Anders W. Mølby Nielsen
Department of Experimental Clinical Oncology,
Aarhus University Hospital, Denmark

Internal mammary node radiotherapy in 4,541 modern-treated breast cancer patients: The DBCG IMN2 study

Anders WM Nielsen, LBJ Thorsen, D Özcan, LW Matthiessen, E Maae, MLH Milo, MH Nielsen, T Tramm, J Overgaard, BV Offersen

DBCG DANISH BREAST CANCER GROUP

Danish Cancer Society

original reports

Internal Mamm
Patients With
Fifteen-Year R
Cancer Group

Lise B.J. Thorsen, MD, PhD[1,2]; Jens O
Lars Stenbygaard, MD[5]; Anders N. Pec
Birgitte Vrou Offersen, MD, PhD[1,2] on

PURPOSE The Danish Breast C
overall survival (OS) with interna
cancer. Here, we present long-te
cohort.

PATIENTS AND METHODS This n
breast cancer to adjuvant radiot
sided cancer received IMNI. P
radiation-induced heart disease.
OS. Secondary end points were
local.

RESULTS During 2003-2007, 3,
cohort, n = 1,598). With a media
died. The corresponding 15-yea
0.86 (95% CI, 0.77 to 0.96; *P* =
35.6% (523 recurrences) and 3
to 0.99; *P* = .04]). The 15-yea
33.9% (537 deaths) without IMN
deaths was similar across grou

CONCLUSION In patients with no
breast cancer laterality, IMNI re
improving long-term survival.

J Clin Oncol 00. © 2022 by American So

Radiotherapy to regional nodes in early breast cancer: an individual patient data meta-analysis of 14 324 women in 16 trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Summary

Background Radiotherapy has become much better targeted since the 1980s, improving both safety and efficacy. In breast cancer, radiotherapy to regional lymph nodes aims to reduce risks of recurrence and death. Its effects have been studied in randomised trials, some before the 1980s and some after. We aimed to assess the effects of regional node radiotherapy in these two eras.

Methods In this meta-analysis of individual patient data, we sought data from all randomised trials of regional lymph node radiotherapy versus no regional lymph node radiotherapy in women with early breast cancer (including one study that irradiated lymph nodes only if the cancer was right-sided). Trials were identified through the EBCTCG's regular systematic searches of databases including MEDLINE, Embase, the Cochrane Library, and meeting abstracts. Trials were eligible if they began before Jan 1, 2009. The only systematic difference between treatment groups was in regional node radiotherapy (to the internal mammary chain, supraclavicular fossa, or axilla, or any combinations of these). Primary outcomes were recurrence at any site, breast cancer mortality, non-breast-cancer mortality, and all-cause mortality. Data were supplied by trialists and standardised into a format suitable for analysis. A summary of the formatted data was returned to trialists for verification. Log-rank analyses yielded first-event rate ratios (RRs) and confidence intervals.

Findings We found 17 eligible trials, 16 of which had available data (for 14 324 participants), and one of which (henceforth excluded), had unavailable data (for 165 participants). In the eight newer trials (12 167 patients), which started during 1989–2008, regional node radiotherapy significantly reduced recurrence (rate ratio 0·88, 95% CI 0·81–0·95; p=0·0008). The main effect was on distant recurrence as few regional node recurrences were reported. Radiotherapy significantly reduced breast cancer mortality (RR 0·87, 95% CI 0·80–0·94; p=0·0010), with no significant effect on non-breast-cancer mortality (0·97, 0·84–1·11; p=0·63), leading to significantly reduced all-cause mortality (0·90, 0·84–0·96; p=0·0022). In an illustrative calculation, estimated absolute reductions in 15-year breast cancer mortality were 1·6% for women with no positive axillary nodes, 2·7% for those with one to three positive axillary nodes, and 4·5% for those with four or more positive axillary nodes. In the eight older trials (2157 patients), which started during 1961–78, regional node radiotherapy had little effect on breast cancer mortality (RR 1·04, 95% CI 0·91–1·20; p=0·55), but significantly increased non-breast-cancer mortality (1·42, 1·18–1·71; p=0·00023), with risk mainly after year 20, and all-cause mortality (1·17, 1·04–1·31; p=0·0067).

Interpretation Regional node radiotherapy significantly reduced breast cancer mortality and all-cause mortality in trials done after the 1980s, but not in older trials. These contrasting findings could reflect radiotherapy improvements since the 1980s.

Funding Cancer Research UK, Medical Research Council.

Lancet 2023; 402: 1991–2003
Published Online November 3, 2023
https://doi.org/10.1016/S0140-6736(23)01087-6

See Comment page 1943

*Members are listed at the end of the Article (see EBCTCG writing committee, EBCTCG secretariat, and EBCTCG steering committee); affiliations are listed in the appendix (pp 46–50)

Correspondence to:
EBCTCG secretariat, Clinical Trial Service Unit, Nuffield Department of Population Health, Oxford OX3 7LF, UK
bc.overview@ndph.ox.ac.uk

See Online for appendix

DBCG

in breast

aclavicular lymph node
cancer (EORTC
andomised, phase 3 trial

aux-Casasnovas, Volker Budach, Femke van der Leij,
rges Noel, Mariacarla Valli, Matthias Guckenberger,
ntoine Engelen, Peter De Brouwer, Henk Struikmans,
Radiation Oncology and Breast Cancer Groups

disease-free survival and distant metastasis-free
on overall survival with the addition of partial or
nts with breast cancer. We present the scheduled
eatment of Cancer (EORTC) 22922/10925 trial,
internal mammary and medial supraclavicular

The DBCG IMN design

Radiation induced cardiac mortality in 10-year survivors → Left-sided patients

1990's

Anthracyclines

2000

No evidence for the gain of IMN RT

National DBCG guideline for all N+ patients

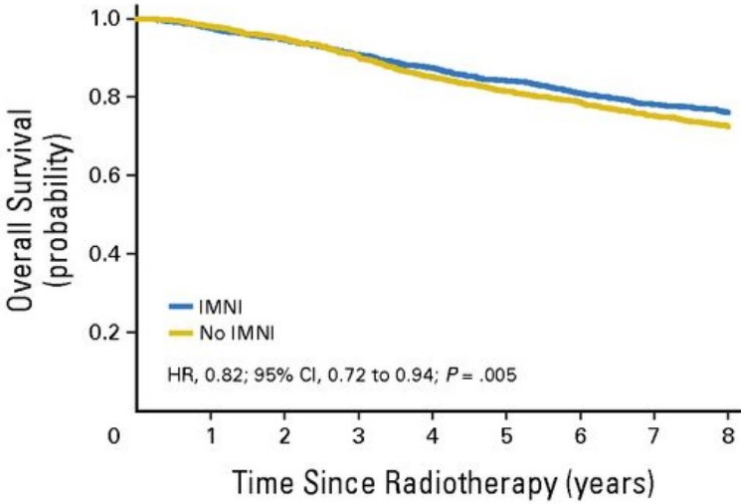
2003

Right side → IMN RT

Left side → No IMN RT

The DBCG IMN studies

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT



DBCG-IMN: A Population-Based Cohort Study on the Effect of Internal Mammary Node Irradiation in Early Node-Positive Breast Cancer

Lise Bech Jellesmark Thorsen, Birgitte Vrou Offersen, Hella Danø, Martin Berg, Ingelise Jensen, Anders Navrsted Pedersen, Sune Jürg Zimmermann, Hans-Jürgen Brodersen, Marie Overgaard, and Jens Overgaard

See accompanying editorial on page 297

A B S T R A C T

2003 DBCG IMN1 study 2007 DBCG IMN2 study 2014

Modern adjuvant therapies


No screening


Chemotherapy


Tamoxifen


No Trastuzumab


Field-based radiotherapy


Nationwide **screening**


Anthracyclines and **taxanes**


Tamoxifen and **letrozol**


Trastuzumab


CT-based radiotherapy

EBCTCG meta-analysis $\neq$ DBCG IMN2 study

(Incl. DBCG IMN1 study, MA.20, EORTC)

Methods

Nationwide prospective population-based cohort study

Inclusion: Node-positive BC patients treated with loco-regional radiotherapy (RT)

Exclusion: Prior malignancies, bilateral BC, primary systemic therapy, recurrence before RT, and non-standard RT

Endpoints were distant recurrence, breast cancer mortality, and overall survival (primary endpoint)

Analyses were intention-to-treat

Patient characteristics

6 centers

4,541 patients included

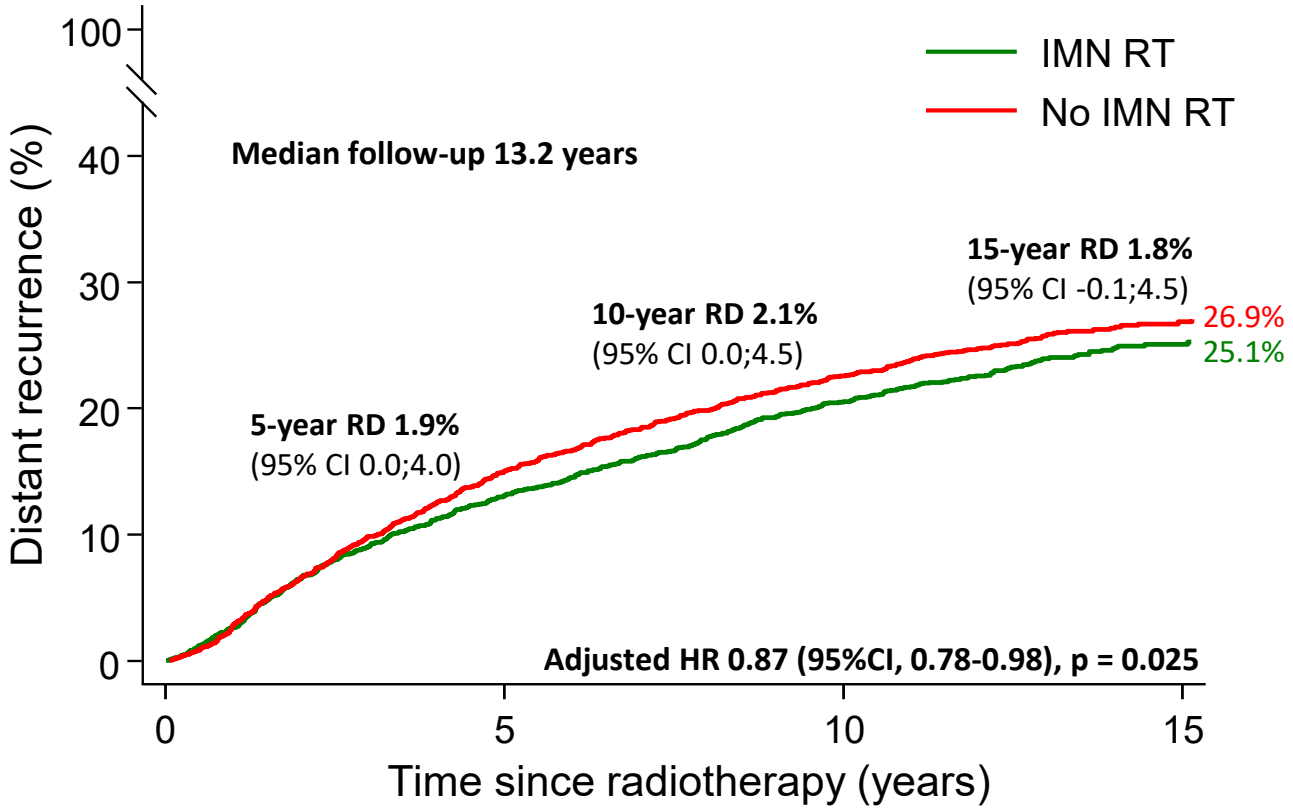
665 patients excluded

Patient-, tumor- and treatment characteristics were evenly distributed between right-sided patients and left-sided patients

Table 1: Patient characteristics

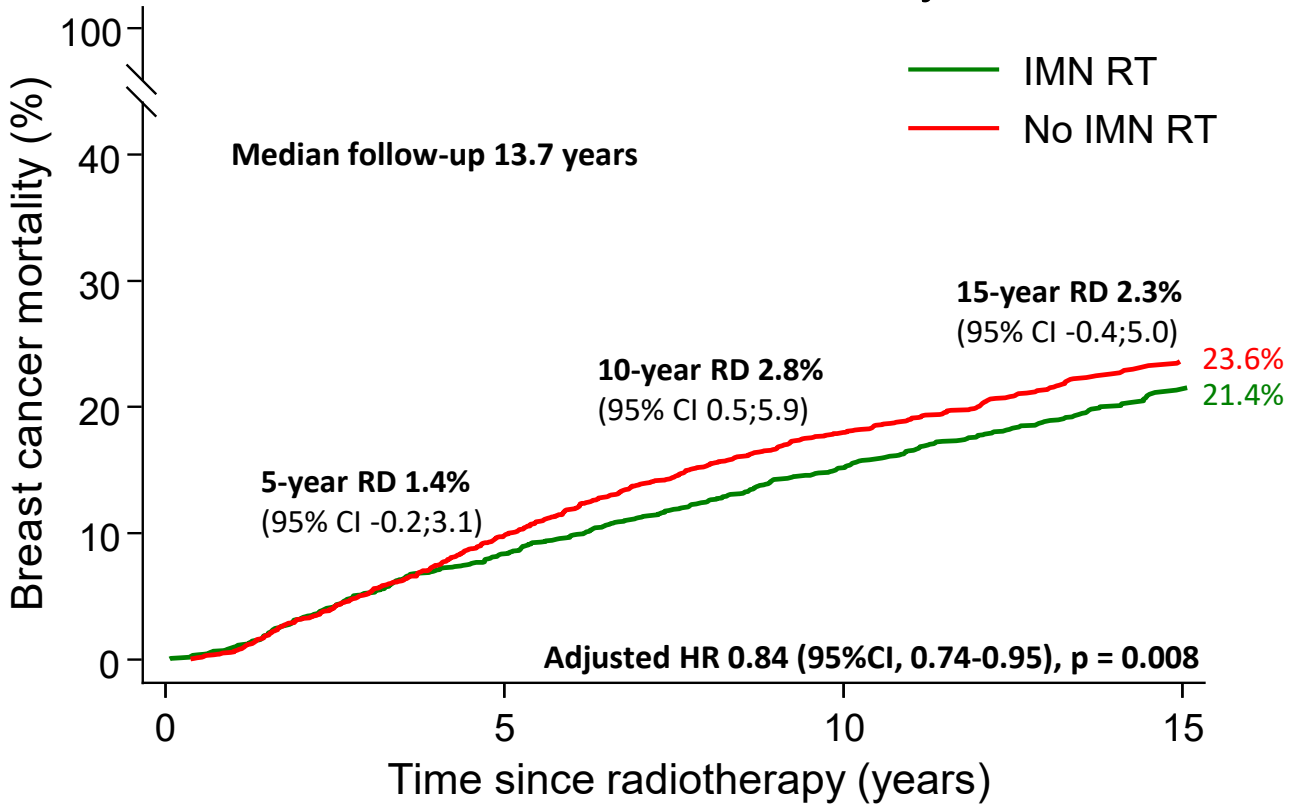
	Laterality					
	Left		Right		Total	
	n=2,347 (51.7%)		n=2,194 (48.3%)		n=4,541	
Age, median (IQR)	59	(50-66)	59	(50-66)	59	(50-66)
Menopausal status						
Premenopausal	681	(29.0%)	648	(29.5%)	1329	(29.3%)
Postmenopausal	1666	(71.0%)	1546	(70.5%)	3212	(70.7%)
Tumor size						
0-20 mm	1130	(48.1%)	1032	(47.0%)	2162	(47.6%)
21-50 mm	1119	(47.7%)	1074	(49.0%)	2193	(48.3%)
>50 mm	98	(4.2%)	88	(4.0%)	186	(4.1%)
Tumor location						
Medial or central	1011	(43.1%)	921	(42.0%)	1932	(42.5%)
Lateral	1335	(56.9%)	1273	(58.0%)	2608	(57.4%)
No primary tumor	1	(0.0%)	0	(0.0%)	1	(0.0%)
Type of surgery						
Mastectomy	1092	(46.5%)	1017	(46.4%)	2109	(46.4%)
Breast conserving surgery	1255	(53.5%)	1177	(53.6%)	2432	(53.6%)
LN removed, median (IQR)	16	(13-20)	17	(14-21)	17	(14-21)
Positive LN						
1-3	1610	(68.6%)	1490	(67.9%)	3100	(68.3%)
4-9	512	(21.8%)	469	(21.4%)	981	(21.6%)
≥ 10	225	(9.6%)	235	(10.7%)	460	(10.1%)
Histologic type						
IDC	2018	(86.0%)	1875	(85.5%)	3893	(85.7%)
ILC	232	(9.9%)	216	(9.8%)	448	(9.9%)
Other	97	(4.1%)	103	(4.7%)	200	(4.4%)
Grade of malignancy						
Grade 1	649	(27.7%)	618	(28.2%)	1267	(27.9%)
Grade 2	1010	(43.0%)	949	(43.3%)	1959	(43.1%)
Grade 3	680	(29.0%)	623	(28.4%)	1303	(28.7%)
Missing	8	(0.3%)	4	(0.2%)	12	(0.3%)
Estrogen receptor status						
Negative	371	(15.8%)	321	(14.6%)	692	(15.2%)
Positive	1976	(84.2%)	1873	(85.4%)	3849	(84.8%)
HER-2 status						
Negative	1893	(80.7%)	1793	(81.7%)	3686	(81.2%)
Positive	420	(17.9%)	374	(17.0%)	794	(17.5%)
Not evaluated	34	(1.4%)	27	(1.2%)	61	(1.3%)
Systemic Therapy						
Endocrine (ET)	893	(38.0%)	831	(37.9%)	1724	(38.0%)
Chemotherapy (CT)	345	(14.7%)	300	(13.7%)	645	(14.2%)
ET+CT	1077	(45.9%)	1026	(46.8%)	2103	(46.3%)
Trastuzumab	326	(13.9%)	288	(13.1%)	614	(13.5%)
None	32	(1.4%)	37	(1.7%)	69	(1.5%)

Distant recurrence



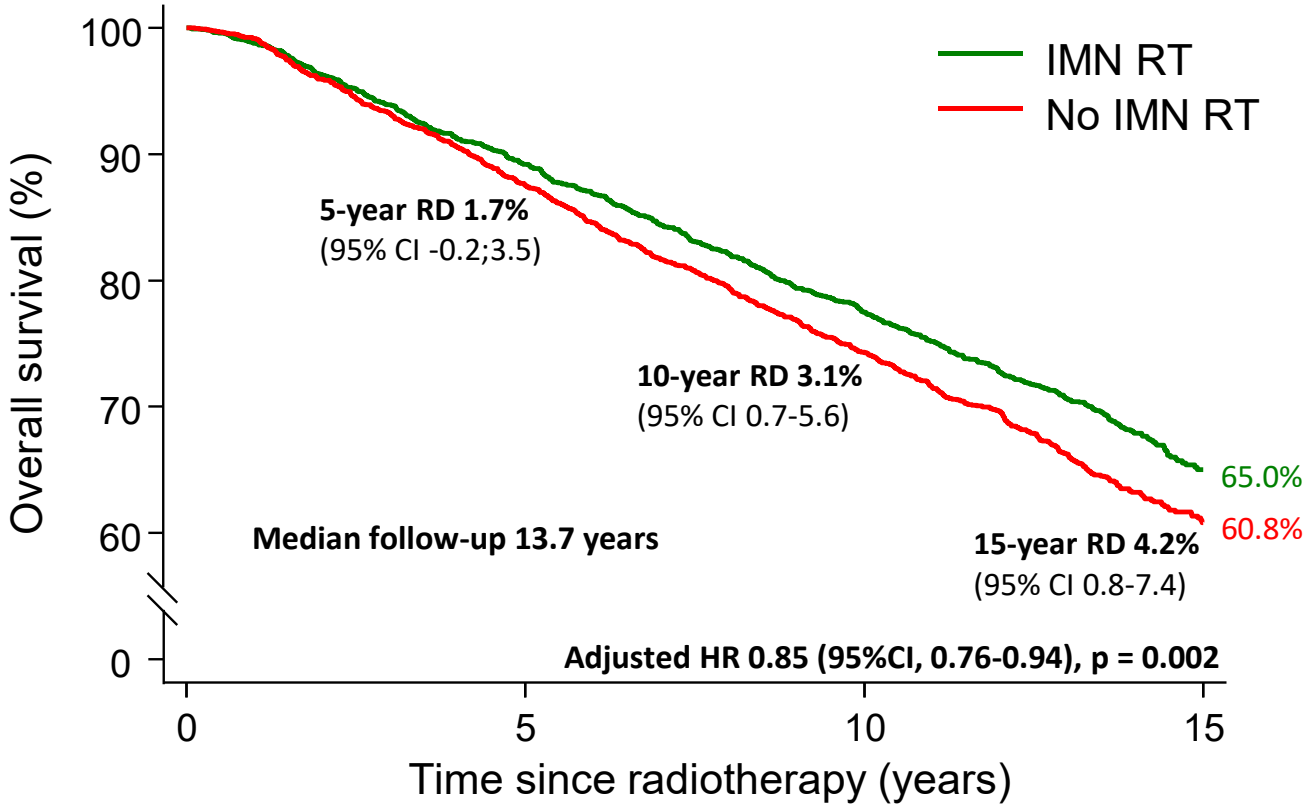
At risk				
IMN RT	2194	1851	1517	324
No IMN RT	2347	1925	1559	309

Breast cancer mortality



At risk				
IMN RT	2194	1954	1629	348
No IMN RT	2347	2047	1665	326

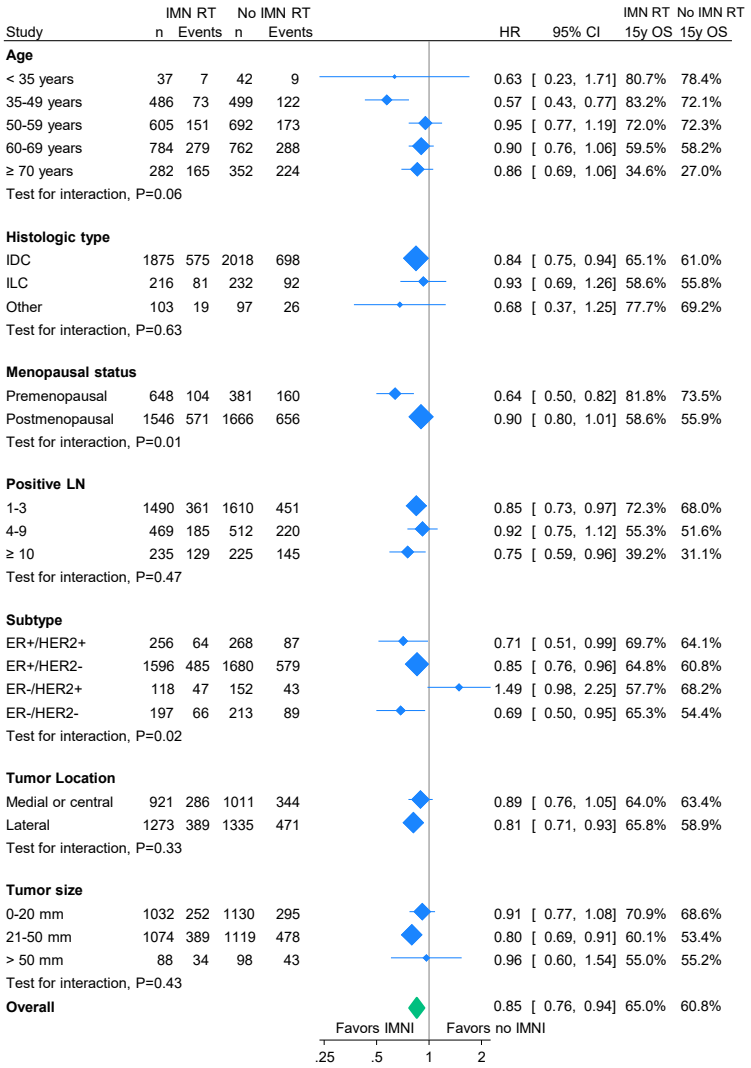
Overall survival



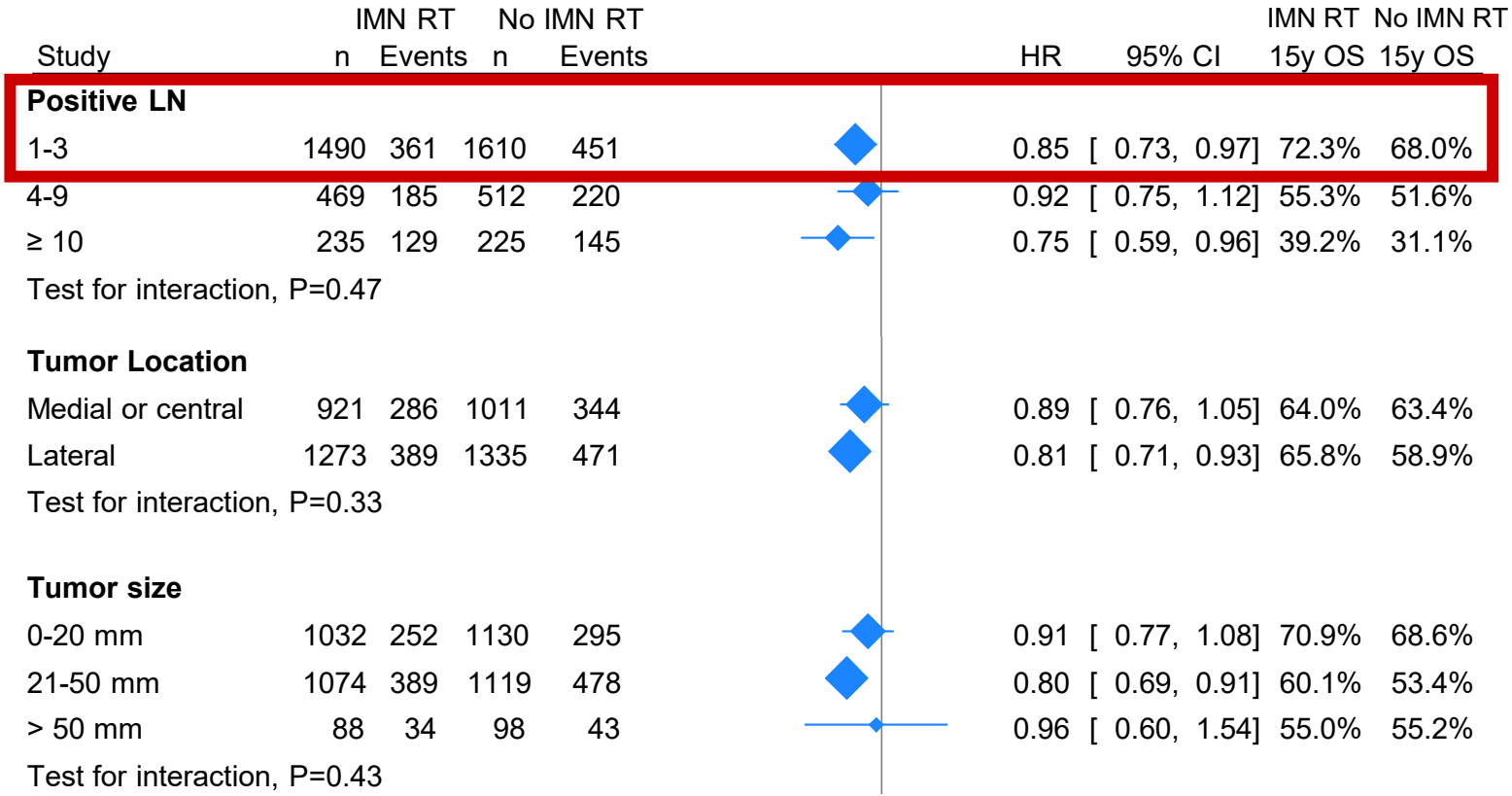
At risk				
IMN RT	2194	1954	1629	348
No IMN RT	2347	2047	1665	326

Subgroup analyses (overall survival)

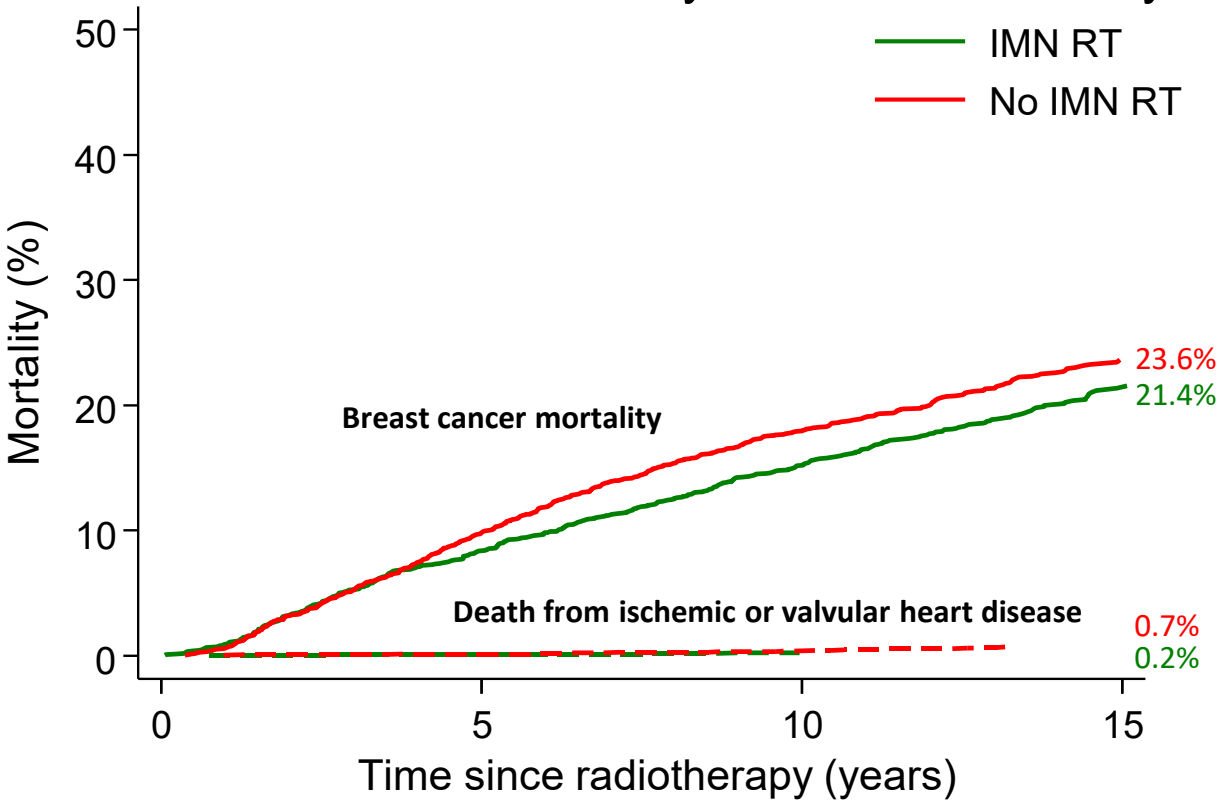
Consistent effect of IMN RT across subgroups



Subgroup analyses (overall survival)



Breast cancer mortality vs cardiac mortality



At risk			
IMN RT2194	1954	1629	348
No IMN RT2347	2047	1665	326

Conclusion

IMN RT reduced distant recurrences and BC mortality leading to an improved overall survival in BC patients, even despite the use of modern adjuvant treatments

No subgroups identified for safe IMN RT omission

Conclusion

Der er lavet grundig kvalitetssikring af RT i dette studie → der var vekslende dosisdækning af IMN på tværs af afdelingerne → sandsynligt at gevinsten af IMN RT er endnu større nu, hvor der i højere grad bruges gating

Acknowledgements

Thanks to all patients, DBCG, participating centers, and all collaborators

DBCG DANISH BREAST CANCER GROUP

Danish Cancer Society