Internal mammary node irradiation in early node-positive breast cancer

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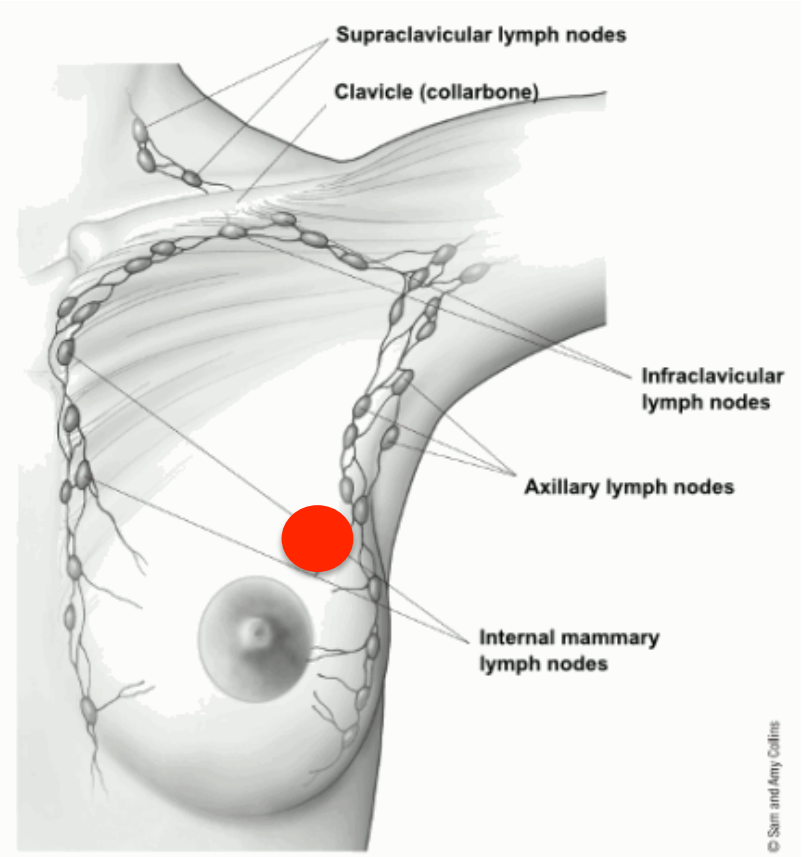
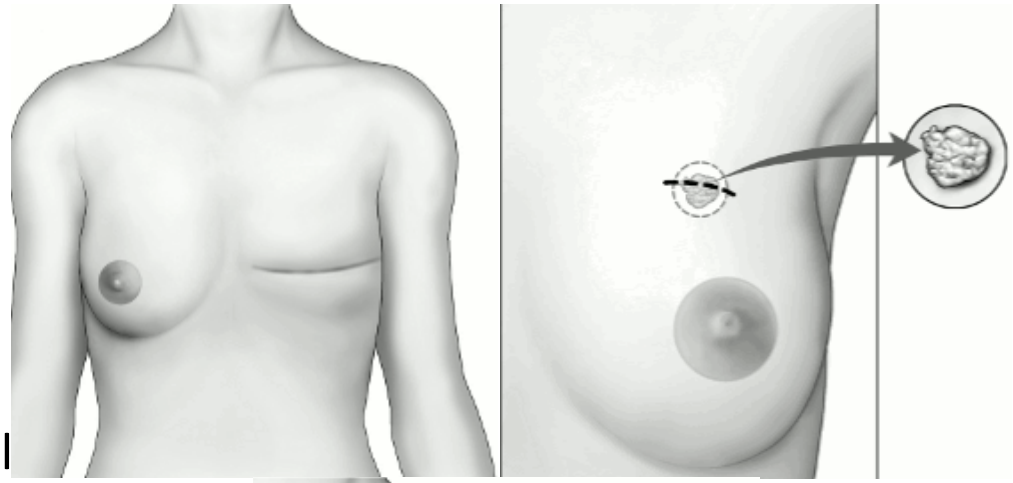
Breast cancer

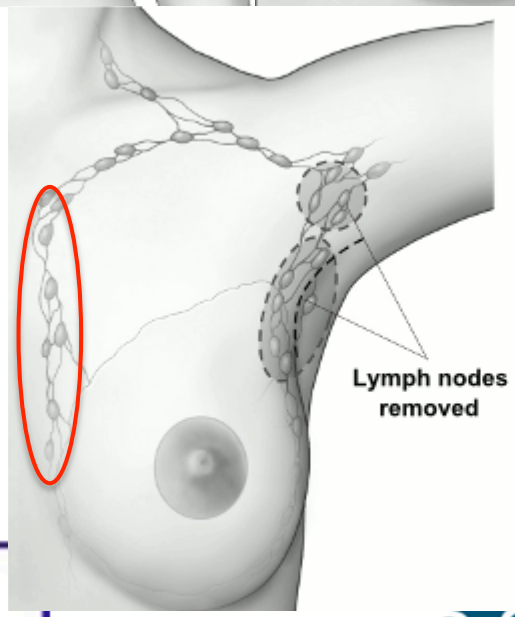
- Women of the western world
- Life-time risk >10%
- 2012: 500,000 new cases in Europe
- Origin in breast
- Spread to regional nodes
- Spread to distant sites



Breast cancer treatment

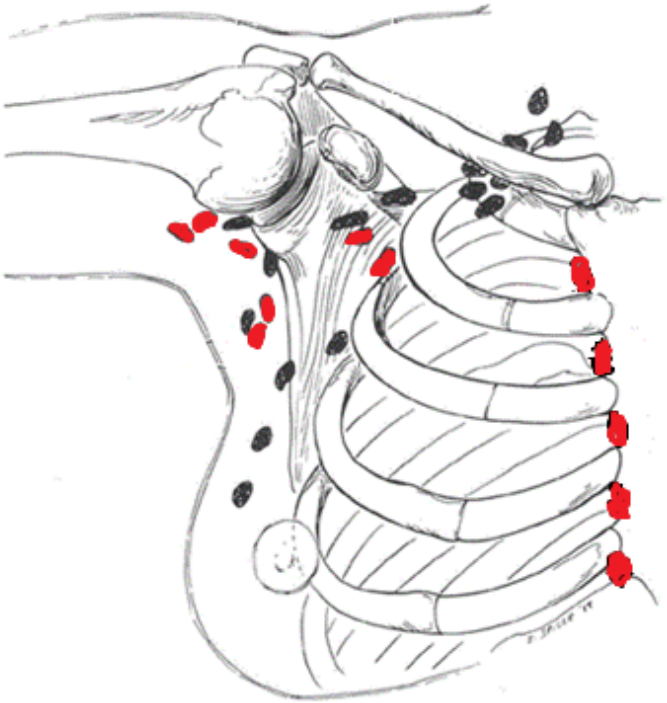
- Loco-regional
  - Surgery
    - Mastectomy
    - Breast conserving surgery/lumpectomy
    - N+: Axillary node removal
  - Radiotherapy
- Systemic treatment
  - Chemotherapy
  - Endocrine treatment
  - Targeted treatment





Internal mammary nodes

- IMN metastases
  - More often w. large/medial tumor/ axillary N+ disease
- IMN metastases: a poor prognostic sign
- 10-year survival
  - IMN N0 & Ax N0: 76%
  - IMN N+ & Ax N+: 25%
- 1960's: Surgical randomized controlled trials: no beneficial effect of IMN dissection
- Retrospective analyses of internal mammary node irradiation: no conclusive results



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- Danish Breast Cancer Group (DBCG) initiated 1976
- National guidelines on diagnosis & treatment of breast cancer
- National DBCG registry since 1977
  - Aim: All Danish patients with primary invasive breast cancer
  - Information: Demography, disease, treatment, follow-up
- National clinical trials

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

2000
Anthracyclines

2003

No evidence for effect of IMN-RT

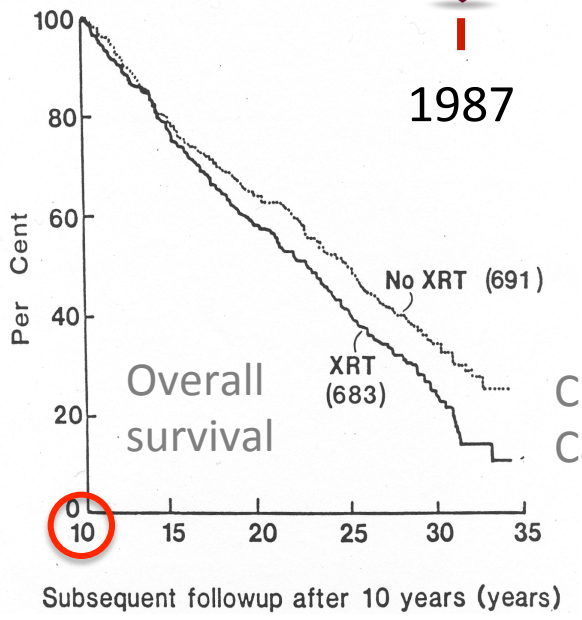
1987

2003

Right side
+ IMN RT

Left side
No IMN-RT

Left side
heart dose high



Overall survival

Cuzick, et al.
Cancer Treat Rep, 1987

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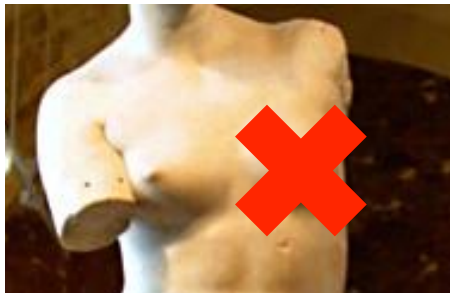
Right side
+ IMN RT



Left side
No IMN-RT

Nation-wide
prospective population based
cohort study

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Hypotheses

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

- Improves overall survival
- Reduces breast cancer mortality
- Reduces the risk of distant recurrence

Study population

- Inclusion:
  - Treated with standard RT [2003 – 2007]
  - Unilateral early BC
  - One or more macrometastatic axillary lymph nodes
  - Stage II-III
  - No prior malignancies
  - Age<70 years

Materials and methods

Data-sources

- DBCG registry
- The Danish Civil Registration system (CPR)
- Registry on causes of death (COD)
- Hospital records
- Treatment-planning systems
- Information from general practitioners

DBCG-IMN: Design

Ineligible	n
No or non-standard RT	134
Recurrence before RT	34
Micrometastases	33
Stage 4 disease at diagnosis	38
Inoperable	24
Prior malignancy	21
Bilateral cancer	4
Total	288

lusion criteria
met (n=55)

lusion criteria
met (n=233)

Right-sided b

(n=1597)

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Patient and tumor characteristics

	IMN RT (n=1492)	No IMN RT (n=1597)
Median age (range)	56 (22-70)	57 (27-70)
Pre-menopausal	612 (41%)	649 (41%)
Estrogen receptor positive (%)	1207 (81%)	1279 (80%)
Invasive ductal carcinoma Invasive lobular carcinoma Other	1311 (88%) 135 (9%) 46 (3%)	1356 (85%) 164 (10%) 77 (5%)
Grade I Grade II Grade III	353 (24%) 715 (48%) 416 (28%)	384 (24%) 747 (47%) 462 (29%)
pT1 pT2 pT3	625 (42%) 773 (52%) 92 (6%)	653 (41%) 836 (52%) 106 (4%)
pN1 pN2 pN3	868 (58%) 401 (27%) 223 (15%)	950 (60%) 417 (26%) 230 (14%)
Lateral Medial/central	907 (61%) 582 (39%)	950 (60%) 644 (40%)

DBCG-IMN: Treatment

	IMN RT (n=1492)	No IMN RT (n=1597)
Radiotherapy: 48 Gy/24 F		
IMN-RT (%)	1437 (97%)	**161 (10%)**
Axillary level II-III-IV (%)	1219 (82%)	1301 (82%)
Axillary level I-II-III-IV (%)	273 (18%)	296 (18%)
Boost after BCS (%)	192 (13%)	192 (12%)
Type of surgery		
Mastectomy + AC(%)	962 (65%)	1054 (66%)
Breast conserving +AC(%)	530 (35%)	543 (34%)
Systemic treatment		
Endocrine therapy (%)	702 (47%)	745 (47%)
Chemotherapy (%)	276 (18%)	310 (19%)
Endocrine + chemotherapy (%)	514 (35%)	542 (34%)

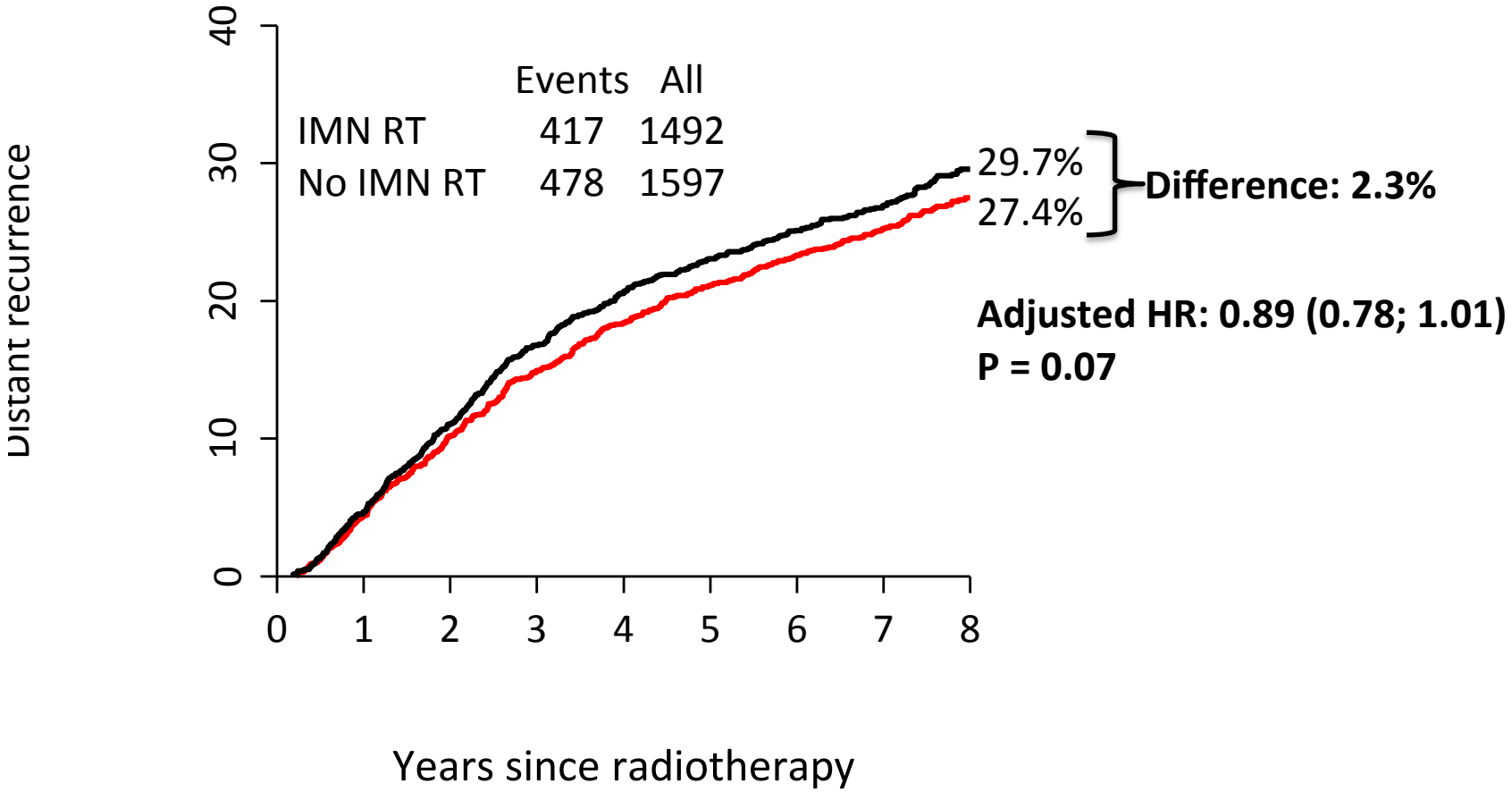
DBCG-IMN: Follow-up

- Follow-up every 6 months for 5 years, then once a year until 10 years
  - Date and site of recurrence
  - Contralateral breast cancer
  - Other malignant disease
  - Death and cause of death

Results

Pattern of recurrence Median FU= 8.0 years	IMN RT (n=1492)	No IMN RT (n=1597)
Local recurrence	29 (1.9 %)	21 (1.3 %)
Regional lymph node recurrence	10 (0.7 %)	15 (0.9 %)
Contralateral breast cancer	39 (2.6 %)	36 (2.3 %)

Distant recurrence



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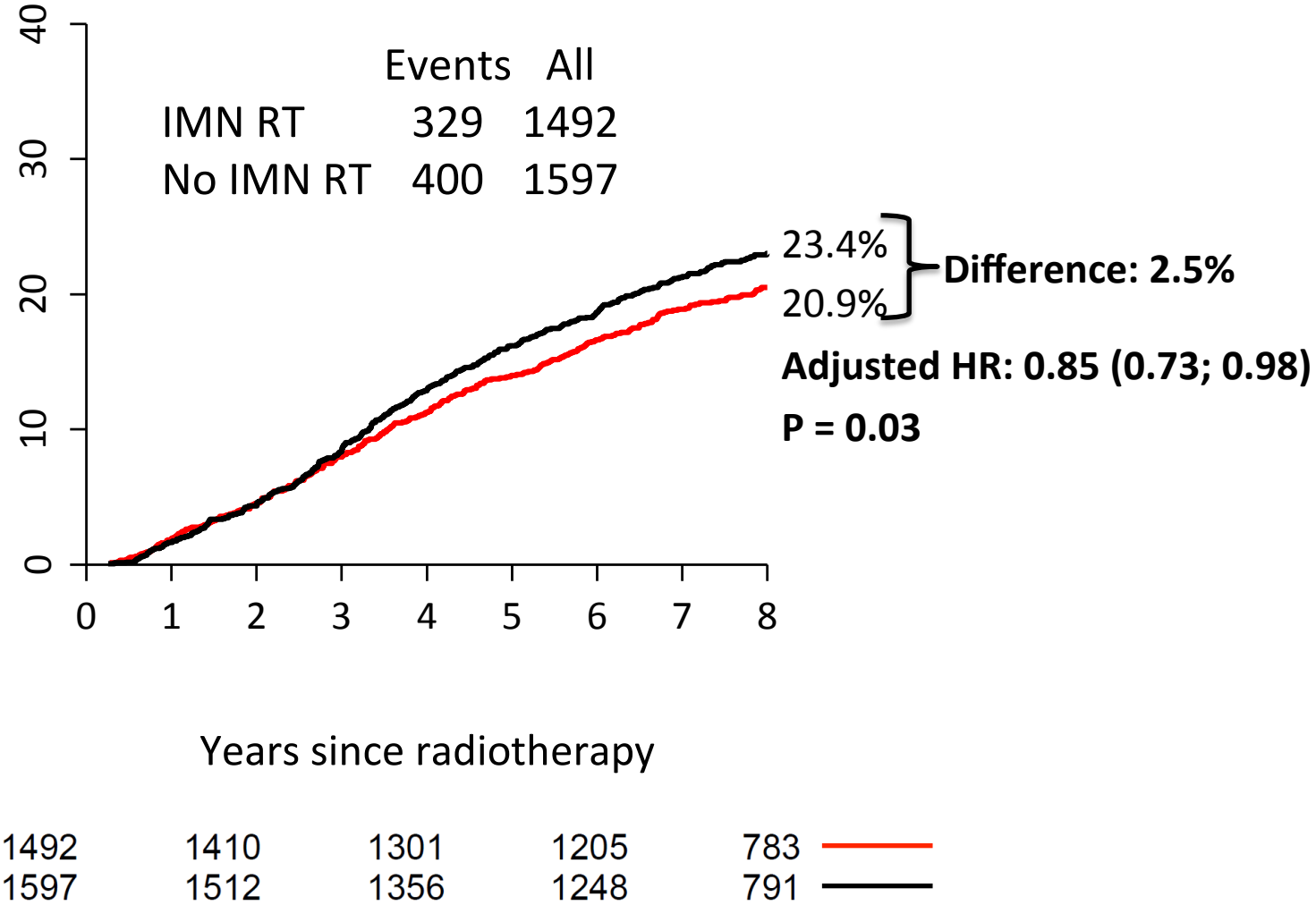
Breast cancer mortality

Cause of death Median FU= 8yrs	IMN RT (n=1492)	No IMN RT (n=1597)
Breast cancer	**329**	**400**
Cardiovascular	**9**	**9**
Other malignancy	26	39
Other	21	32
Unknown	0	3

Breast cancer mortality



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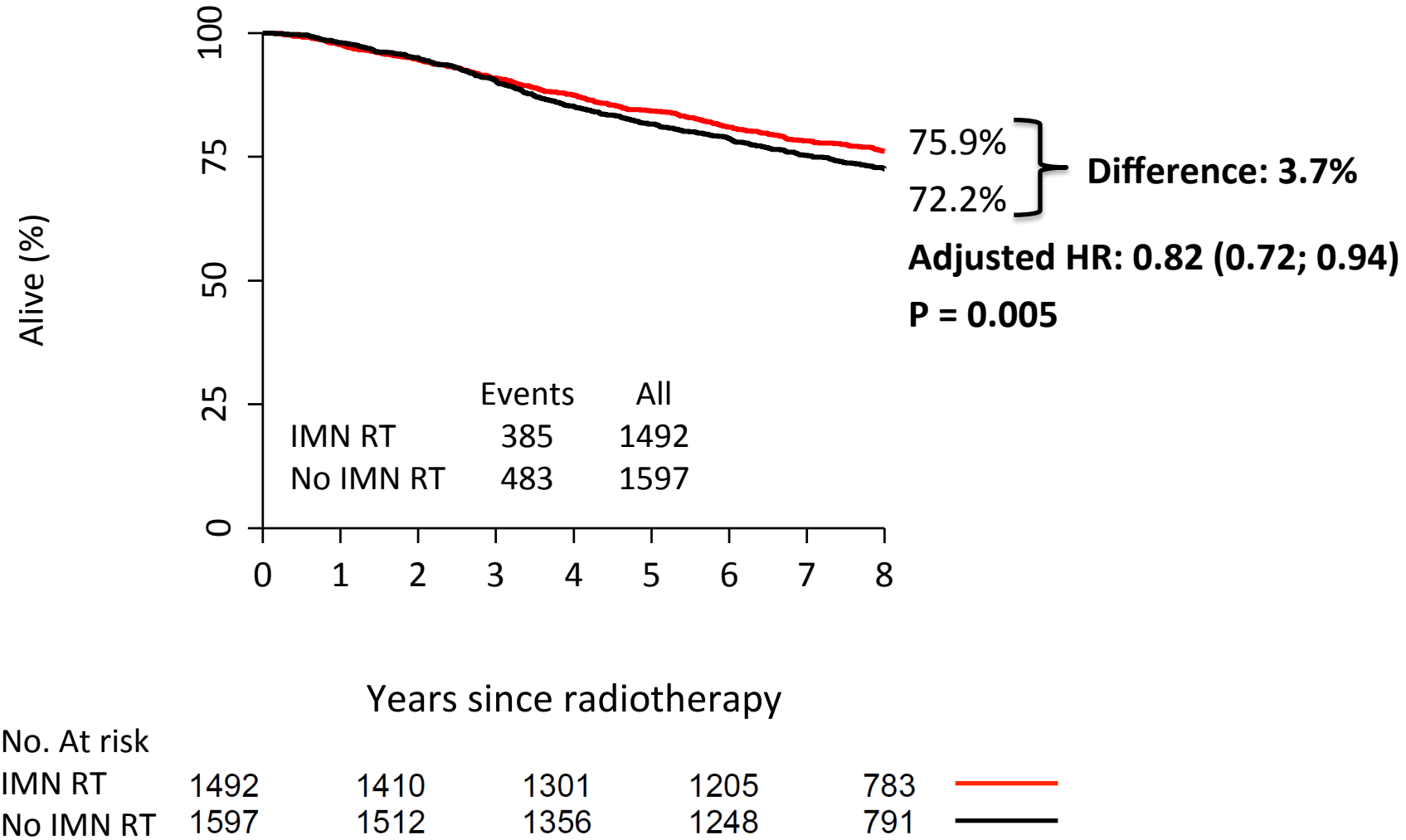
Primary endpoint: Overall Survival



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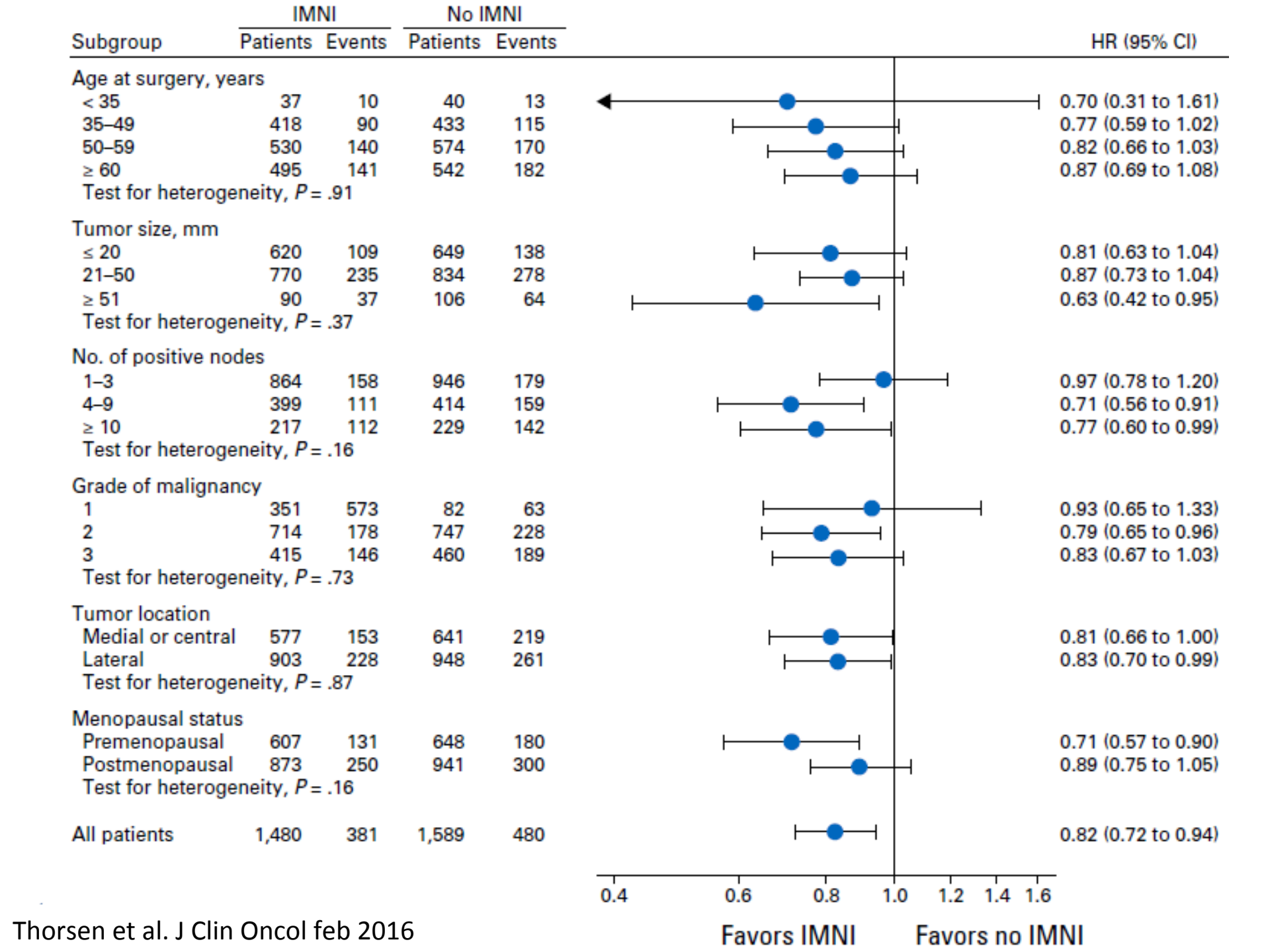
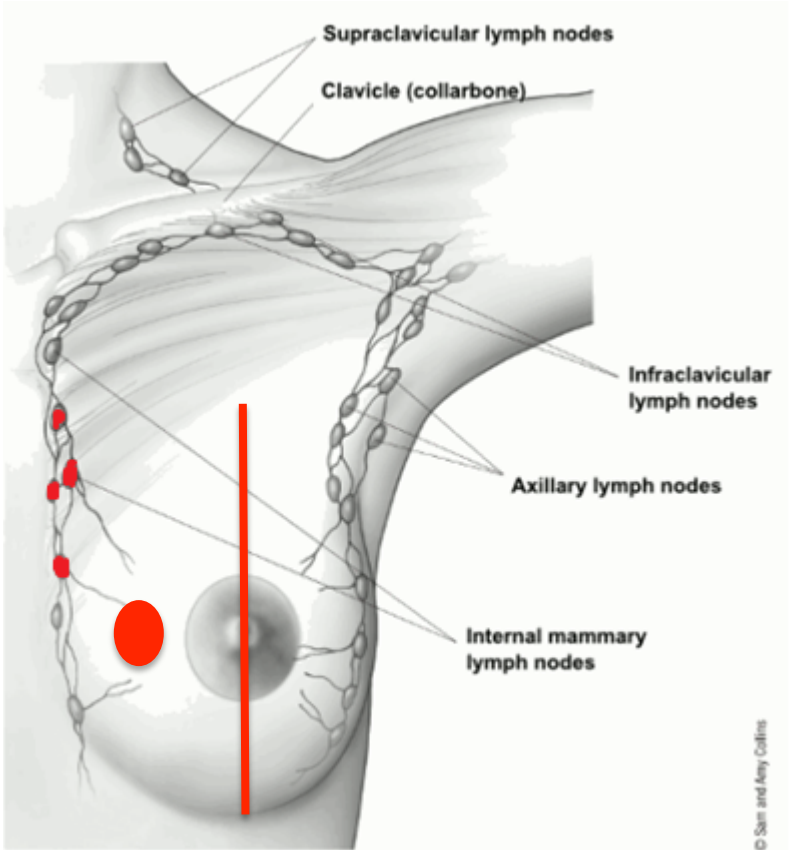


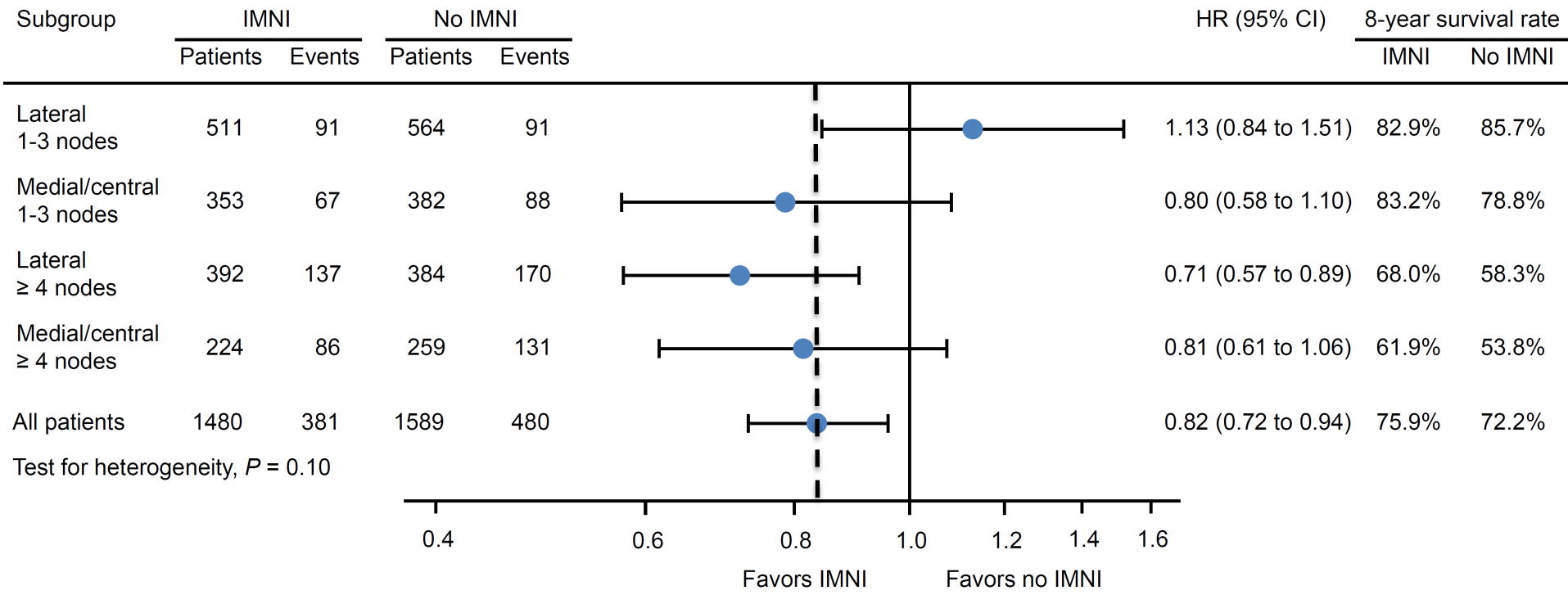
Thorsen et al. J Clin Oncol feb 2016

Association: ✓- Causality?

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



Subgroup analysis
Endpoint: Overall survival



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Hypotheses

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

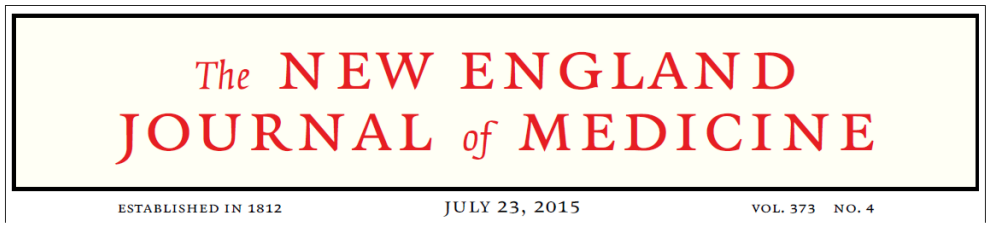
- Improves overall survival ✓
- Reduces breast cancer mortality ✓
- Reduces the risk of distant recurrence (✓)

Consequence

New 2014 radiotherapy guidelines:

- All Danish patients with node-positive early breast cancer are offered internal mammary node irradiation as part of adjuvant radiotherapy
- Treatment is provided using organ-sparing radiotherapy techniques

Results in context



Whelan et al.: MA.20, 2000-2007

- 1832 pts. The majority stage I-II breast cancer, randomised to whole breast irradiation (WBI) versus WBI + regional RT. MFU 9.5 years
- Improved disease free survival and distant disease free survival
- Breast cancer specific survival and OS not significant

Poortmans et al.: EORTC 22922-10925, 1996-2004

- 4004 pts. with stage I-III breast cancer. Medial/central tumor and/or N+ disease randomised to medial supraclavicular (MS) and IMN-RT. MFU 10.9 years
- Improved disease free survival, distant disease free survival and breast cancer specific survival with MS+IMN-RT
- Overall survival borderline significant

Future perspectives

In favor of IMN-RT:

- Consistent effect across studies: Improves survival
- New RT-techniques: Low doses to organs at risk: ↓ risk of toxicity
- Developments in treatment of cardiovascular disease: Amelioration of toxicity ?

Against IMN-RT:

- Efficient systemic therapy:
  - ↓ recurrence rates
  - ↓ absolute gains w. RT
- Early detection: Changing biology→Less aggressive disease?
- Risk of cardiac damage and second cancer*

*Grantzau T, Radiother Oncol. 2015 Jan;114(1):56-65

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Future perspectives

- Who needs IMN-RT?
  - Identification of sub-groups with larger effect of IMN-RT
  - Detection of IMN-metastases (Sentinel node? PET?)
- Who does not need IMN-RT?
  - Genetic profiles may predict lack of benefit from radiotherapy in breast cancer*
- Methods for weighing benefits against harm
  - Personalizing treatment

*Tramm T et al: Clin Cancer Res. 2014 Oct 15;20(20):5272-80

Acknowledgements

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