DBCG-IMN

Effect of adjuvant radiotherapy to the internal mammary lymph nodes in patients with early node-positive breast cancer

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On behalf of the DBCG Radiotherapy Committee

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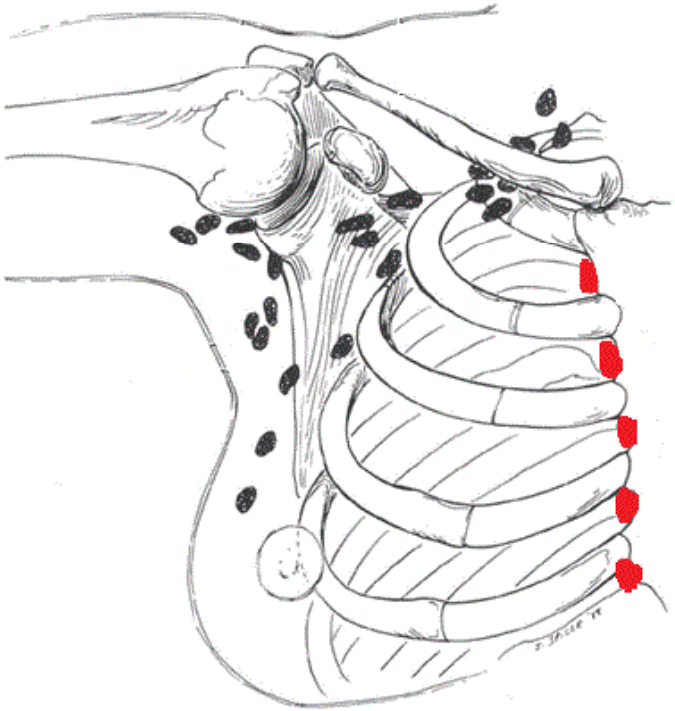
DBCG-IMN

- IMN metastasis
  - Often w. medial tumor/N+ disease
  - A poor prognostic sign
- Surgical studies: no beneficial effect IMN dissection
- IMN-RT: increased toxicity with earlier techniques
- No consensus on whether IMN-RT is useful



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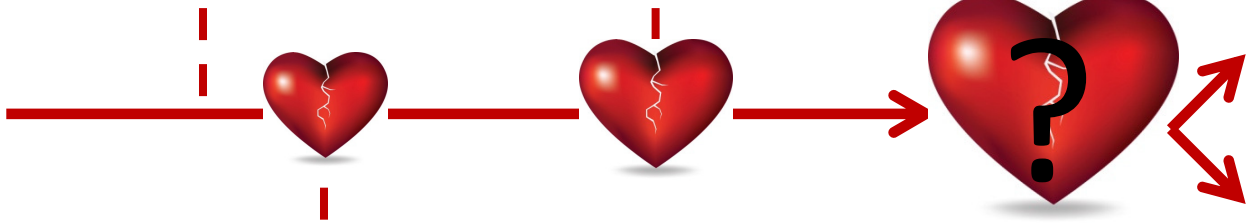
1980's
Internal mammary node (IMN) RT for all N+ breast cancer patients

2000
Anthracyclines

No evidence for effect of IMN-RT

2003

Right side
+ IMN RT



Left side
No IMN-RT

1990's
Increased awareness on RT-induced heart disease

Left side
heart dose high

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Right side
+ IMN RT

Left side
No IMN-RT

↑ Breast cancer death

↓ Heart death

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Hypotheses

In patients with early node positive breast cancer, IMN-RT

- Improves overall survival
- Prevents distant recurrence
- Decreases breast cancer mortality

DBCG-IMN: Design

- Nation-wide population based cohort study
- Inclusion: 2003-2007
  - operable unilateral early BC
  - one or more macrometastatic axillary lymph nodes
  - no prior malignancies
  - age<70 years
  - Treated with standard RT after introduction of new internal mammary node guidelines
  - No recurrence earlier than 30 days after RT

DBCG-IMN: Design

Ineligible	N
No or non-standard RT	134
Early recurrence	52
Micrometastases	33
Stage 4 disease at diagnosis	38

ion criteria
et (n=306)

Right-sided b

(n=1586)

Primary endpoint: Overall Survival
Secondary endpoints: Metastatic disease, Breast cancer death

Multivariate model adjusting for known prognostic factors: age, menopausal status, pT, pN, and grade, tumor location, stratified for receptor status and histological type

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Patient and tumor characteristics

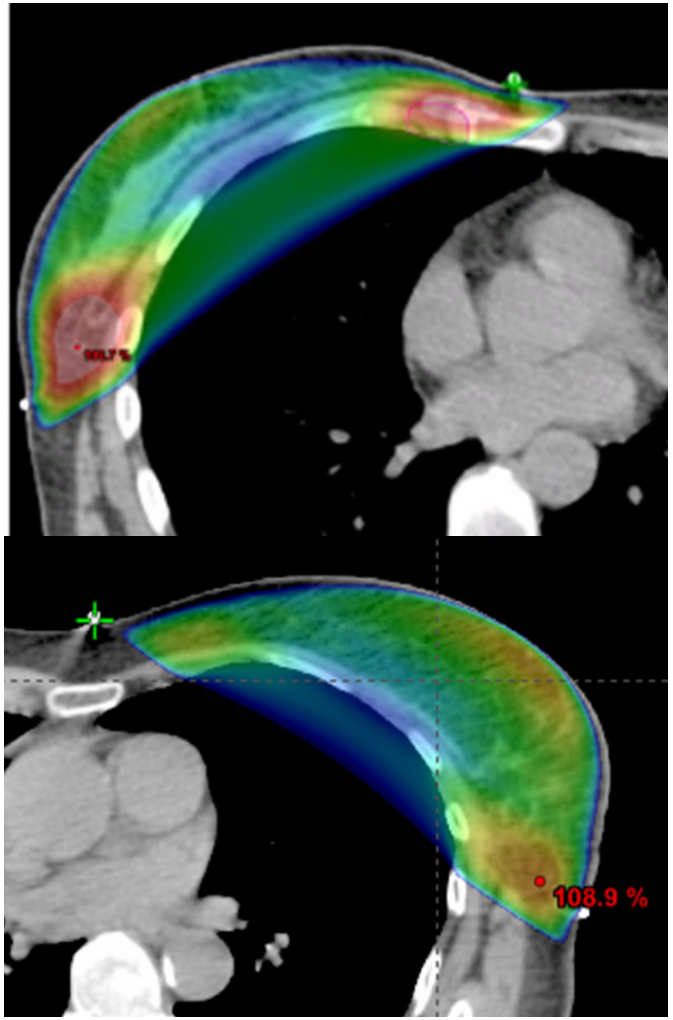
	IMN RT (n=1485)	No IMN RT (n=1586)
Median age (range)	56 (23-70)	57 (27-70)
Pre-menopausal	611 (41%)	646 (40%)
Estrogen receptor positive (%)	1202 (81%)	1274 (80%)
Invasive ductal carcinoma Invasive lobular carcinoma Other	1305 (88%) 134 (9%) 46 (3%)	1346 (85%)* 163 (10%) 77 (5%)
Grade I Grade II Grade III	307 (19%) 710 (48%) 414 (28%)	307 (19%) 743 (47%) 456 (29%)
pT1 pT2 pT3	527 (36%) 830 (56%) 126 (9%)	556 (35%) 905 (57%) 124 (8%)
pN1 pN2 pN3	867 (58%) 396 (27%) 222 (15%)	949 (60%) 412 (26%) 225 (14%)
Lateral Medial/central	904 (61%) 578 (39%)	943 (60%) 640 (40%)

DBCG-IMN: Treatment

	IMN RT (n=1485)	No IMN RT (n=1586)
Radiotherapy: 48 Gy/24 F		
IMN-RT (%)	1431 (96%)	161 (10%)
Axillary level II-III (%)	1213 (82%)	1294 (82%)
Axillary level I-II-III (%)	272 (18%)	292 (18%)
Boost after BCS (%)	176 (33%)	164 (30%)
Type of surgery		
Mastectomy + AC(%)	959 (65%)	1048 (66%)
Breast conserving +AC(%)	526 (35%)	538 (34%)
Systemic treatment		
Anti-hormonal therapy (%)	697 (47%)	741 (47%)
Chemotherapy (%)	274 (19%)	304 (19%)
Both (%)	514 (35%)	541 (34%)

DBCG-IMN: QA RT-techniques

- Doses to normal tissues acceptable
- IMN-RT intended: Some underdosage
- IMN-RT NOT intended: Some dose unavoidable
- ->Possible dilution of measurable IMN-RT effect!



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Pattern of recurrence

Pattern of recurrence Median FU= 8.0 years	IMN RT (n=1485)	No IMN RT (n=1586)
Local recurrence	29 (2.0 %)	21 (1.3 %)
Regional lymph node recurrence	10 (0.7 %)	15 (0.9 %)
Contralateral breast cancer	39 (2.6 %)	36 (2.3 %)

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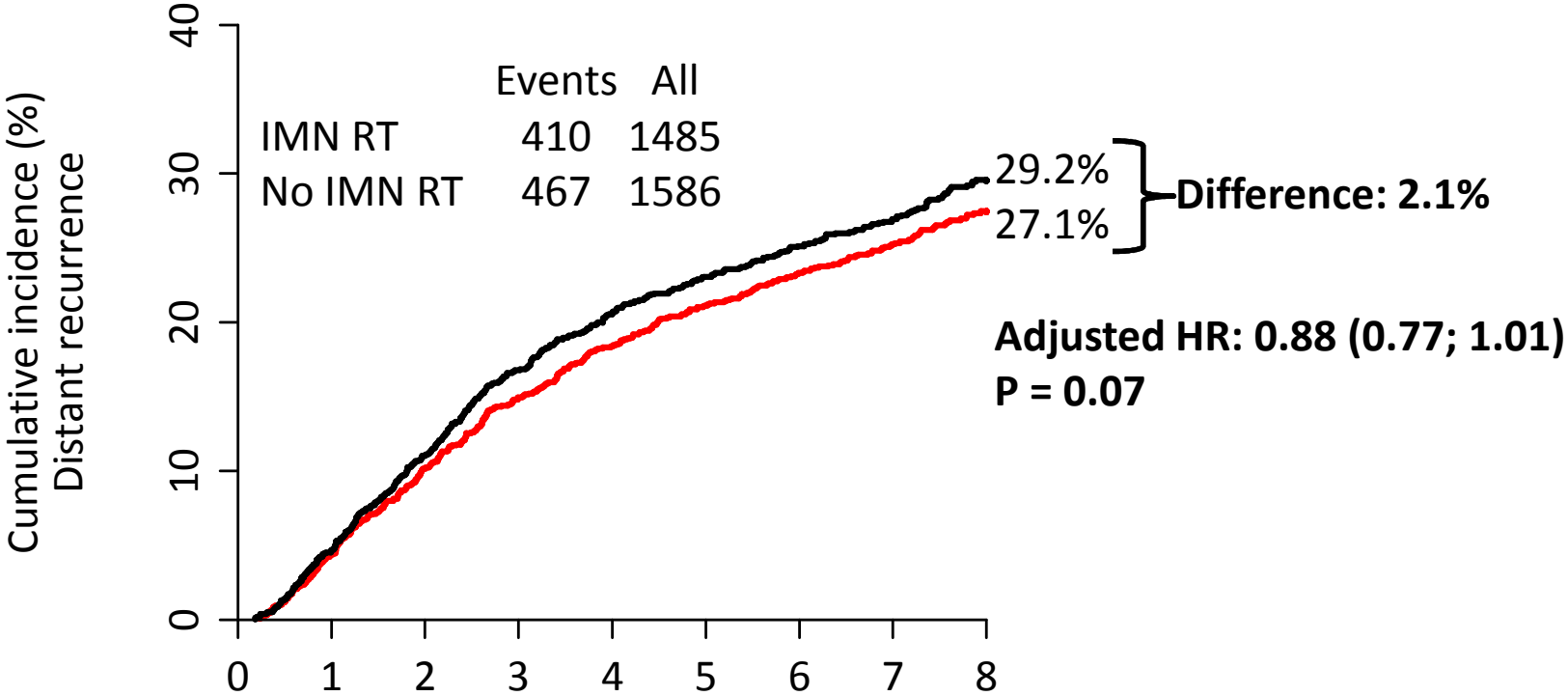
Distant recurrence



At risk					
IMN RT	1485	1322	1193	1043	521
No IMN RT	1586	1401	1229	1075	500

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Secondary endpoint
Breast cancer mortality

Cause of death Median FU= 8yrs	IMN RT (n=1485)	No IMN RT (n=1586)
Breast cancer	**324**	**390**
Cardiovascular	**9**	**9**
Other malignancy	26	39
Other	21	32
Unknown	0	3

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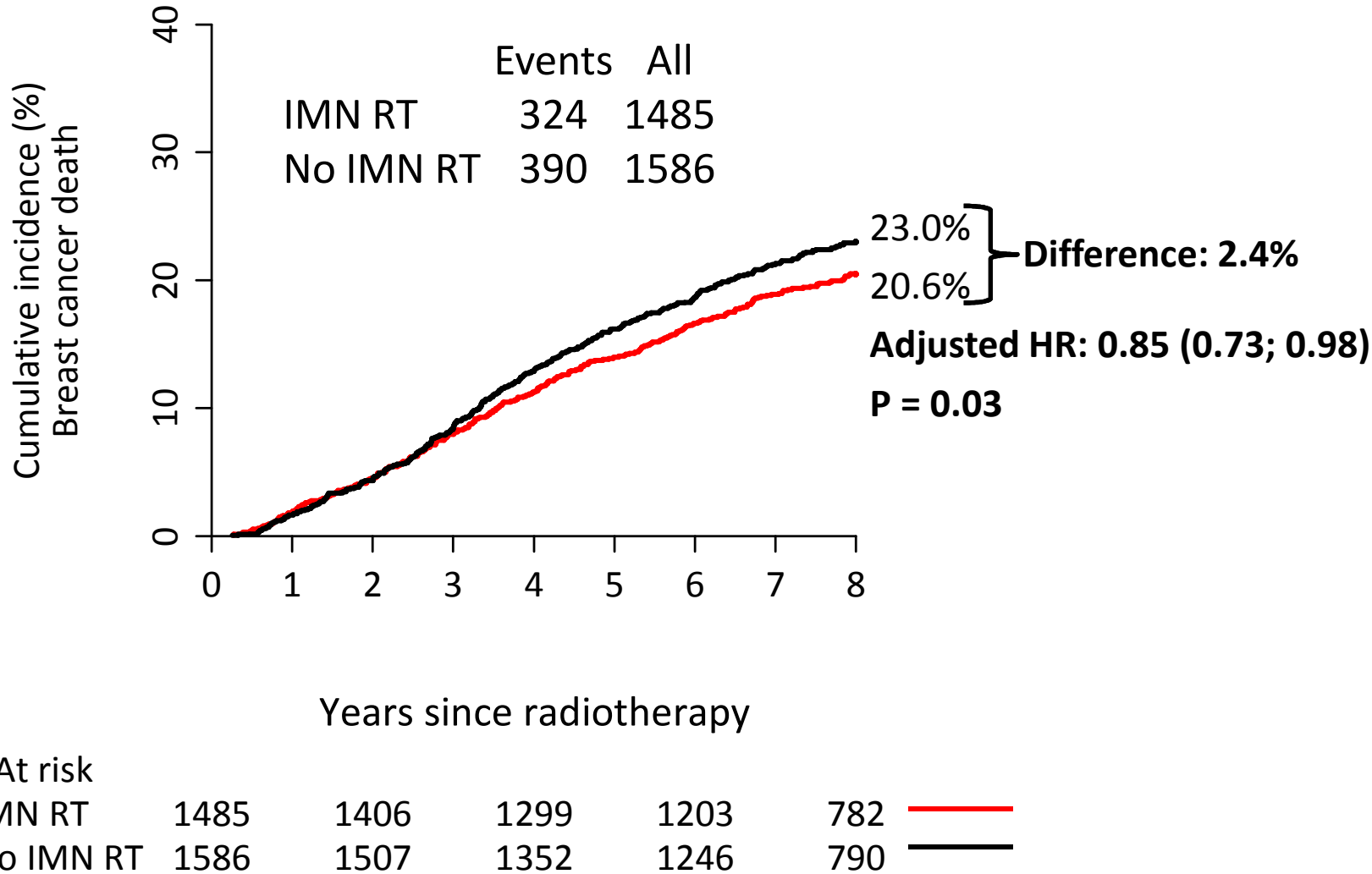
Breast cancer mortality



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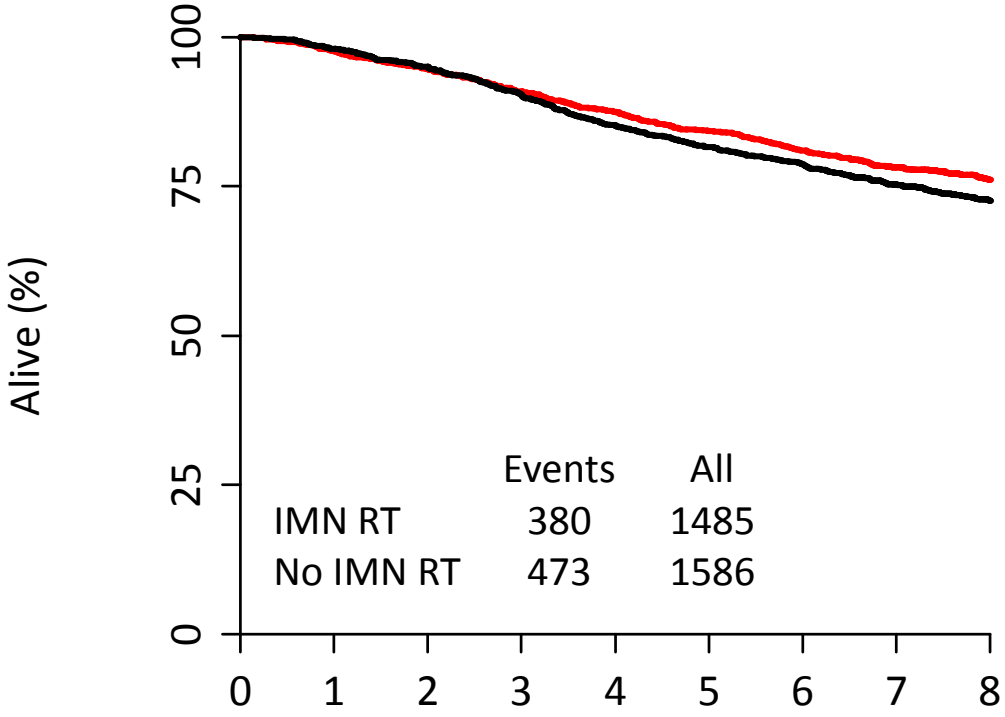
Primary endpoint: Overall Survival



76.1%
72.6%
Difference: 3.5%

Adjusted HR: 0.83 (0.72; 0.95)

p = 0.006

At risk					
IMN RT	1485	1406	1299	1203	782
No IMN RT	1586	1507	1352	1246	790

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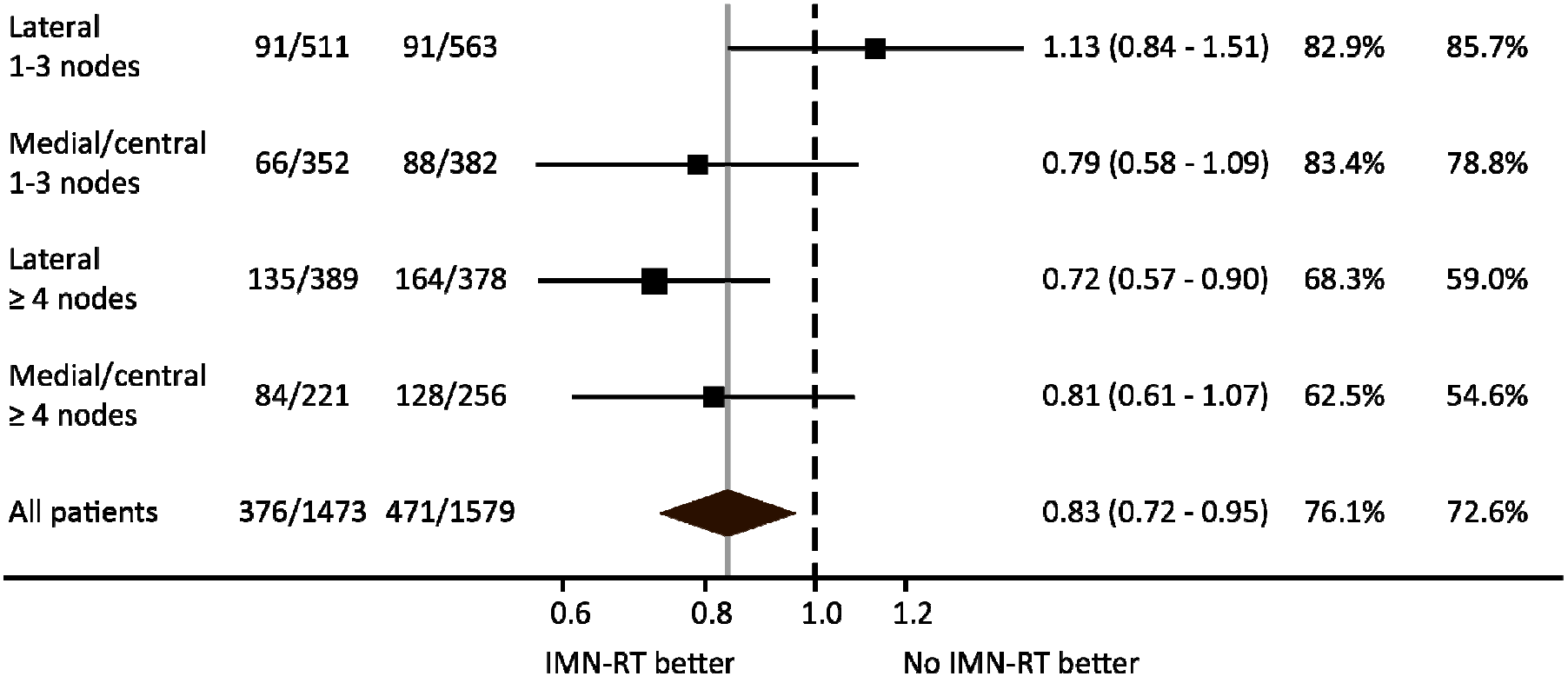
Association: ✓- Causality?

- Increasing risk of IMN metastasis with:
  - Increasing number of positive axillary lymph nodes
  - Medial/central tumor location

Subgroup analysis
Endpoint: Overall survival

Subgroup	Events/patients		HR (95% CI)	8-year survival rate	
	IMN-RT	No IMN-RT		IMN-RT	No IMN-RT
Lateral 1-3 nodes	91/511	91/563	1.13 (0.84 - 1.51)	82.9%	85.7%
Medial/central 1-3 nodes	66/352	88/382	0.79 (0.58 - 1.09)	83.4%	78.8%
Lateral ≥ 4 nodes	135/389	164/378	0.72 (0.57 - 0.90)	68.3%	59.0%
Medial/central ≥ 4 nodes	84/221	128/256	0.81 (0.61 - 1.07)	62.5%	54.6%
All patients	376/1473	471/1579	0.83 (0.72 - 0.95)	76.1%	72.6%



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DBCG-IMN: Conclusion

- Overall survival improved with IMN-RT
- Risk of metastatic disease decreased with IMN-RT
- Risk of breast cancer death decreased with IMN-RT

DBCG-IMN: Conclusion

Benefit increased with

- Increasing number of lymph nodes involved
- Medial or central tumor location

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Evidence 2013-14

- **EBCTCG meta-analysis**
  - RT after mastectomy+axillary dissection
  - 20 years results: RT reduced breast cancer mortality (BCM) for all (n=3086) N+ patients, effect both in pts with 1-3 and 4+ positive nodes
- **EORTC 22922-10925**
  - 4004 pts. with medial/central tumor and/or N+ disease randomised to medial supraclavicular (MS) and IMN-RT
  - 10 year results: Improved DFS and D-DFS with MS+IMN-RT, OS borderline significant
- **MA.20**
  - 1832 pts. randomised to whole breast irradiation (WBI) versus WBI + regional RT, 85 % of patients with 1-3 nodes positive
  - 5 year results: Improved DFS and D-DFS with addition of regional RT, OS borderline significant

The Role of Irradiation of the Internal Mammary Lymph Nodes in High-Risk Stage II to IIIA Breast Cancer Patients After High-Dose Chemotherapy: A Prospective Sequential Nonrandomized Study

Long-term effect of internal mammary chain treatment. Results of a multivariate analysis of 1195 patients with operable

Retrospective and non-randomized: Bias and confounding
Small: Insufficient power to detect an effect
Old: Surgical and systemic treatment (if any) are outdated

Invasive Breast Carcinoma

Influence of internal mammary node irradiation on long-term outcome and contralateral breast cancer incidence in node-negative breast cancer patients

Long-term Survival Outcomes Following Internal Mammary Node Irradiation in Stage II-III Breast Cancer: Results of a Large Retrospective Study With 12-Year Follow-up