONS

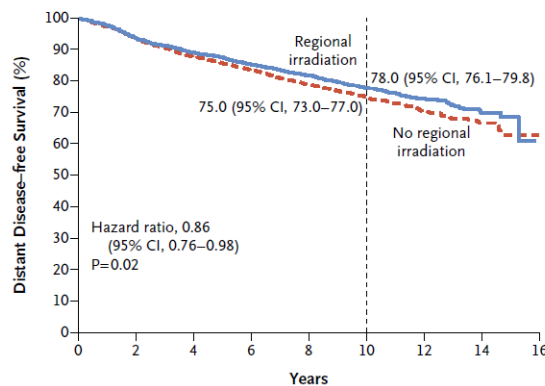
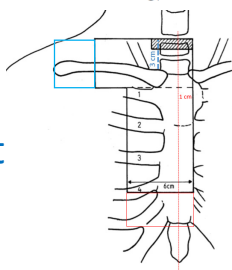
Among women with node-positive or high-risk node-negative breast cancer, the addition of regional nodal irradiation to whole-breast irradiation did not improve overall survival but reduced the rate of breast-cancer recurrence.

ORIGINAL ARTICLE

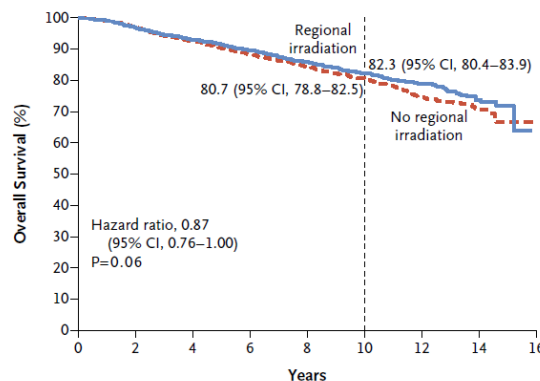
Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer

P.M. Poortmans, S. Collette, C. Kirkove, E. Van Limbergen, V. Budach, H. Struikmans, L. Collette, A. Fourquet, P. Maingon, M. Valli, K. De Winter, S. Marnitz, I. Barillot, L. Scandolaro, E. Vonk, C. Rodenhuis, H. Marsiglia, N. Weidner, G. van Tienhoven, C. Glanzmann, A. Kuten, R. Arriagada, H. Bartelink, and W. Van den Bogaert, for the EORTC Radiation Oncology and Breast Cancer Groups*

- Stage 1-3 central/inner
- Or axilla + outer quadrant
- Mastectomy (¼ of cases)



No. at Risk	2002	1862	1728	1606	1382	890	403	113	No. of Events
No regional irradiation	2002	1866	1764	1650	1464	939	437	117	523
Regional irradiation	2002	1866	1764	1650	1464	939	437	117	462



No. at Risk	2002	1926	1819	1698	1475	969	434	119	No. of Events
No regional irradiation	2002	1931	1839	1732	1532	988	466	124	429
Regional irradiation	2002	1931	1839	1732	1532	988	466	124	382

Treat 39 pts to prevent 1 breast ca death
Treat 30 pts to prevent breast ca relapse

CONCLUSIONS

In patients with early-stage breast cancer, irradiation of the regional nodes had a marginal effect on overall survival. Disease-free survival and distant disease-free survival were improved, and breast-cancer mortality was reduced.

Table 2. Events in the Intention-to-Treat Population.

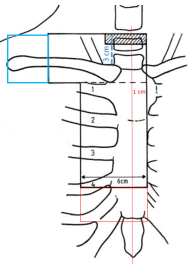
Event	Control Group (N=2002)	Nodal-Irradiation Group (N=2002)	Total (N=4004)
<i>no. of patients (%)</i>			
Recurrence			
Local	107 (5.3)	112 (5.6)	219 (5.5)
Regional*	85 (4.2)	54 (2.7) % 1.5	139 (3.5)
Axillary	38 (1.9)	27 (1.3)	65 (1.6)
Medial supraclavicular	41 (2.0)	30 (1.5)	71 (1.8)
Internal mammary	16 (0.8)	4 (0.2)	20 (0.5)
Distant disease	392 (19.6)	319 (15.9) % 3.7	711 (17.8)
Second cancer			
Any	222 (11.1)	191 (9.5)	413 (10.3)
Ipsilateral or contralateral breast cancer	105 (5.2)	97 (4.8)	202 (5.0)

* Multiple locations of regional recurrence may have been observed.

ORIGINAL ARTICLE

Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer

P.M. Poortmans, H. Struikmans, L. C. S. Marnitz, I. Barill N. Weidner, G. v H. Bartelink, and V



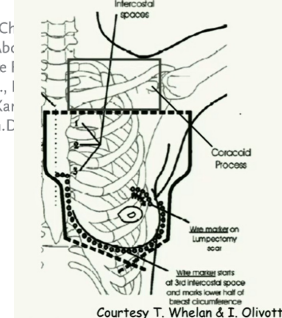
n Limbergen, V. Budach, gon, M. Valli, K. De Winter, Rodenhuis, H. Marsiglia, A. Kuten, R. Arriagada, ORTC Radiation Oncology ps*

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Regional Nodal Irradiation in Early-Stage Breast Cancer

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ar, M.D., Ida Ackerman, M.D., 1.B., B.S., Ph.D., Julia R. White, M.D., chul, M.D., Susan Chafe, M.D., David R. McCready, M.D., Judy-Anne W. Chapman, Ph.D., 0 Study Investigators*

Courtesy T. Whelan & I. Olivetto

- Any Lung toxicity (fibrosis, dispne, pneumonia)
 - 4.3 % [LNI] – 1.3 % p < 0.0001
- Cardiac toxicity
 - 0,3 % [LNI] – % 0,4 p = NS
- Lymphedema
 - % 12 [LNI] – %10,5 p=NS
- No performance impairment with LNI

- Pneumonia
 - 1.2 % [LNI] – 0,2 % p < 0.01
- Cardiac toxicity
 - % 0,4 [LNI] – % 0,9 p = NS
- Lymphedema
 - 8,4 % [LNI] – 4,5 % p=0,001

Poortmans, NEJM, 2015

Whelan, NEJM, 2015

Postmastectomy Radiotherapy: An American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Focused Guideline Update

Is PMRT indicated in patients with T1-2 tumors and a positive SNB who do not undergo completion ALND?

Recommendation For patients with clinical T1-2 tumors with clinically negative nodes, SNB is now generally performed at the time of mastectomy, with omission of ALND if the nodes are negative. ALND has generally been performed if the nodes are positive, but there is increasing controversy about whether this is always necessary, especially if there is limited disease in the affected nodes. The panel recognizes that some clinicians omit axillary dissection with one or two positive sentinel nodes in patients treated with mastectomy. This practice is primarily based on extrapolation of data from randomized trials of patients treated exclusively or predominantly with breast-conserving surgery and whole-breast irradiation or breast plus axillary irradiation. In such cases where clinicians and patients elect to omit axillary dissection, the panel recommends that these patients receive PMRT only if there is already sufficient information to justify its use without needing to know that additional axillary nodes are involved (type: informal consensus; evidence quality: weak; strength of recommendation: moderate).

Further treatment of axilla postmastectomy pT1-2 N1(sn)

T 1-2	PMRT		Axillary RT		ALND	
SLN status	ER + / cerbB2 -	ER-/cerbb2+	ER + / cerbB2 -	ER-/cerbb2+	ER + / cerbB2 -	ER-/cerbb2+
1 + micro.	-	+	-	+	-	-
2+ micro.	+/-	+	+/-	+	-	-
≥ 3 micro	+ (postALND)	+ (postALND)	+ (postALND)	+ (postALND)	+/-	+
1-2 + macro.	+	+	+	+	-	-
≥ 3 + macro.	+ (postALND)	+ (postALND)	+ (postALND)	+ (postALND)	+	+

Conclusion

-We can limit the use of ALND in pts with + SLN and PMRT

If patient has ALND + then PMRT is done. Lymphedema will be more prominent

-New randomized trials

UK POSNOC (ACOSOG Z-11 including mastectomy) SLN (1-2 +)

Holland (BOOG) Z11 for mastectomy SLN (1-3 +)