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Evolution of Regional Nodal Management of Breast Cancer

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What is the rationale and benefit of regional lymphatic irradiation?

Clearly radiation oncologists are now driving the need for nodal status in decision making regarding radiation field selection-what is the rationale for this?

Regional Nodal Irradiation Rationale/Evidence

- **Significant Percentage of Breast Cancer Patients Harbor Subclinical Microscopic Disease in the Regional Lymphatics which have not been surgically removed and may not be controlled or eradicated with systemic therapy**
- **Randomized Data Demonstrates RNI improves Local-regional control, disease-free and overall survival in patients at significant risk for subclinical microscopic disease in the regional lymphatics**

How well does RNI work in comparison to surgery?

- **Retrospective and prospective randomized data clearly demonstrate high rates of regional nodal control with standard doses of radiation**
- **Control of disease in the axilla is nearly as effective as axillary surgery**
- **Control of disease in the supraclav/infraclav and internal mammary, where surgery is impractical, remains highly effective with acceptable toxicity**

Radiation Alone Is Effective in Controlling the Axilla

Series: No SNODE Axillary Eval: Low Regional Recurrences

• Haffty	327 pts	3%
• Wong	92 pts	1%
• Wazer	73 pts	1%
• Zurrida	221 pts	0.5%
• Hoebers	105 pts	2%
• Kuznetsova	456 pts	0%

NSABP B-04

- **Patients with clinically N0 disease — Regional Recurrence**
  - **Radical mastectomy (ALND): 36% +LN — 4%**
  - **Total mastectomy + XRT (XRT of ALND) — 4%**
  - **Total mastectomy (ALN untreated) — 19%**

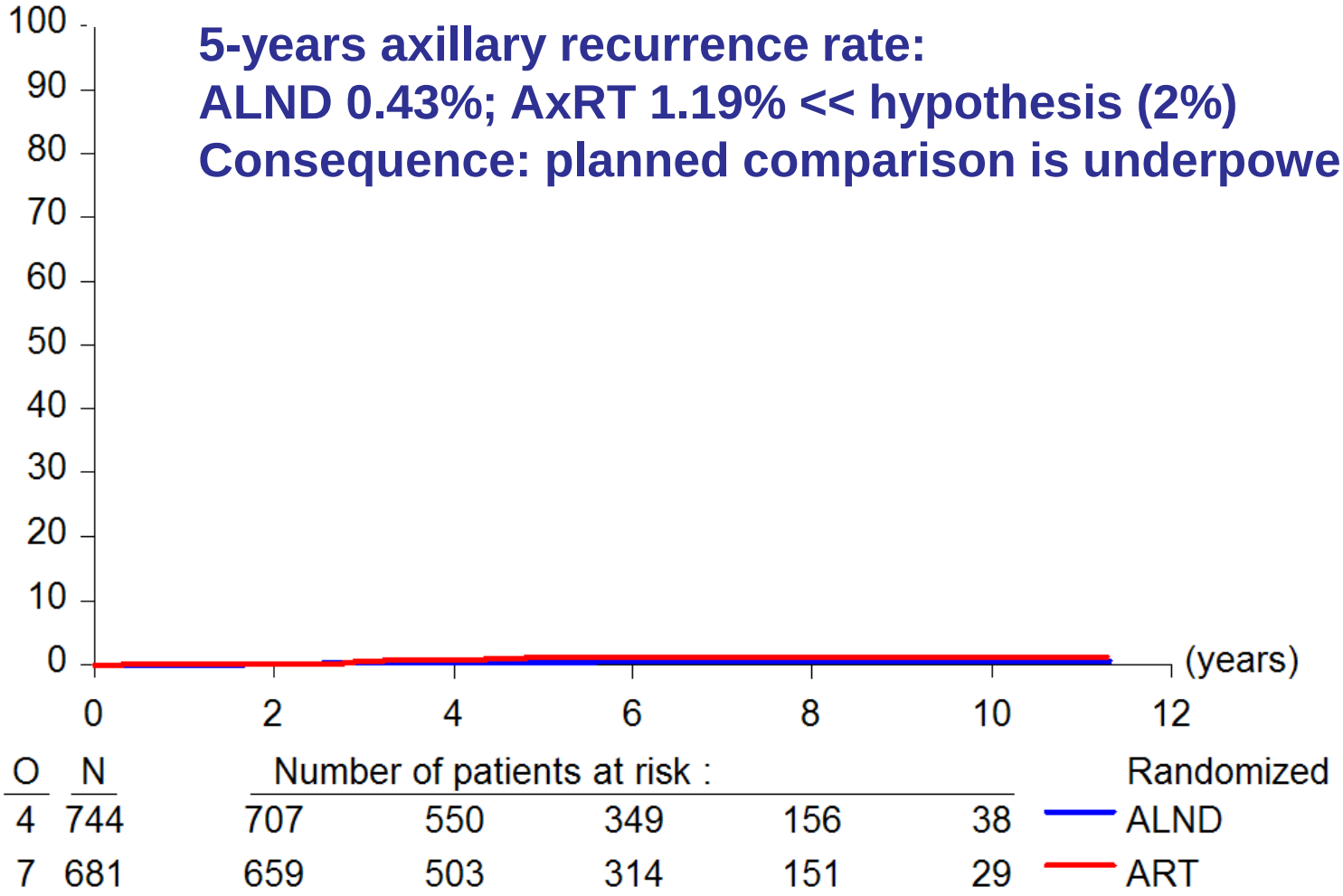
N Engl J Med 2002;347(8):567-575

AMAROS

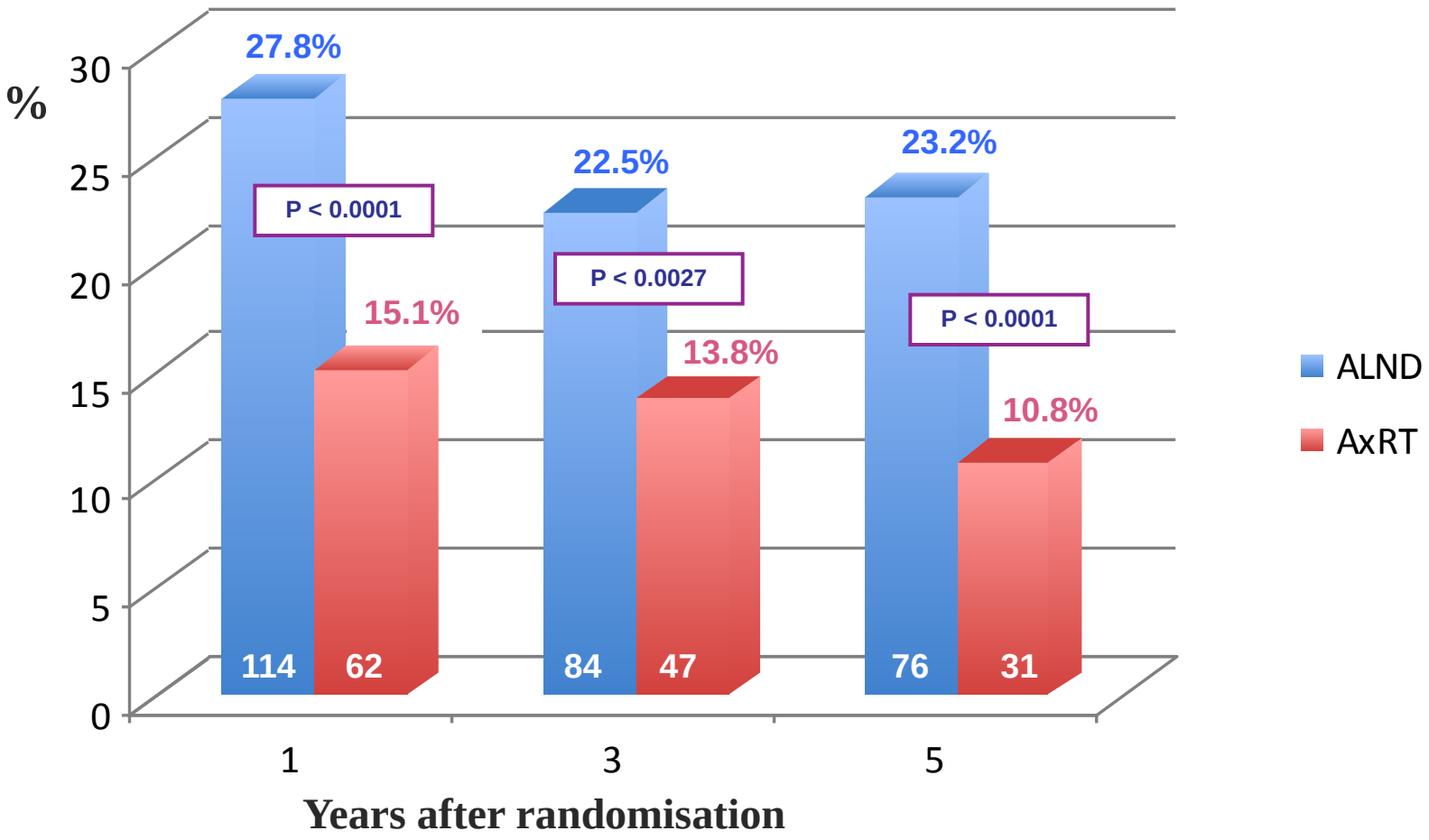
- Randomized trial of axillary dissection vs. axillary radiation in sentinel node positive patients
  - 1425 Sentinel Node Positive Patients Randomized to axillary dissection (744) vs Axillary RT (681)
- Both arms showed excellent local-regional control with less then a 2% axillary recurrence rate
- Less lymphedema in radiation patients (23% vs 10%)
- **CONCLUDE: Radiation to the axilla can be considered standard treatment in sentinel node positive patients.**

Axillary recurrence rate

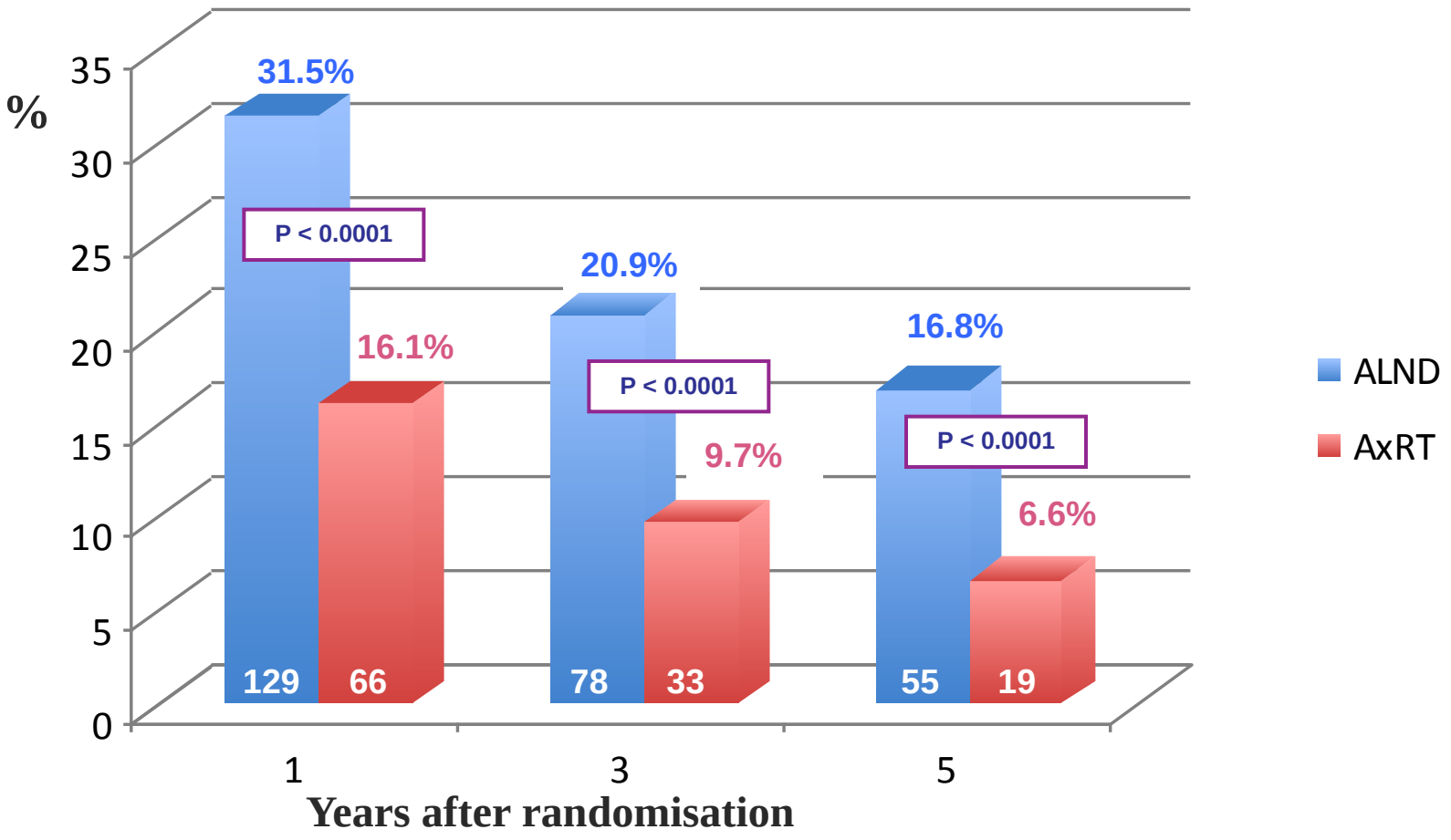
5-years axillary recurrence rate:
ALND 0.43%; AxRT 1.19% << hypothesis (2%)
Consequence: planned comparison is underpowered



Lymphedema: clinical observation



Lymphedema: treatment



Conclusion

Both ALND and AxRT provide excellent and comparable locoregional control in AxSN+ patients

Significantly less lymphedema after AxRT

AxRT can be considered standard

Radiation Control of Microscopic Regional Nodal Disease

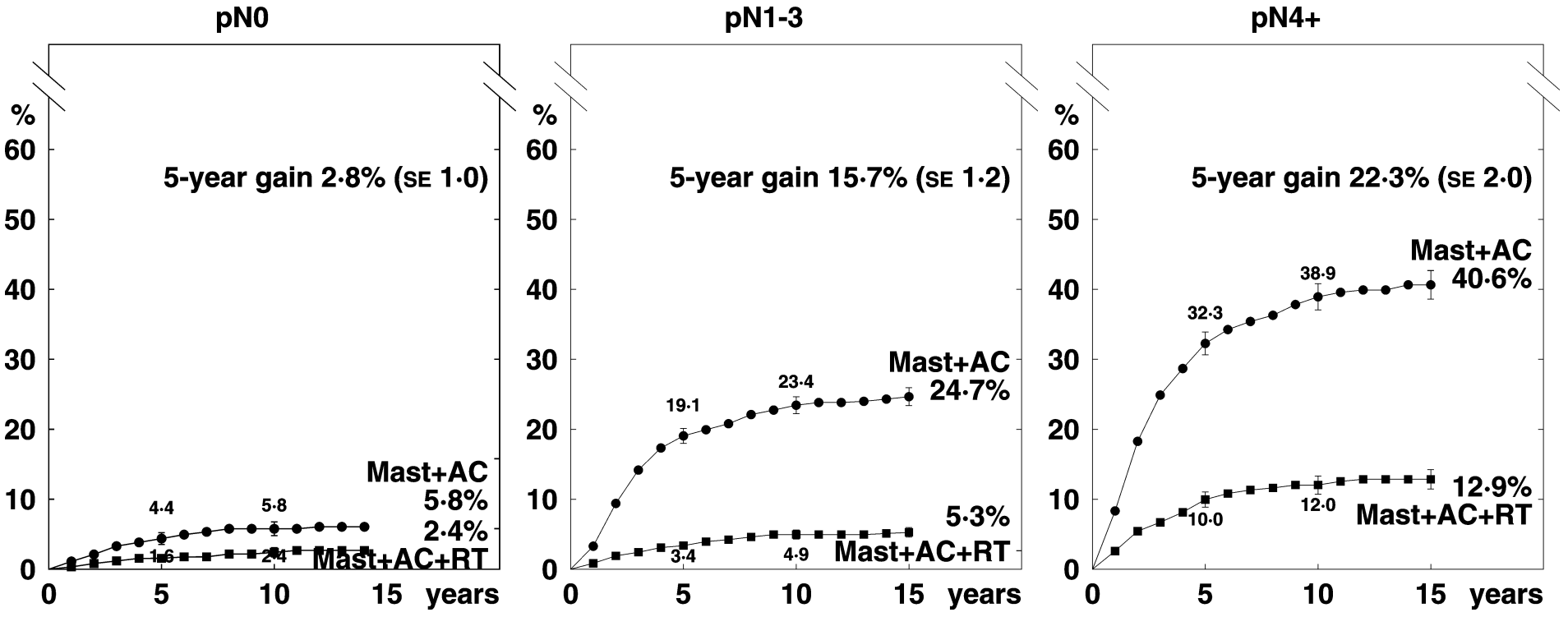
- **Available data demonstrates not all microscopic disease left untreated will become clinically overt**
  - **Host Response, Systemic Therapy, Dormant Disease**
- **Radiation is likely as effective as surgery in controlling subclinical microscopic disease**
- **Particularly effective in regions at high risk where surgery is impractical**
  - **Level III, supraclav, Internal Mammary**
- **Radiation will significantly reduce the clinically overt regional relapse rate by at least 50-70% of the expected rate if left untreated**

What are the indications for RNI following mastectomy?

- **Node Negative-Generally no role except:**
  - **Consider for T3,N0; Any T4; Extensive LVI; TN; Involved Margins**
- **N1 (1-3 Positive Nodes)**
  - **Individualized but discuss for All.**
  - **Possible exclusions:Micromets; Elderly/Comorbidities**
  - **Strongly recommend: Young age, LVI, ECE, TN,**
- **N2/3 (> 3 Positive Nodes)-Recommend**
- **Locally Advanced-Recommend**
- **Following Neo-adjuvant-Recommend for all locally advanced; Individualize for earlier stages depending on initial presentation and/or response to Systemic Tx.**

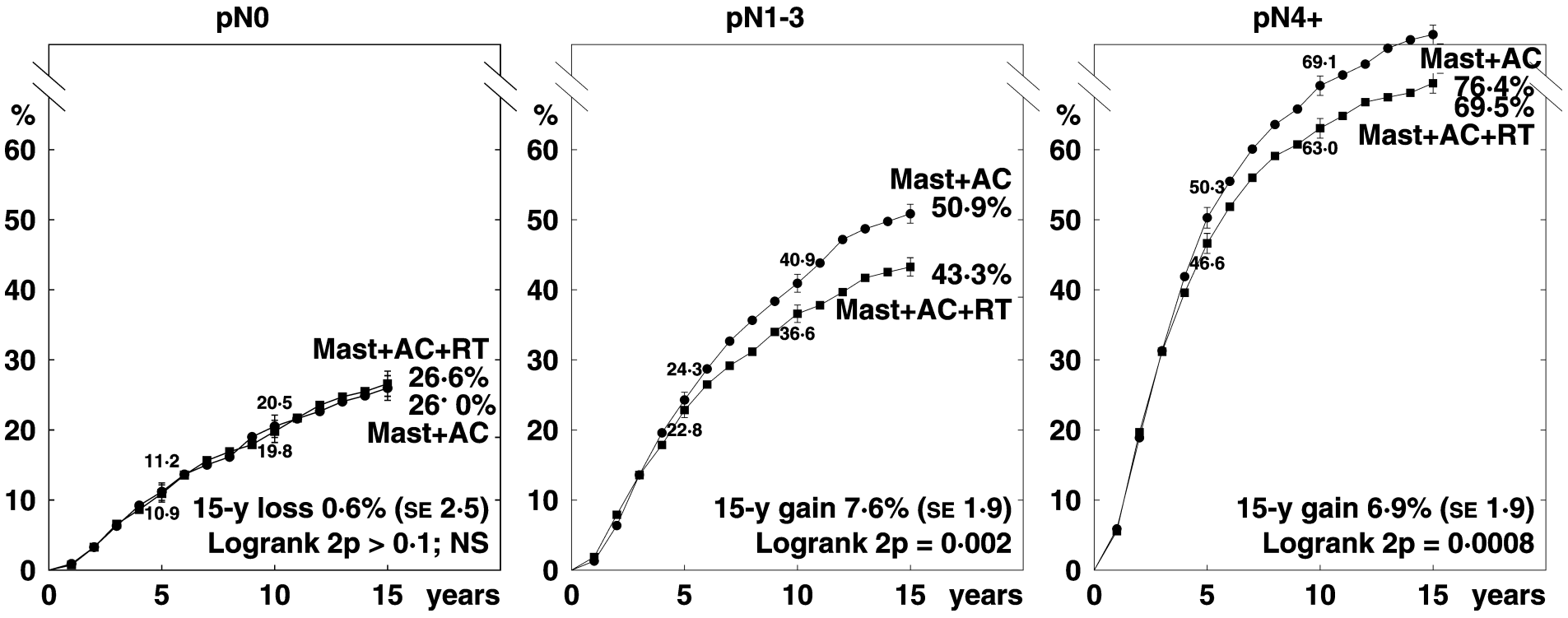
Mast+AC+RT vs. Mast+AC

Isolated local recurrence by pathological nodal status



Mast+AC+RT vs. Mast+AC

Breast cancer mortality by pathological nodal status



Survival Benefits in 1-3 +LN

<u>OS Survival Benefits</u>

• CMF vs. none	15%
• Anthra vs. CMF	4%
• Taxane vs. none	(approx 3%)
• Increase Density	(approx 3%)
•Radiation Therapy	(around 3-5%)

Recently reported MA.20 Trial

Whelan et al. NEJM, 2015

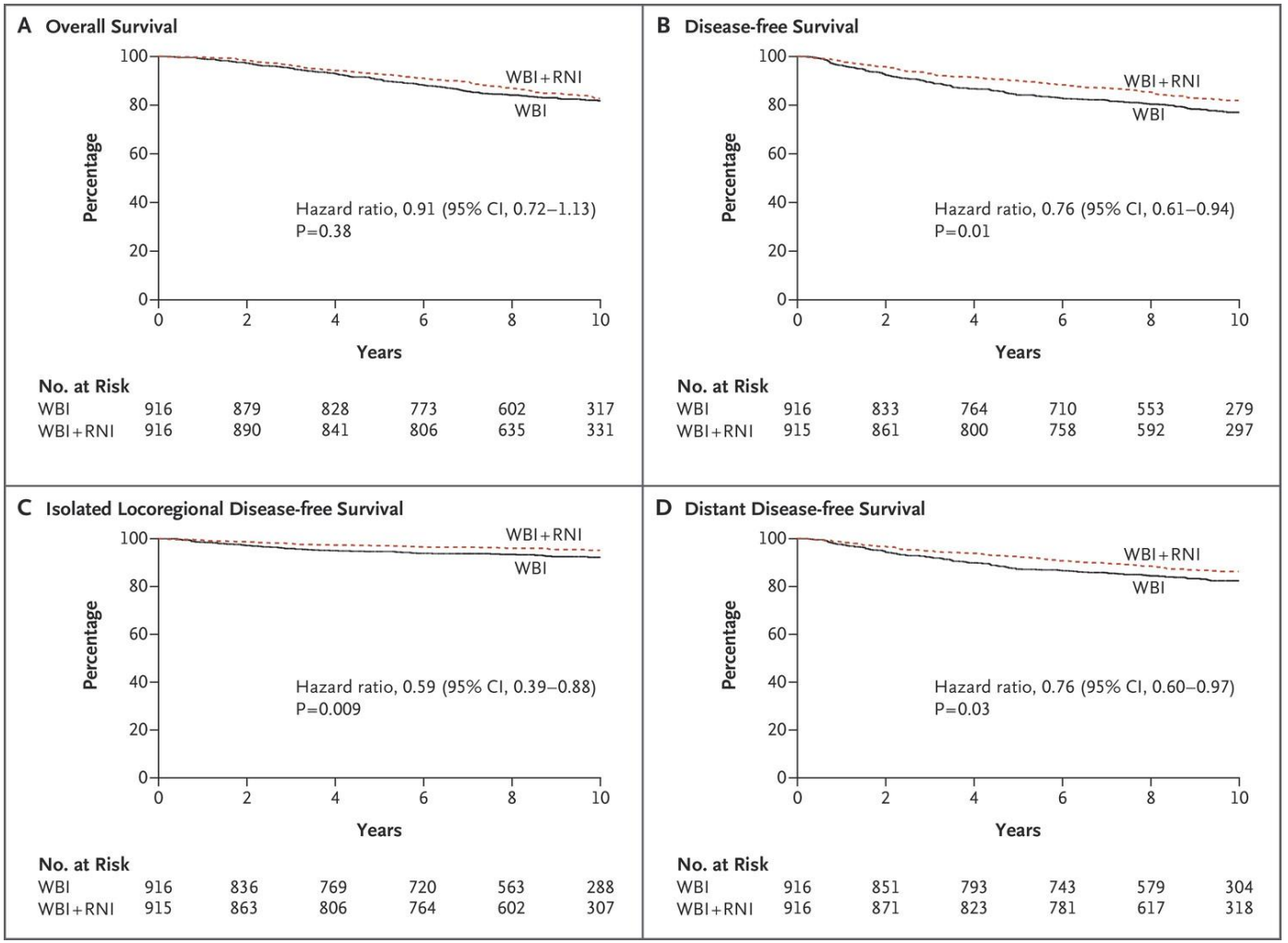
- **High Risk Node Negative and Node Positive patients undergoing BCS+RT**
- **Randomized to Tangents Only vs. Tangents +RNI (Supraclav and Internal Mammary-Predominantly Partially Wide Tangents)**
- **85% of Patients Had 1-3 + Nodes**

Key Results of the MA.20 Trial

Important Findings

- Did not reach its primary goal of demonstrating an overall survival benefit: 82.1% vs. 81.8%
- LN radiation reduced risk of LRR: 95.2% vs. 92.2%, p= .009
- improved disease free survival: 82% vs. 77%, p=.01
- decreased subsequent distant metastases free survival: 86.3 vs. 82.4%, p=.01
- impact on overall survival in pre-specified subgroup of patients with hormone receptor negative disease: 81.3% RNI vs. 73.9% without, p= p.05
- acceptable morbidity tradeoffs

10-Year Kaplan–Meier Estimates of Survival.



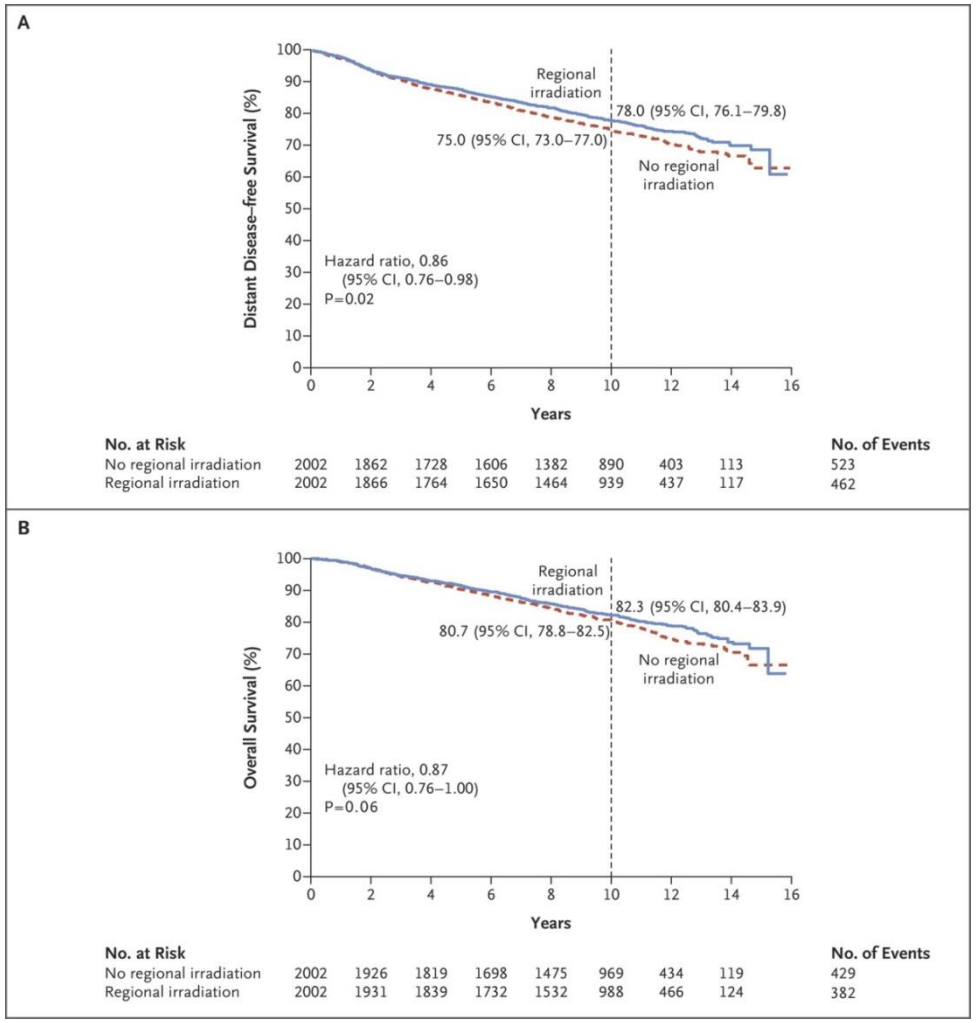
Whelan TJ et al. N Engl J Med 2015;373:307-316.

RNI vs NO RNI

Poortmans et al. NEJM, 2015

- **EORTC 22922 Trial confirmed the results of MA.20**
- **4004 Pts randomized to breast/chestwall vs. breast/chestwall +regional nodes (Int Mamm+Sclav)**
- **76% BCS and 24% Mastectomy**
- **RT to regional nodes significantly improved DFS, Metastasis, breast cancer mortality. Overall survival borderline at .06**
- **382 Deaths in the RNI group vs. 429 in the NO-RNI group**
- **No increase in non-breast cancer related mortality**

Distant Disease-free and Overall Survival.

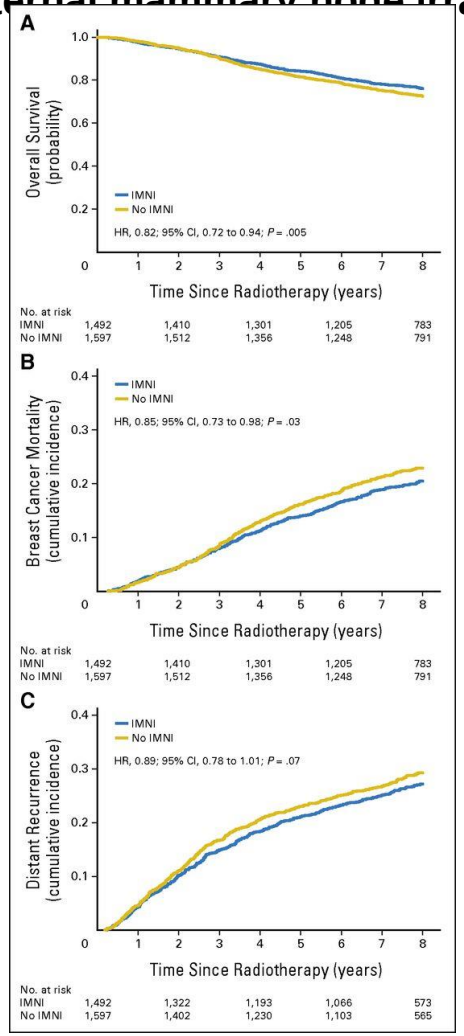


Poortmans PM et al. N Engl J Med 2015;373:317-327.

Internal Mammary Radiation

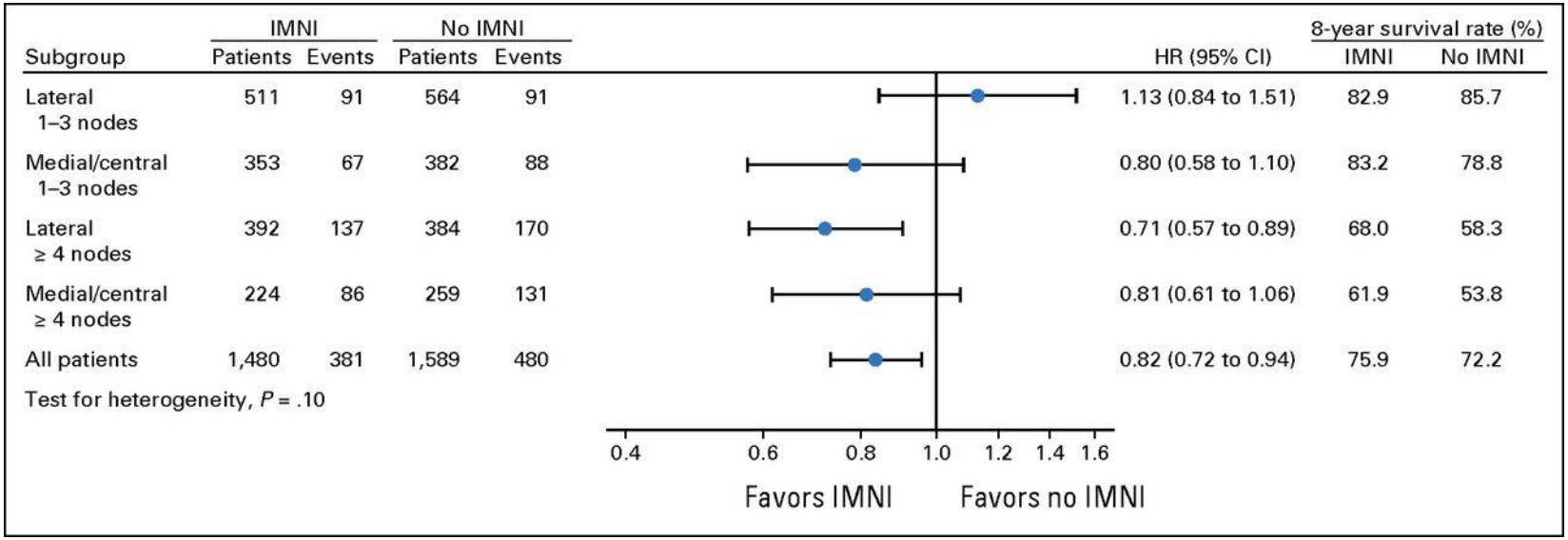
- Danish DBCG-IMN Study
- Over 3000 node positive post-mastectomy and lumpectomy patients prospectively treated per National Guidelines
- Of 3,327 eligible patients, only 288 were excluded due to no radiation or con-compliant radiation
- Right Side-Internal Mammary RT
- Left Side-No Internal Mammary RT
- 2 Groups well balanced for all prognostic factors
- Internal Mammary group had improved survival rate
- Editorial: Haffty, Whelan, Poortmans
  - Internal mammary radiation should be considered in appropriately selected node positive patients provided it can be accomplished with acceptable normal tissue constraints.

Kaplan-Meier estimates and associated hazard ratios (HRs) of (A) overall survival, (B) cumulated incidence of breast cancer mortality, and (C) distant recurrence in patients with and without internal mammary node irradiation (IMNI).



Lise Bech Jellesmark Thorsen et al. JCO 2016;34:314-320

Overall survival rates and corresponding hazard ratios (HR) with versus without internal mammary node irradiation (IMNI) within subgroups defined by tumor location and the number of axillary nodes involved.



Subgroup	IMNI Patients	IMNI Events	No IMNI Patients	No IMNI Events	HR (95% CI)	8-year survival rate (%) IMNI	8-year survival rate (%) No IMNI
Lateral 1–3 nodes	511	91	564	91	1.13 (0.84 to 1.51)	82.9	85.7
Medial/central 1–3 nodes	353	67	382	88	0.80 (0.58 to 1.10)	83.2	78.8
Lateral ≥ 4 nodes	392	137	384	170	0.71 (0.57 to 0.89)	68.0	58.3
Medial/central ≥ 4 nodes	224	86	259	131	0.81 (0.61 to 1.06)	61.9	53.8
All patients	1,480	381	1,589	480	0.82 (0.72 to 0.94)	75.9	72.2

Test for heterogeneity, $P = .10$

Lise Bech Jellesmark Thorsen et al. JCO 2016;34:314-320

Internal Mammary Treatment

- Regardless of whether you are an advocate or not of internal mammary treatment, you need to know how to treat the internal mammary nodes with at least the following techniques
  - Partially wide tangents
  - Separate internal mammary field
- Treatment should be particularly considered for:
  - Positive IM nodes on imaging
  - High probability if IM involvement based on nodal status and location

RNI in Node Positive Patients

- **Given the survival benefit in patients with 1-3 nodes noted in the updated meta-analysis, the distant metastasis benefit in MA.20 and the survival and disease free survival benefit in EORTC 22922, as well as the Danish IMN study, it is important that we at least discuss the pros and cons of regional nodal irradiation in node positive breast cancer patients whether treated with breast conserving surgery or mastectomy**

How has the routine employment of sentinel node sampling modified our approach?

SNB + Disease

- Prior to Z0011 standard of care was to perform cALND in patients with a positive SLN
- Z0011 and retrospective series report good regional control with SLN+ patients with no axillary dissection…however
- Most patients received radiation to the breast and likely some radiation to Level I/II nodes
- Some radiation oncologists treat supraclavicular/axillary nodes in sentinel node positive patients
- AMAROS demonstrated that radiation to the supraclav and axilla is equivalent to surgery in sentinel node positive disease with less morbidity/toxicity

Overall Characteristics of Patients in Z0011

- Patients in the trial were enriched for a relatively favorable group of patients who had a low axillary burden, estrogen receptor positive, post-menopausal, micro-metastasis.
- Still, approximately 30% of the SLNB positive patients presumably had residual microscopic disease which was “untreated” by axillary dissection
- Why then was the nodal relapse rate so low (4/425 or 0.9%) ???

Did Radiation Contribute to Regional Control

- All patients in Z011 received standard whole breast irradiation
- The protocol specified that the radiation oncologist should not treat the supraclavicular/axillary nodes
- However… the protocol did not specify where the superior border of the breast field should be placed
- Furthermore, as published in JCO, many patients received high tangential field radiation and...
  - NEARLY 20% RECEIVED A THIRD SUPRACLAVICULAR AXILLARY RADIATION FIELD!

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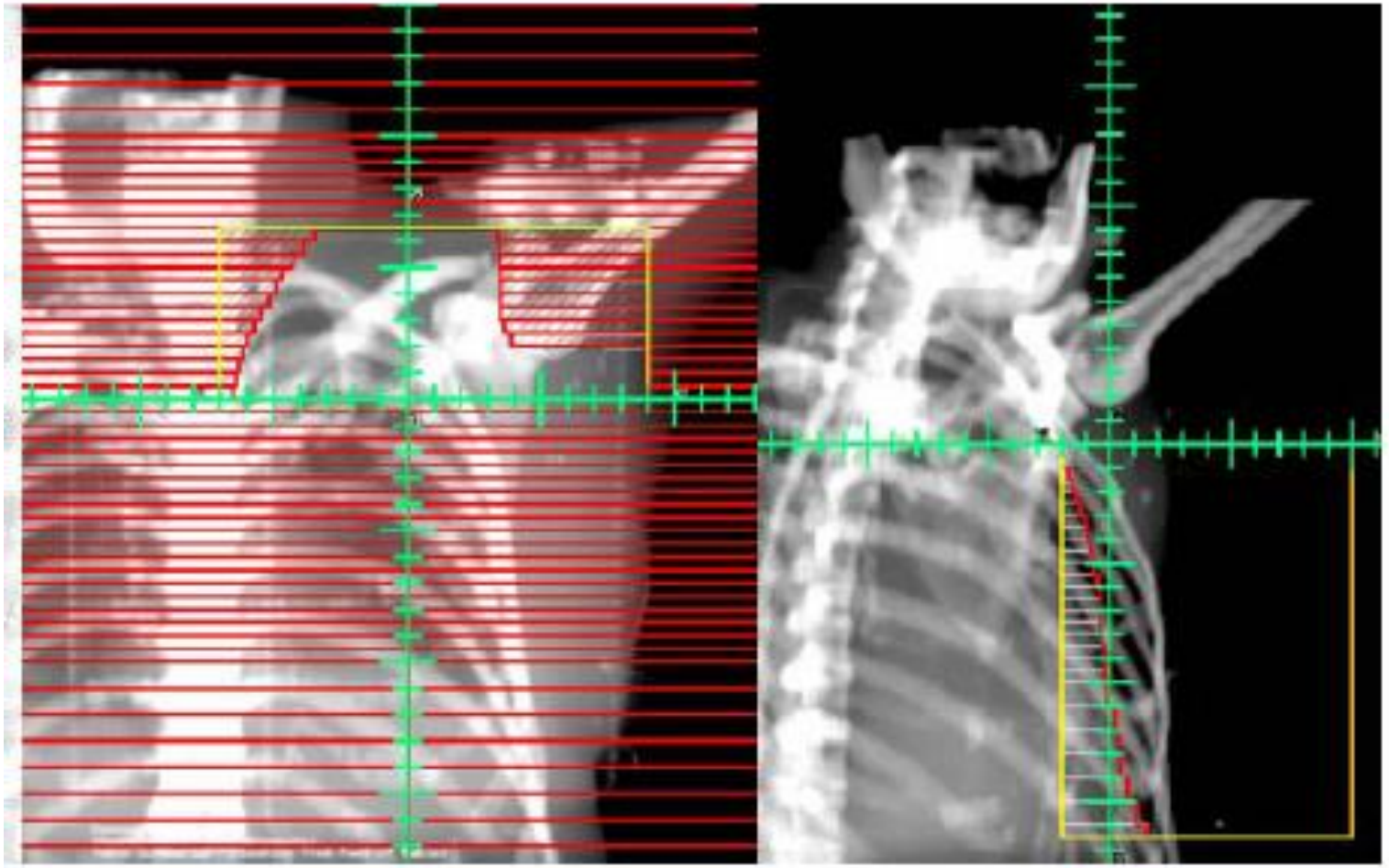
ORIGINAL REPORT

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

- Radiation fields were reviewed and published in JCO (Jagsi et al. JCO, 2014)
- Non-Trivial (Approximately 20%) of patients actually had a 3rd field treated in both the dissection and no dissection arms.
- The use of a 3rd field highly correlated with the nodal burden
- Use of “High Tangents” was also frequent (NEARLY 50%)in both the dissection and no-dissection arms

A radiation field from a patient in Z0011



Tangents with third field

Suggested Approach for patients with Positive Sentinel Node

Very Low Risk	**T1a, ER+, IHC only in 1 of 3 nodes** **Risk*: 3-8%**	**Standard Tangents**
Moderate Risk	**T1c, macromet in 1 of 2 nodes** **Risk*: 29-34%**	**High Tangents** **Or Regional Nodal Irradiation**
Very High Risk	**T2, macromet in 2 of 3 nodes, +LVI, ER-multifocal, young** **Risk*: 57-71%**	**Strongly Consider 3rd field**

Risk-Risk of additional non-sentinel nodes calculated by MSKCC, MDACC Nomograms*

Where to go from here? How to reconcile Z0011 and MA.20 and EORTC for sentinel node positive patients

- Likely Z0011 patients were overall lower risk then MA.20 and EORTC, though the percentage of patients with 4 or more nodes involved were similar in the axillary dissection arms of the 3 studies (Approx 12% EORTC, 15% MA.20, 13% Z0011)
- OF NOTE, nearly 20% of the Z0011 patients actually received regional nodal irradiation, particularly those with higher nodal burdens.
- Ultimately this issue can best be resolved by randomizing patients with sentinel node positive disease to tangents only vs. tangents plus regional nodal irradiation.
- Outside of such a trial, my bias is to treat the majority of SNODE positive patients with RNI given the benefit of RNI in predominantly patients with 1-3 Nodes, demonstrated in MA.20, EORTC and EBCTG meta-analysis, along with the low lymphedema rate of Supraclavicular axillary RT reported from AMAROS

Thank you for your attention

Bruce G. Haffty, MD