Mammakarzinom- Refresherkurs DEGRO 2014

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Invasives Mammakarzinom

Pathologie

TNM

Empfehlungsgrad A	a.	- pTNM-Status (Tumorgröße, axillärer Lymphknotenbefall, Fernmetastasierung)
Level of Evidence 1a		(Bundred, NJ 2001; Carter, CL et al. 1989; NCCN 2011; NZGG 2009; Page, DL et al. 1992; Page, DL et al. 1998; Rosen, PP et al. 1991; Rosen, PP et al. 1993)

Schnittrand

Empfehlungsgrad A	b.	- Resektionsrand (R-Klassifikation) und Sicherheitsabstände
Level of Evidence 1b		(Bundred, NJ 2001; Kurtz, JM et al. 1989; NCCN 2011; NICE 2009; NZGG 2009; Park, CC et al. 2000)

Histol. Typ

Empfehlungsgrad A	c.	- histologischer Typ
Level of Evidence 2b		(Fisher, ER et al. 1990; NCCN 2011; NZGG 2009)

Grading

Empfehlungsgrad A	d.	- Grading
Level of Evidence 2a		(Elston, CW et al. 1991; NCCN 2011; NZGG 2009)

ER/PR-Status

		Für die adjuvante Therapie sollen folgende prädiktive Faktoren erhoben werden:
Empfehlungsgrad A	h.	- Östrogen-/Progesteronrezeptorstatus für eine endokrine Systemtherapie
Level of Evidence 1a		(Bundred, NJ 2001; EBCTCG 1992; EBCTCG 1998; NCCN 2011; Osborne, CK 1998)

Her2-Status

Empfehlungsgrad A	i.	- HER2/neu-Status für eine zielgerichtete Anti-HER2-Therapie
Level of Evidence 1b		(NCCN 2011; NICE 2009; Nothacker, M et al. 2007; NZGG 2009)

Empfehlungsgrad B	e.	- Lymphgefäß- und Blutgefäßeinbruch (Lx, Vx)
Level of Evidence 2b		(Colleoni, M et al. 2007; Gasparini, G et al. 1994; Kato, T et al. 2003; NCCN 2011; NZGG 2009)
Empfehlungsgrad 0	g.	Beim nodal-negativen Mammakarzinom kann die Bestimmung der Tumorkonzentrationen von uPA und PAI-1 mittels ELISA weitere prognostische Informationen liefern.
Level of Evidence 1a		(Harbeck, N et al. 2009; Harris, L et al. 2007; Janicke F et al. 2001; Look, MP et al. 2002)
	k.	Der prognostische und prädiktive Wert des Proliferationsmarkers Ki-67 ist nicht ausreichend belegt. Außerhalb von Studien kann er daher nicht zur Subtypisierung ER-positiver Mammakarzinome (z. B. Ki-67 < 14 %: Luminal A; Ki-67 > 14 %: Luminal B) als Entscheidungsgrundlage für die systemische Therapie klinisch angewendet werden.
GCP		(de Azambuja, E et al. 2007; Dowsett, M et al. 2011; Stuart-Harris, R et al. 2008; Yerushalmi, R et al. 2010)
	l.	Der Einsatz von Analysen der Genexpression – PCR-basiert oder mittels Microarrays – zur Beurteilung der Prognose oder des Therapieansprechens (Prädiktion) ist für den Routineeinsatz nicht ausreichend validiert und kann daher nicht empfohlen werden.
GCP		(EGAPP Working Group 2009; Marchionni, L et al. 2008; Paik, S et al. 2004; Paik, S et al. 2006)

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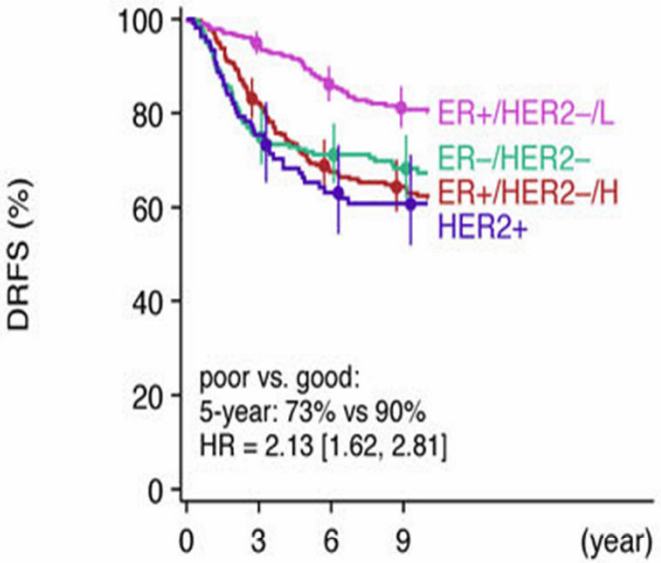
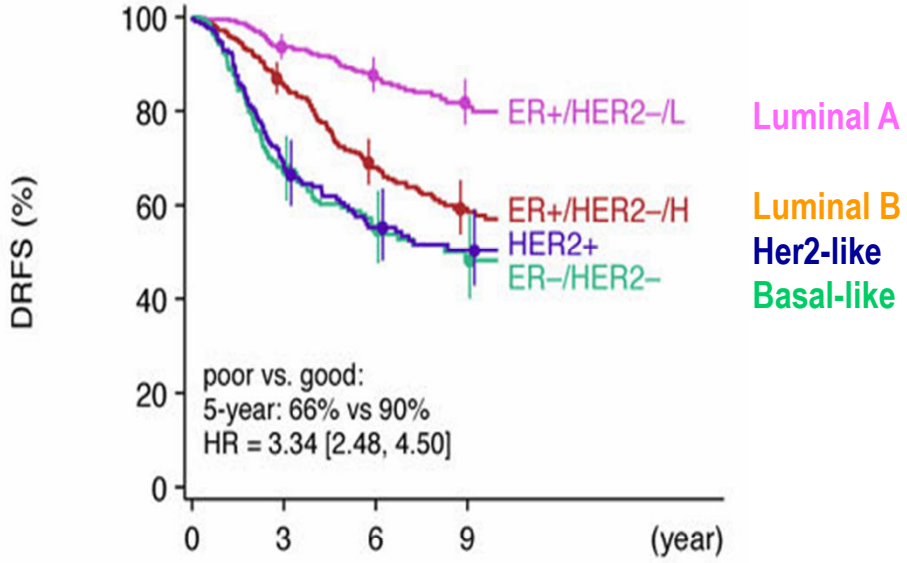
Meta-analysis: Gene Expression Profile and Prognosis

no systemic therapy



follow-up:	0	3	6	9	(year)
group:	number at risk:				events
ER+/HER2–/H	306	247	188	137	110
ER+/HER2–/L	335	310	265	173	61
ER–/HER2–	202	148	125	77	62
HER2+	107	75	54	36	40
total	950	780	632	423	273

systemic therapy



follow-up:	0	3	6	9	(year)
group:	number at risk:				events
ER+/HER2–/H	427	308	182	83	135
ER+/HER2–/L	387	309	205	85	52
ER–/HER2–	216	110	65	26	83
HER2+	205	112	68	38	81
total	1235	839	520	232	351

Luminal A

Luminal B

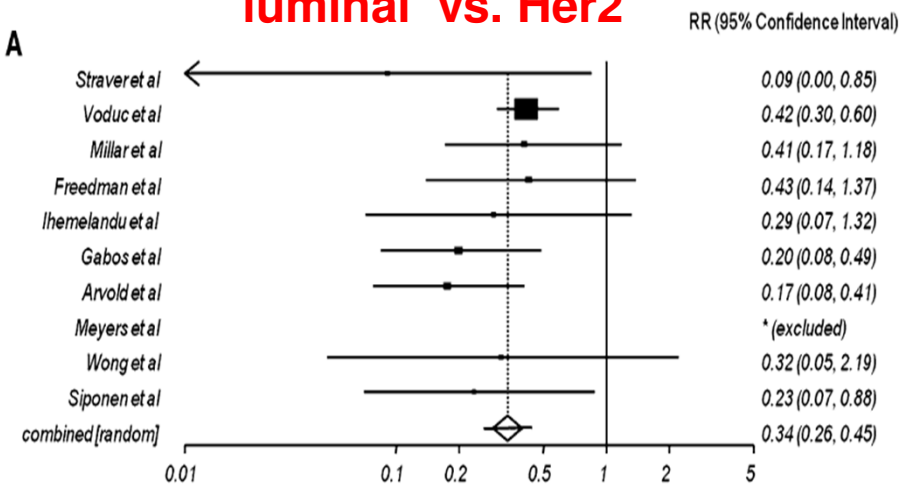
Her2-like

Basal-like

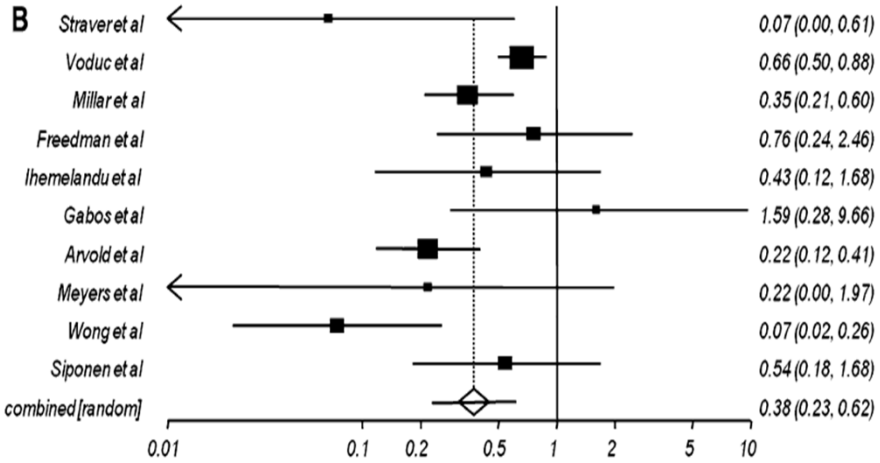
Wirapati et al Breast Can Res 2008

Breast cancer: Locoregional recurrence after BCT by molecular subtype

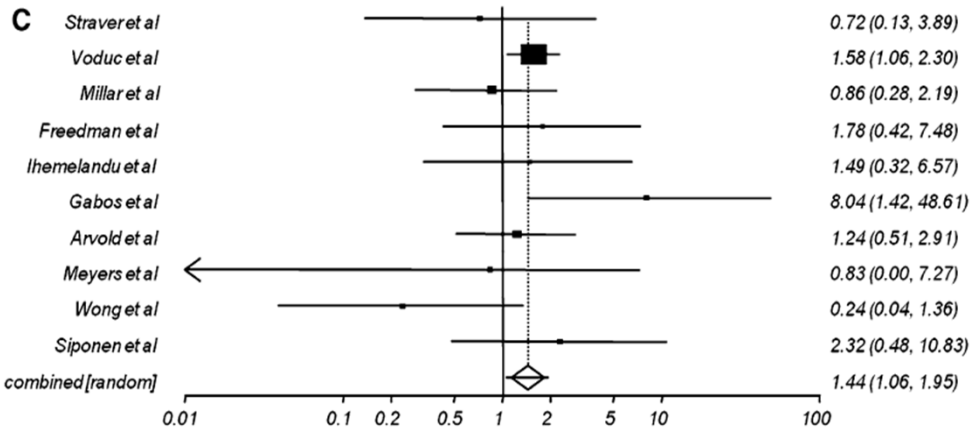
luminal vs. Her2



luminal vs. triple neg.



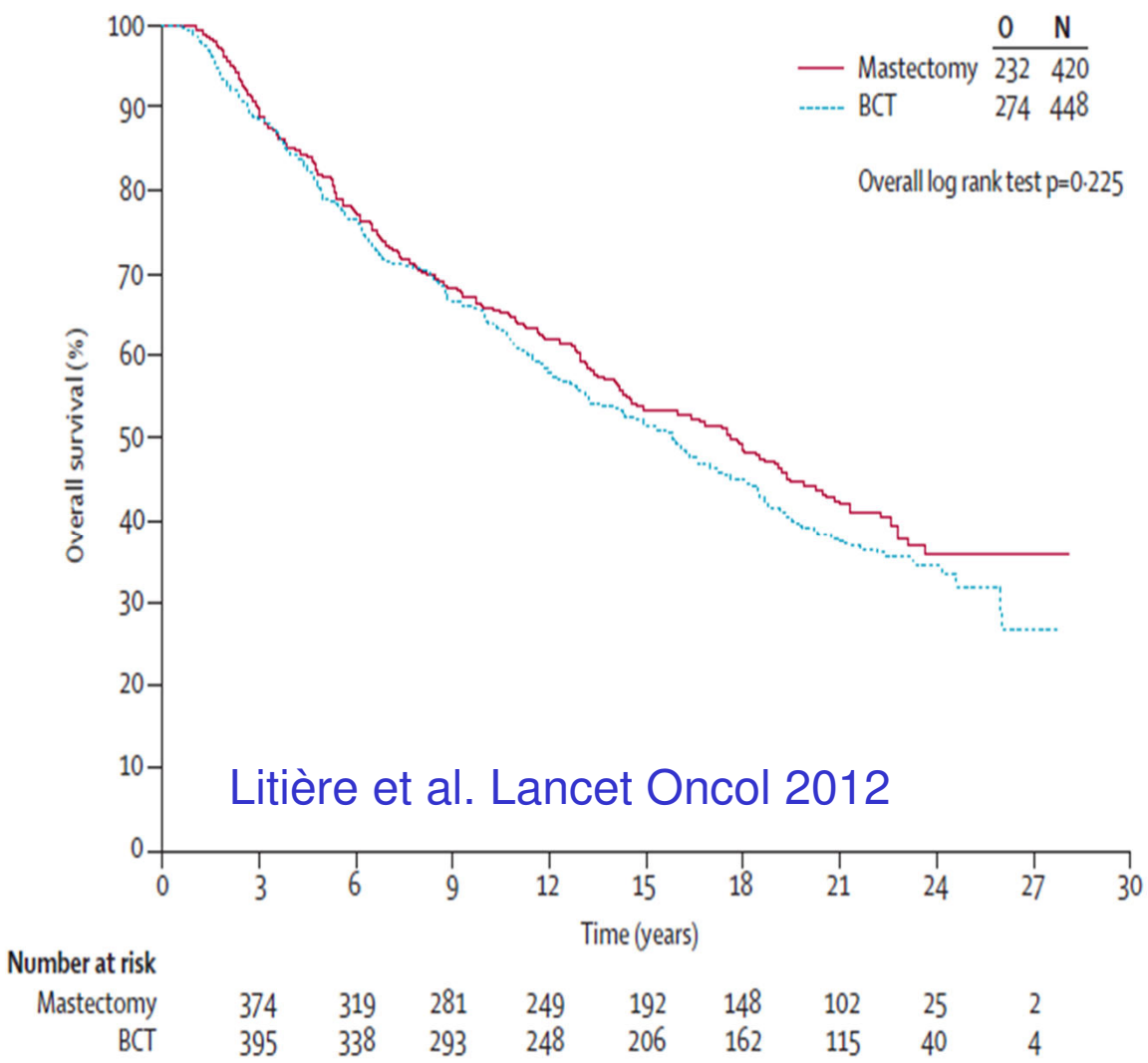
triple neg. vs. Her2



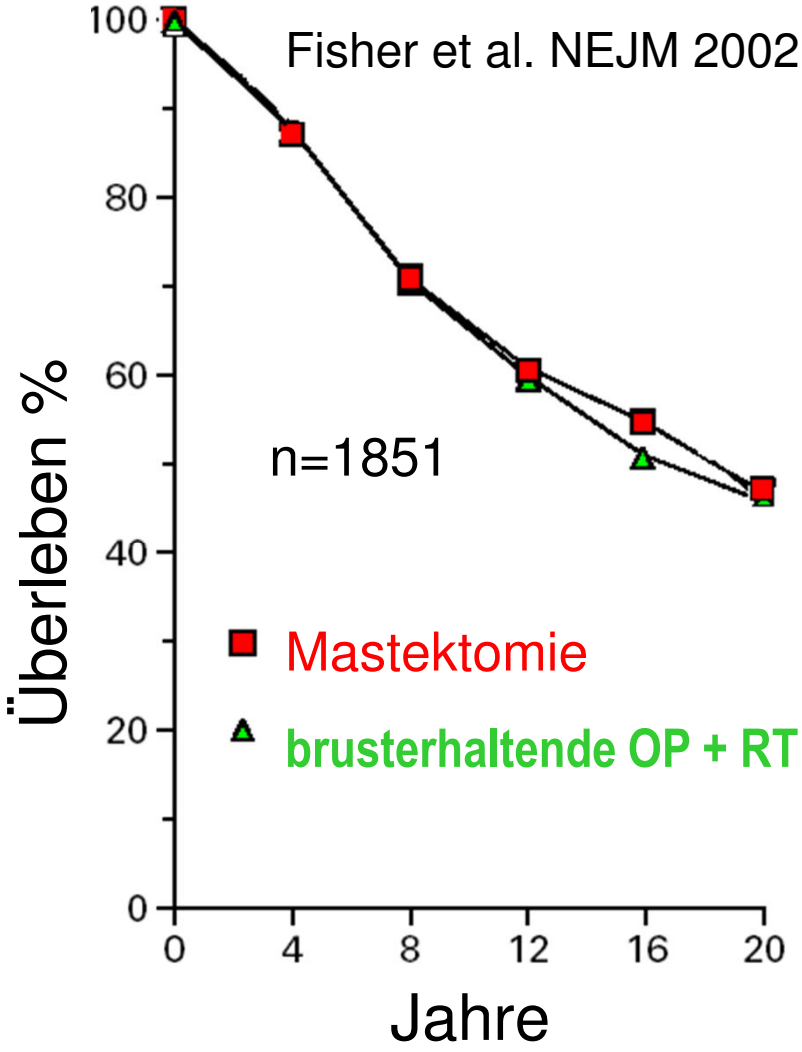
Lowery et al. Breast Cancer Res Treat 2012

Brusterhaltende Operation vs. radikale Mastektomie beim Mamma-Ca.

Metaanalyse der EBCTCG, n=3100, NEJM 1995



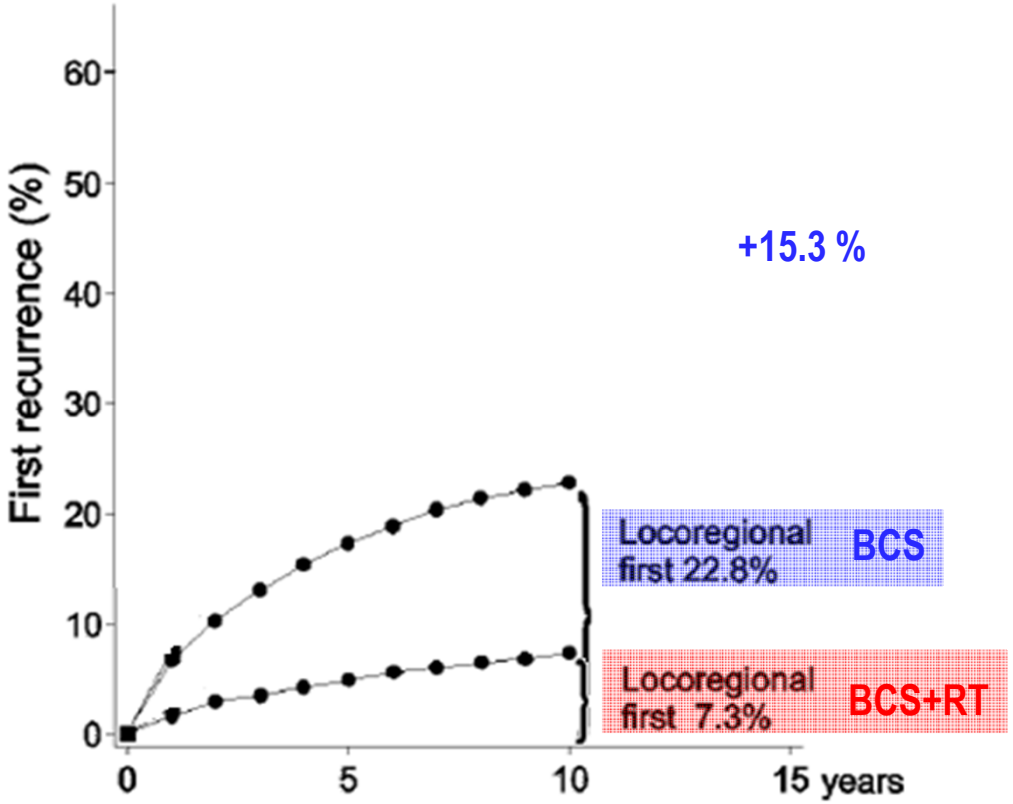
Litière et al. Lancet Oncol 2012



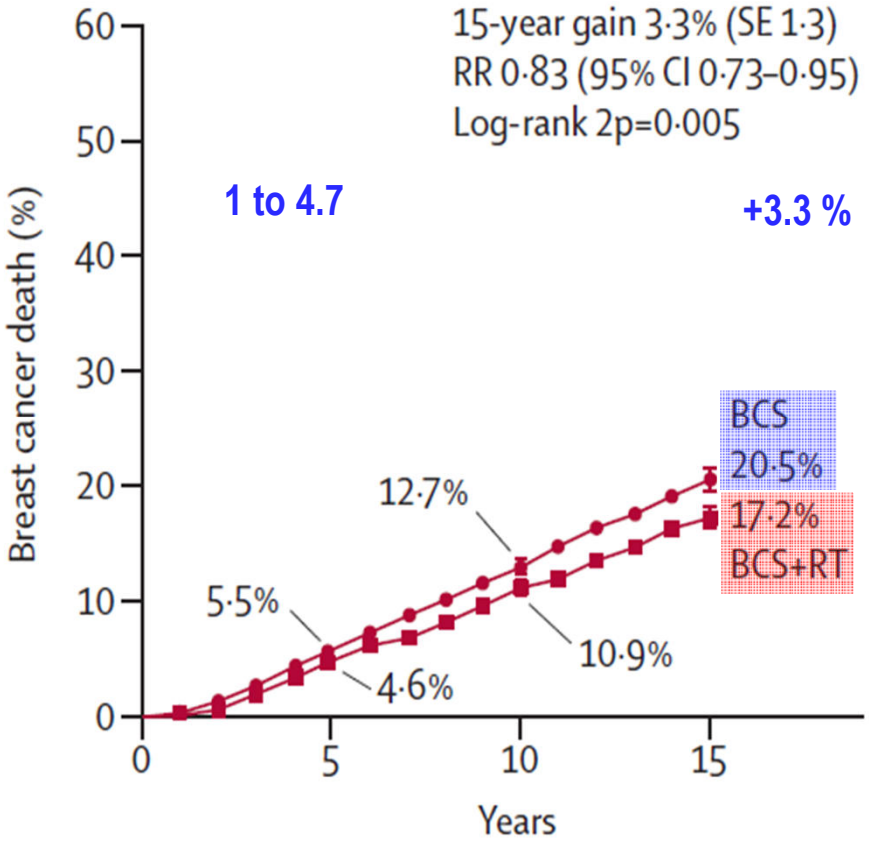
Radiotherapy after breast-conserving surgery

(7287 women, 10 years results) EBCTCG Lancet 2011

pN0: locoregional relapse



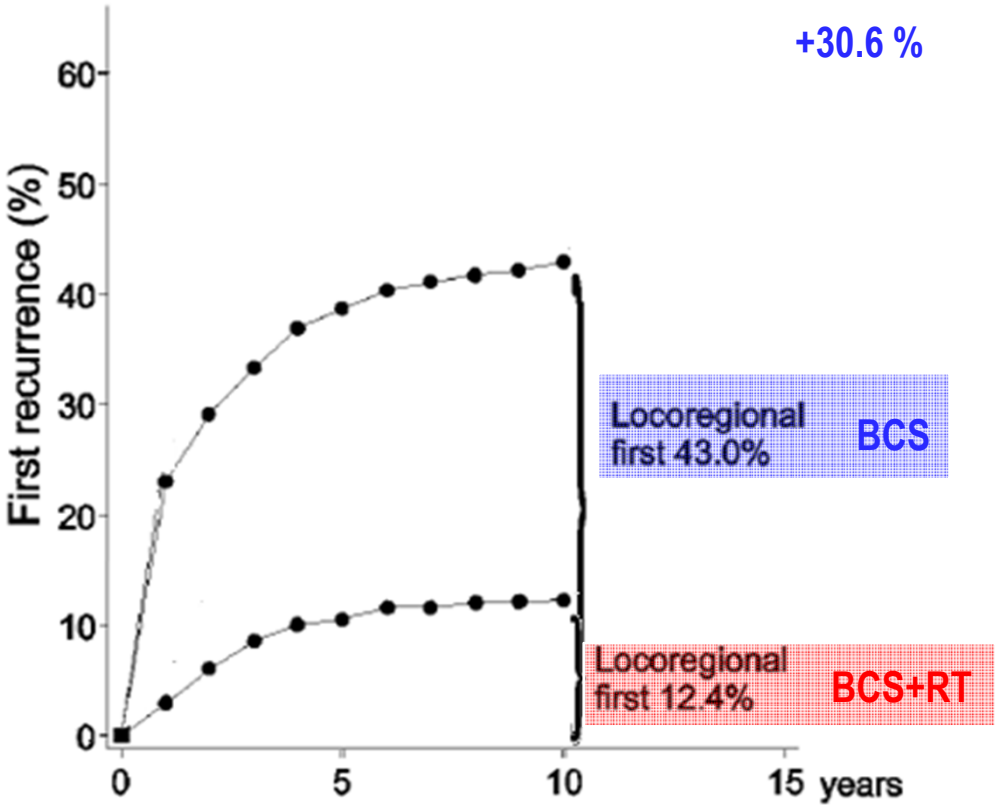
pN0: breast cancer death



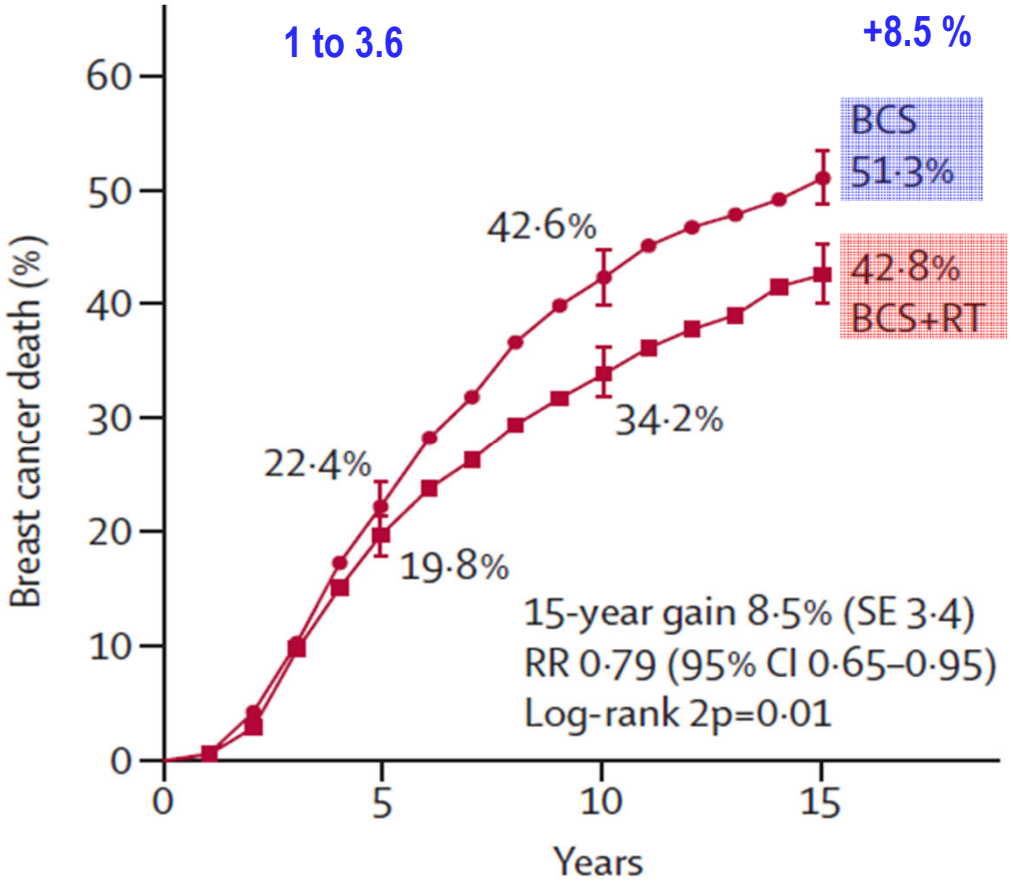
Radiotherapy after breast-conserving surgery

(1050 women, 10 years results) EBCTCG Lancet 2011

pN+: locoregional relapse

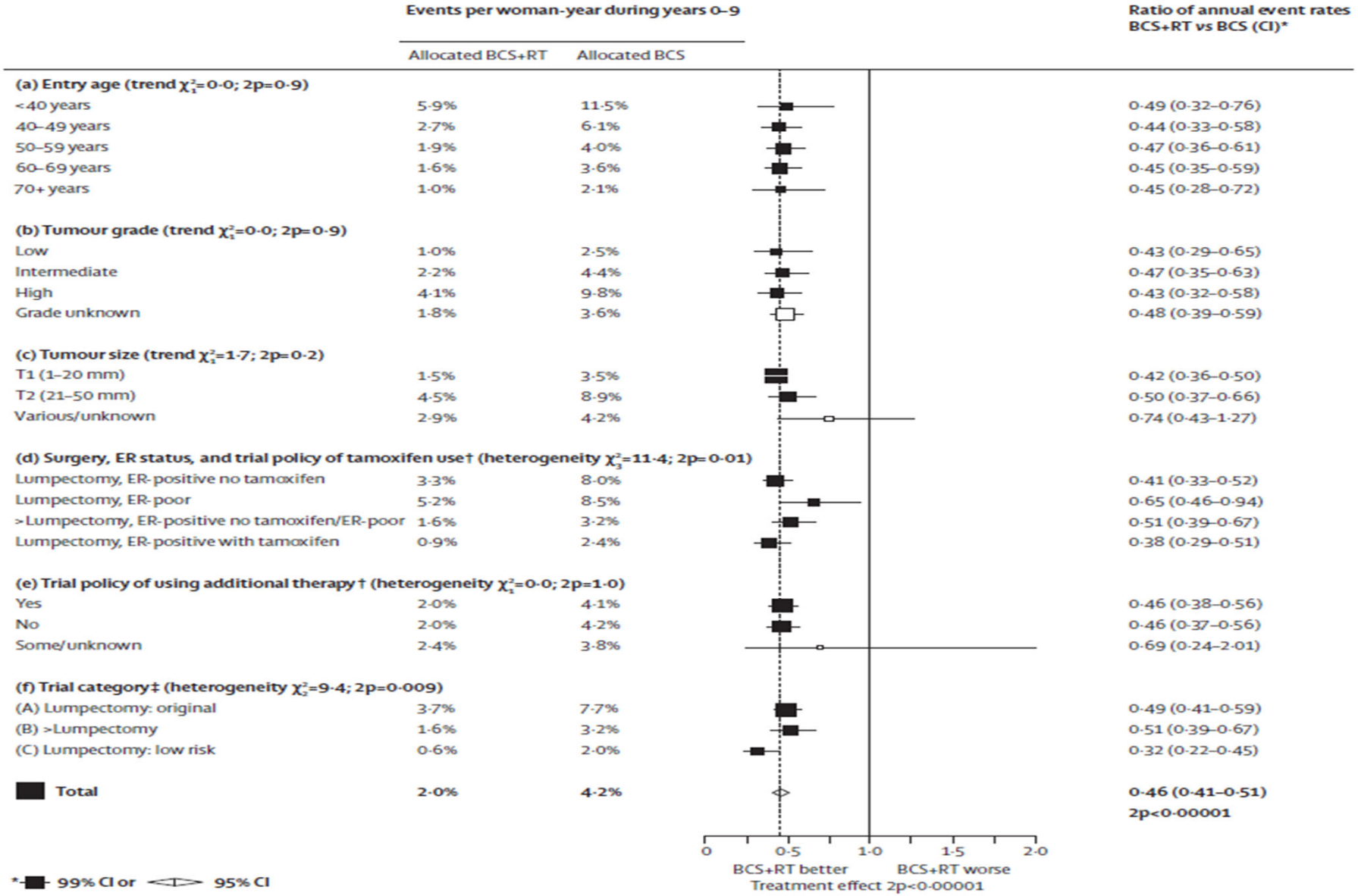


pN+: breast cancer death



Radiotherapy after breast-conserving surgery, generally with axillary clearance (BCS±RT) in all women (node-negative or node-positive)

(10801 women, 15 years median follow up) EBCTCG Lancet 2011



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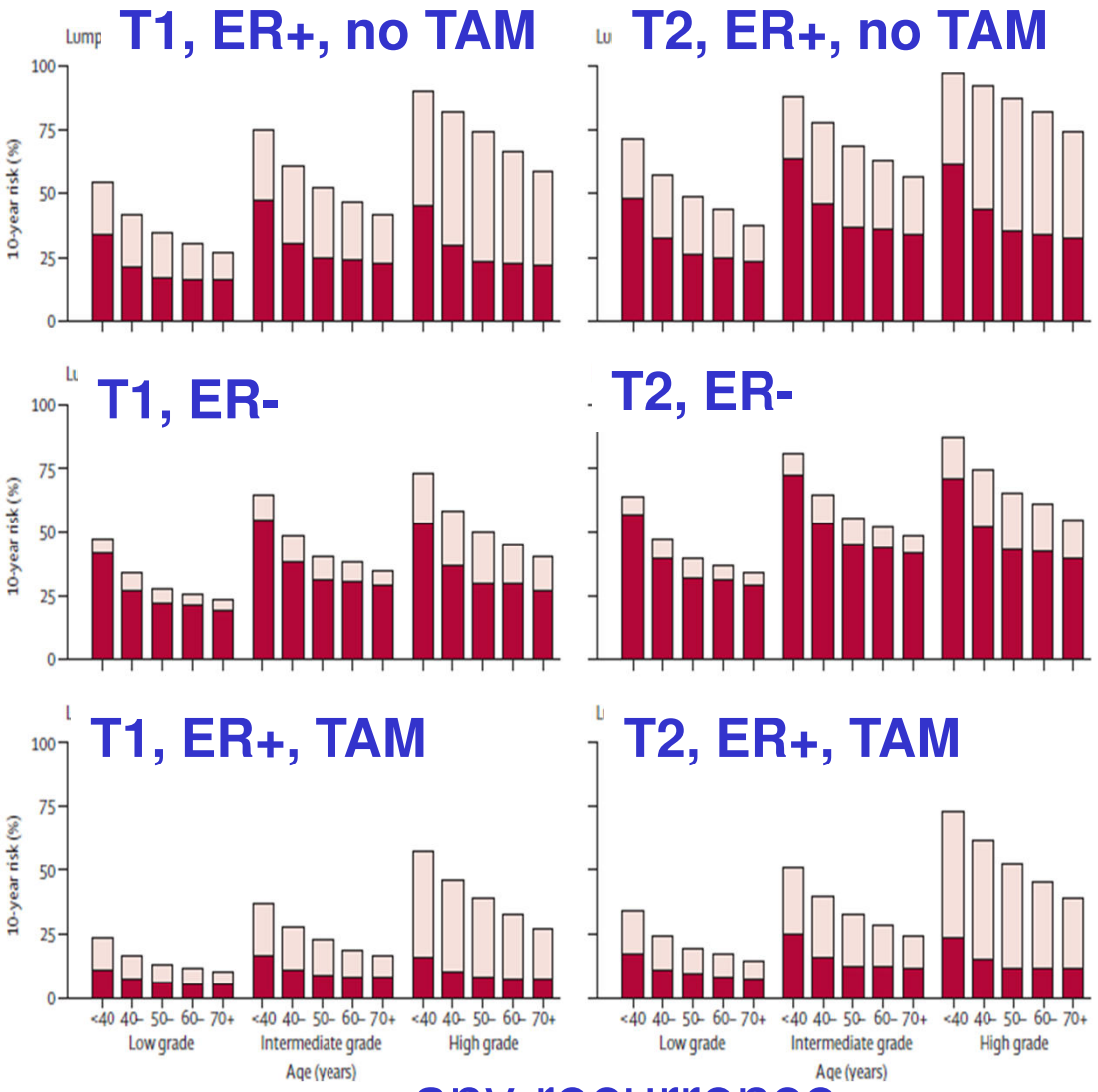

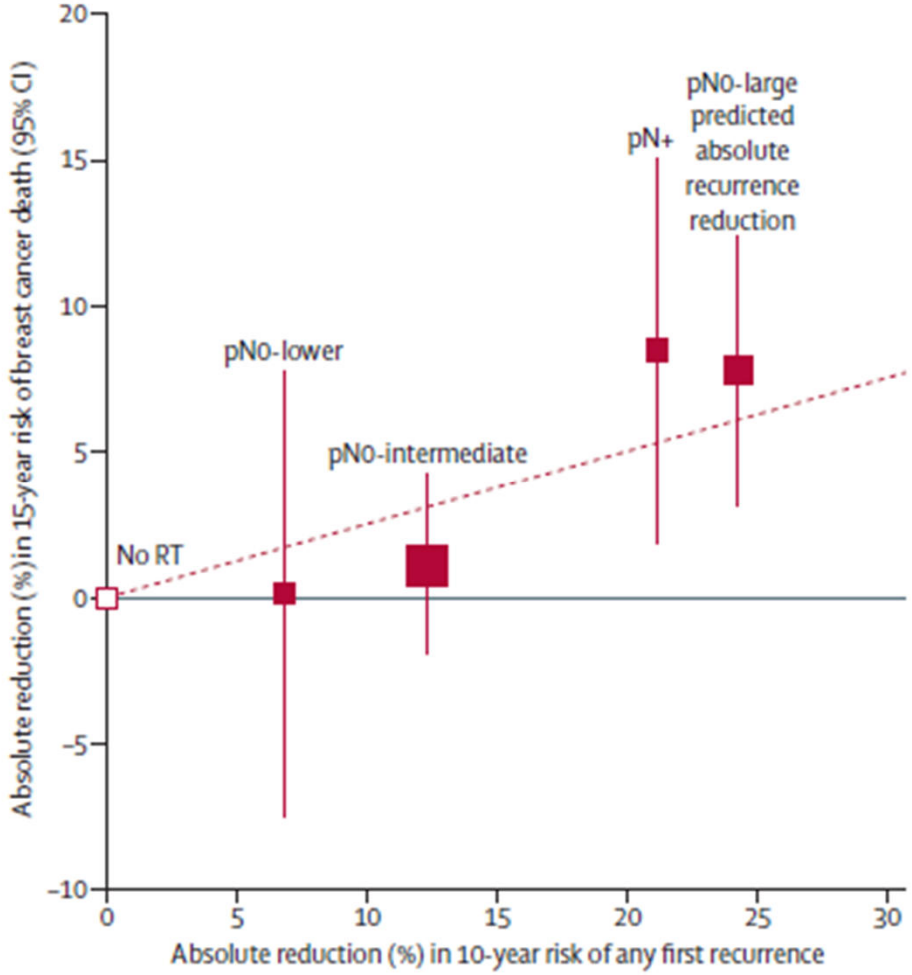

any recurrence

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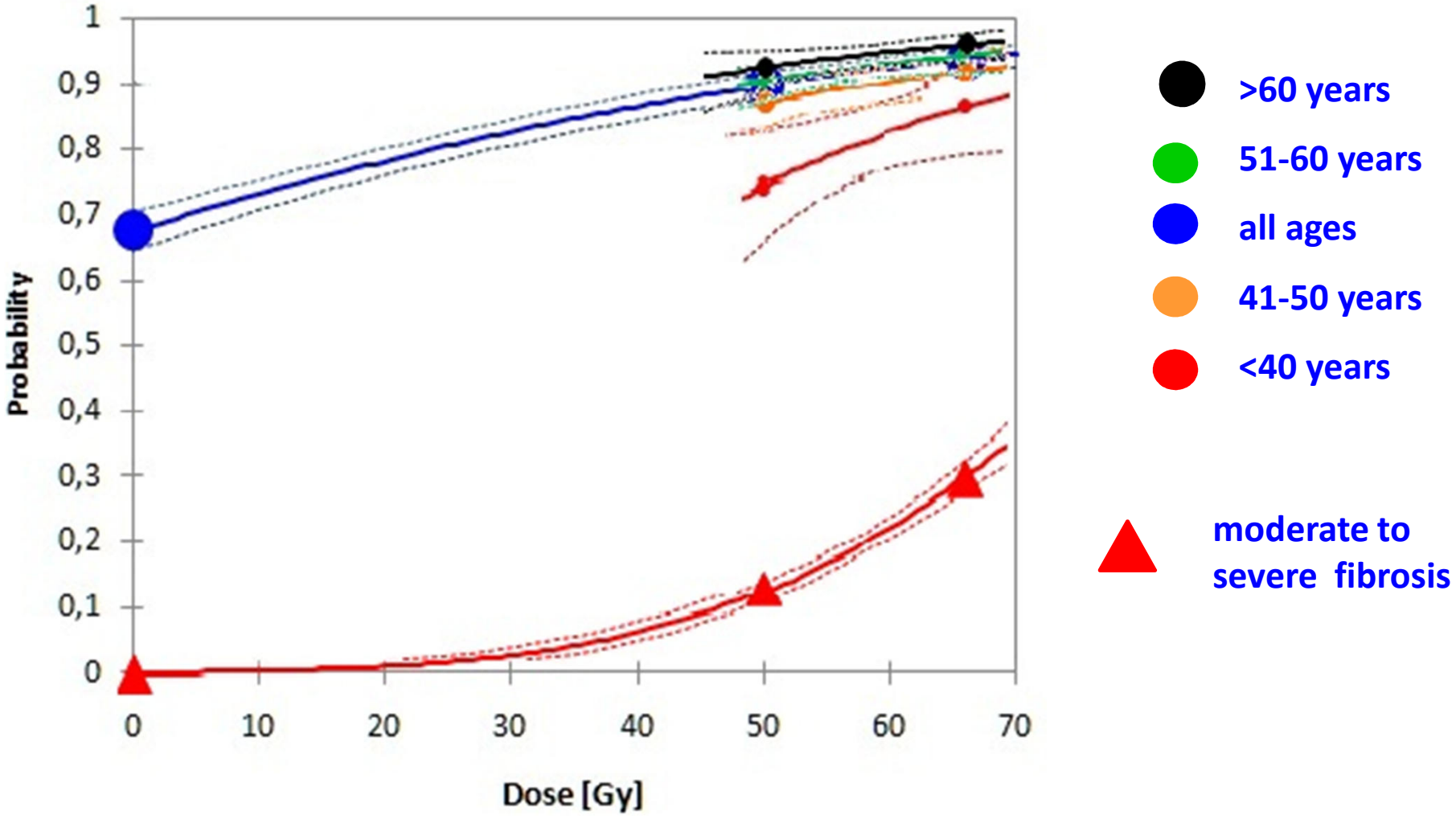
4.6. Adjuvante Strahlentherapie des Mammkarzinoms

4.6.1. Radiotherapie nach brusterhaltender operativer Therapie

RT-1	Radiotherapie nach brusterhaltender operativer Therapie (allgemein)
Empfehlungsgrad **A**	Bei invasivem Karzinom soll eine Bestrahlung der betroffenen Brust nach brusterhaltender Operation durchgeführt werden.
Level of Evidence **1a**	(Clarke, M et al. 2005; EBCTCG 2011: Darby, S et al. 2011; EBMG 2006; Harnett, A et al. 2009; NZGG 2009; Peto, R 2006)

EORTC Boost trial (22881-10882): Dose respone: local control and fibrosis



Collette et al. 2008, EBCTCG 2006, Bartelink et al. JCO 2007

Mutivariate Analyse: Lokale Rückfälle: Boost vs. kein Boost

Multivariable model on time to local recurrence

	Central review		Local pathology	
	P-value	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)
Age	<0.0001	See Fig. 1	<0.0001	See Fig. 1
Boost	0.0003	0.55 (0.42 0.73)	0.0003	
Age treatment interaction	0.97		0.97	
DCIS present[a]	0.068	1.49 (0.97–2.28)	0.074	1.47 (0.96–2.26)
Receptor estrogen positive[b]	0.56	0.91 (0.65–1.26)	0.62	0.92 (0.66–1.28)
Receptor Progesterone positive[b]	0.42	0.88 (0.63–1.21)	0.43	0.88 (0.64–1.21)
Total Size excisional biopsy specimen (log)[c]	0.0037	0.84 (0.74–.94)	0.011	0.86 (0.76–0.96
Tumor size (Diameter largest lesion log)[c]	0.0004	1.27 (1.11–1.45)	0.0003	1.27 (1.12–1.45)
Invasive tumor margin (central review)[c]	0.61	0.95 (0.77–1.16)		
Invasive tumor margin (local pathology)[c]	–	–	0.27	0.88 (0.70–1.10
Adjuvant hormonal treatment	0.018	0.62 (0.42- 0.92)	0.021	0.63 (0.43–0.93)
Adjuvant chemotherapy	0.021	0.65 (0.45–0.94)	0.026	0.66 (0.46–0.95)
Invasive tumor grade low		1		1
Intermediate	0.076	1.59 (0.95–2.66)	0.067	1.62 (0.97–2.70)
High	0.034	1.73 (1.04–2.86)	0.029	1.76 (1.06–2.92)

[a] Compared to patients with no DCIS.
[b] Compared to patients with negative receptor status.
[c] Hazard ratio presented for 1 standard deviation.

EORTC trial 22881-10882, (update) Antonini et al. 2007

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Boost

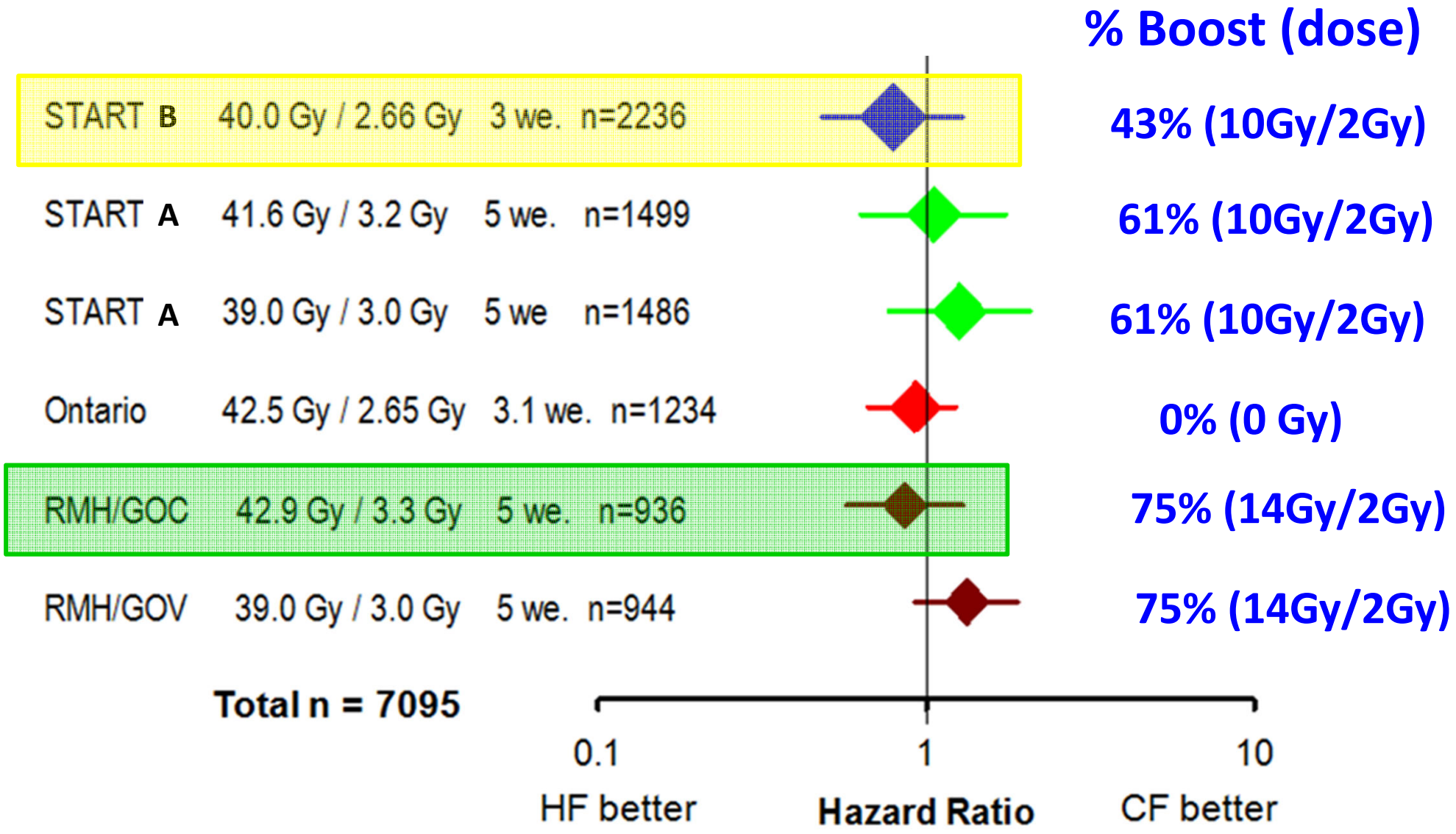
Empfehlungsgrad **A**	d.	Eine lokale Dosisaufsättigung (Boost-Bestrahlung) des Tumorbettes senkt die lokale Rezidivrate in der Brust, ohne dadurch einen Überlebensvorteil zu bewirken. Die Boost-Bestrahlung ist in der Regel indiziert. Die empfohlene Boost-Dosis beträgt (10-)16 Gy in konventioneller Fraktionierung (5 x 1,8 - 2,0 Gy/Woche).
Level of Evidence **1a**		(Antonini, N et al. 2007; Bartelink, H et al. 2007; Jones, HA et al. 2009; Livi, L et al. 2009; Poortmans, P 2007; Poortmans, PM et al. 2008; Poortmans, PM et al. 2009; Romestaing, P et al. 1997; Romestaing, P et al. 2009; Sautter-Bihl, ML et al. 2007; SIGN 2005)
Empfehlungsgrad **C**	e.	Bei postmenopausalen Patientinnen mit sehr niedrigem Lokalrezidivrisiko (insbes. Alter > 60 Jahre, kleinen Tumoren und günstigen Prognosefaktoren) ist der absolute Vorteil der Boost-Bestrahlung geringer. In dieser Subgruppe kann ggf. auf eine Boost-Bestrahlung verzichtet werden.
Level of Evidence **2a**		(EBCTCG 2011: Darby, S et al. 2011; NZGG 2009)

Patients characteristics in hypofractionaton trials

Holloway et al. The Breast 2010

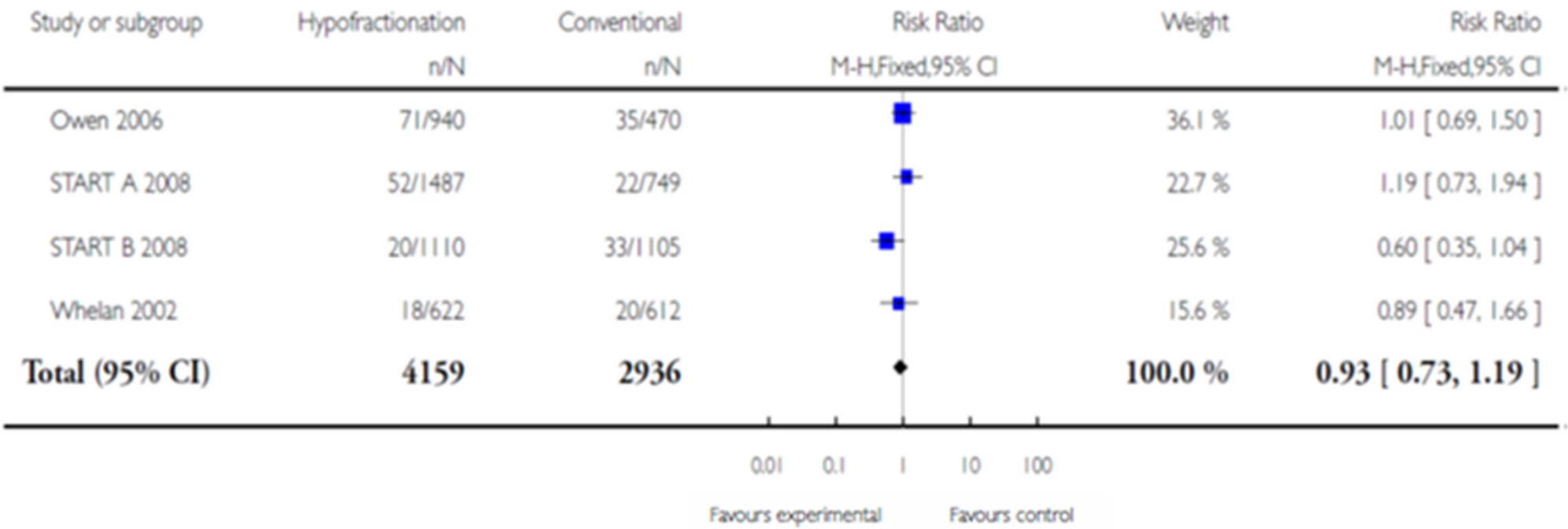
	RMH/GOC	START A	START B	Canadian
Site	UK	UK	UK	Canada
Years accrual	1986–98	1998–2002	1999–2001	1993–96
Standard arm	50 Gy/25F	50 Gy/25F	50 Gy/25F	50 Gy/25F
Experimental arm A	42.9 Gy/13F	41.6 Gy/13F	40 Gy/15F	42.5 Gy/16F
Experimental arm B	39 Gy/13F	39 Gy/13F	N/A	N/A
Mean age (years)	54.5	57.2	57.4	Not reported
Node + (%)	32.7	28.8	22.8	0
Mastectomy (%)	0	15	8	0
Tumor size ≥ T2 (%)	42.5[a]	48.6	35.9	20
Boost (%)	74.5	60.6	42.6	0
Chemotherapy (%)	13.9	35.5	22.2	11
Regional RT (%)	20.6	14.2	7.3	0

Standard 50 Gy / 2 Gy vs. Hypofractionation: local control



Adjuvant RT in breast cancer: Hypofractionated RT vs. Standard fractionated RT

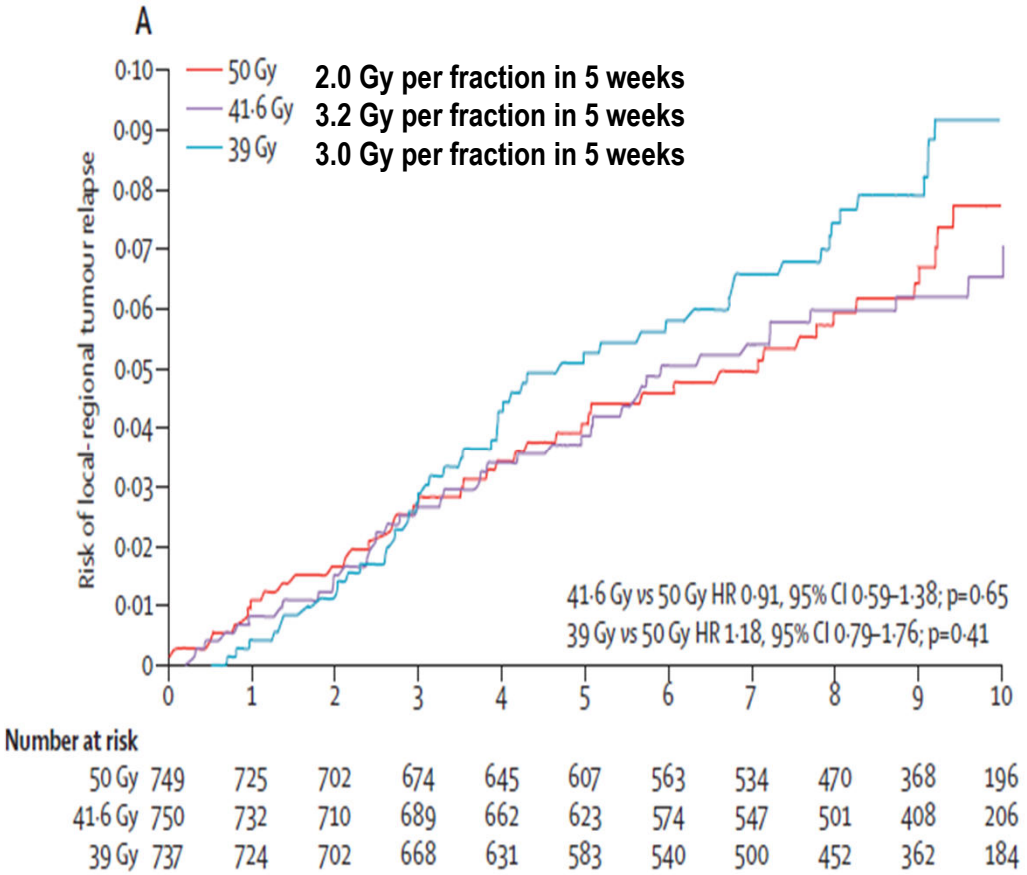
Local tumor control



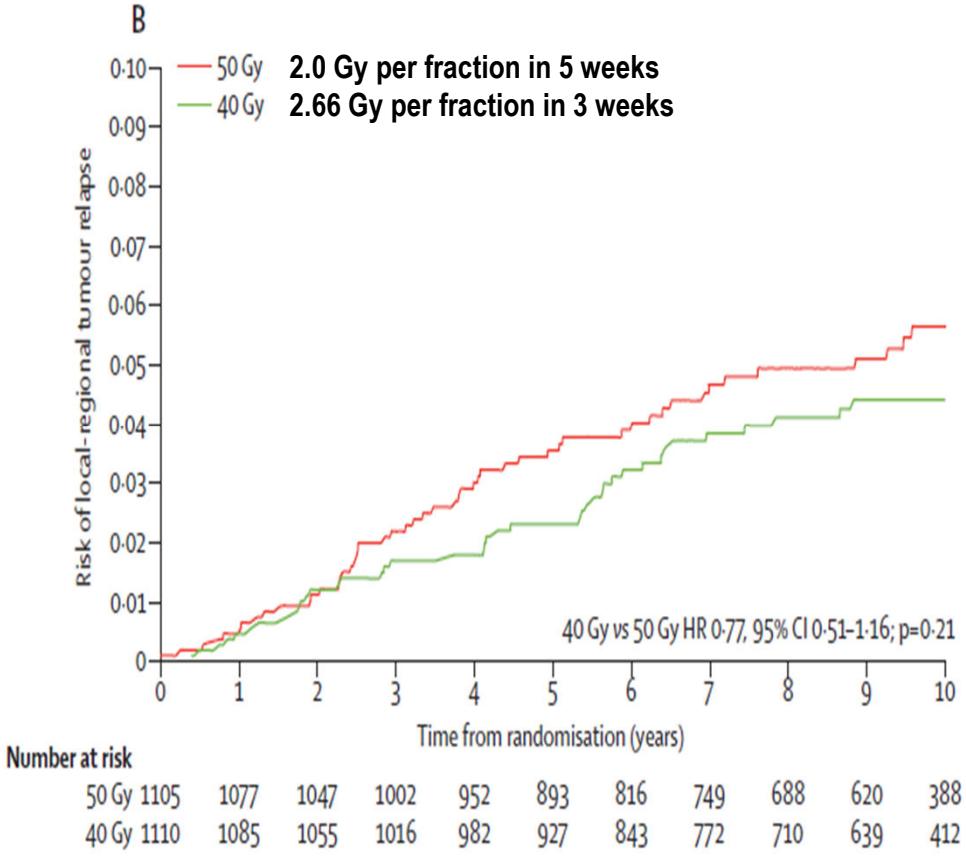
James et al. Cochrane Review 2010

10 y. Update START A and START B
Locoregional Relapse Rate

START A



START B



Haviland et al. Lancet Oncology 2013

Meta-analysis of the α/β values for local control and breast appearance

Meta-analysis of START pilot & START A Direct estimates of α/β

Adverse effects assessed from photographs (815 events/2263 pts):

α/β = **3.1 Gy** (95%CI 2.0 - 4.2 Gy)

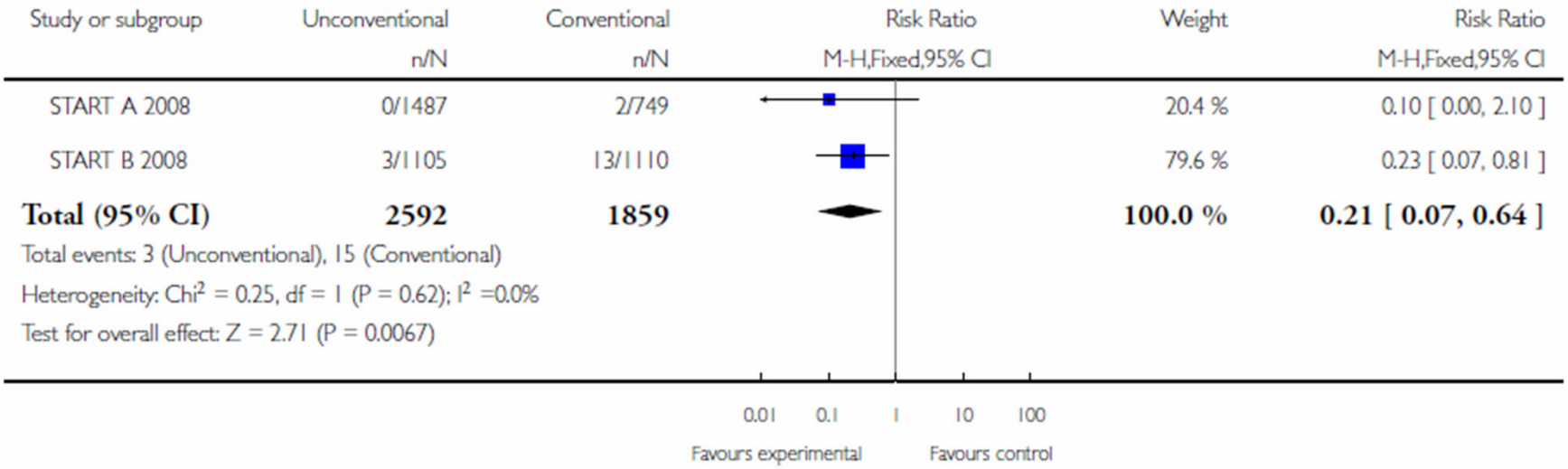
Tumour relapse (349 events/3646 pts):

α/β = **3.5 Gy** (95%CI 1.2 - 5.7 Gy)

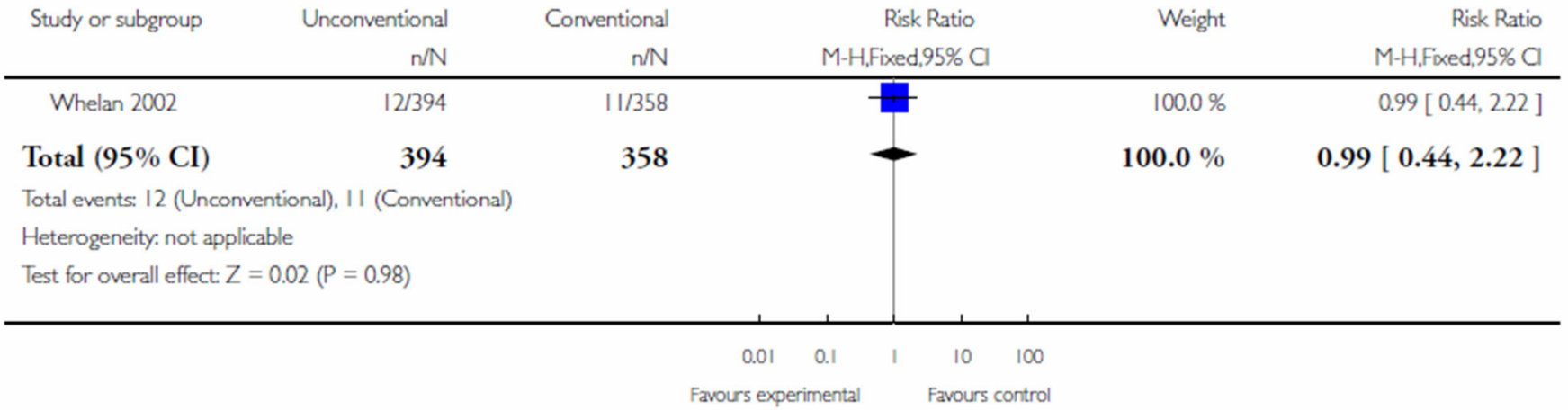
Consistent with hypothesis that small fractions are as gentle on breast cancer as on healthy tissues

Adjuvant RT in breast cancer: Hypofractionated RT vs. Standard fractionated RT

Acute skin toxicity



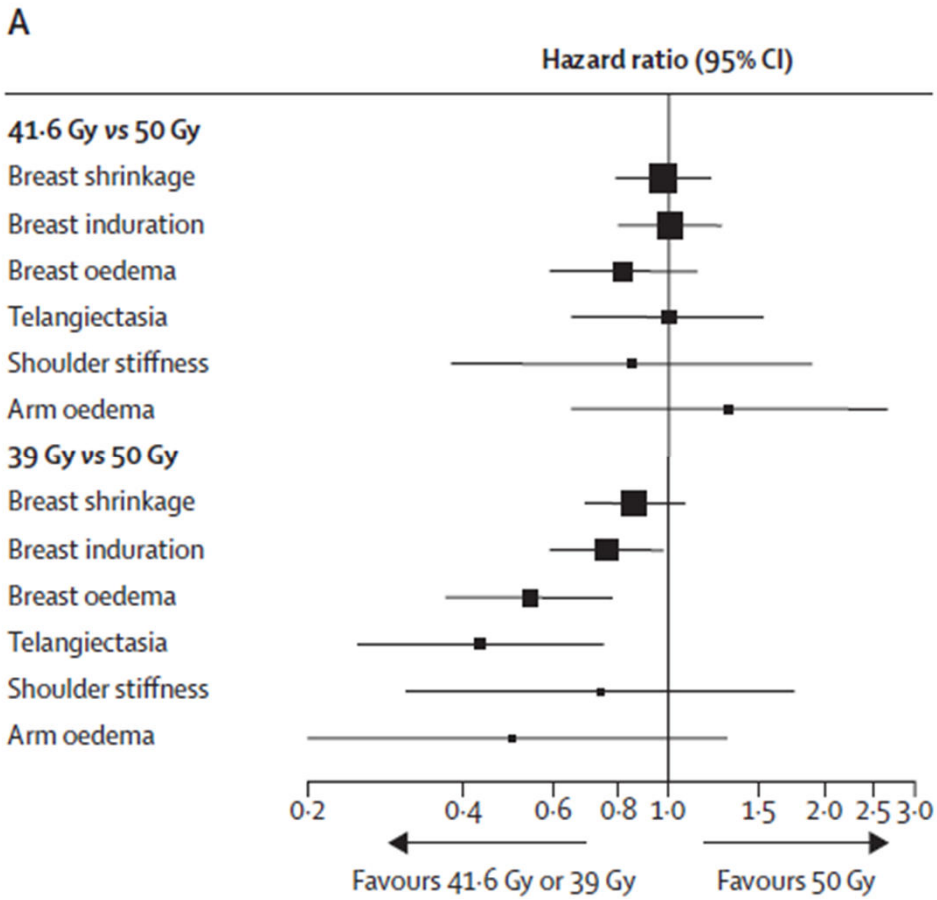
Late skin toxicity



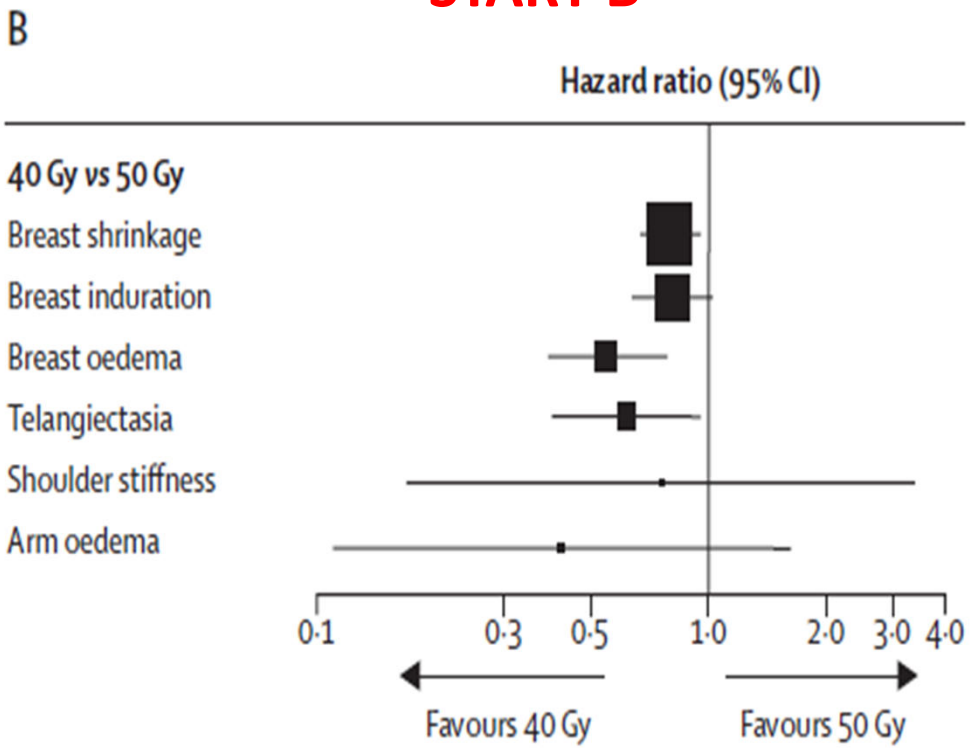
James et al. Cochrane Review 2010

10 y. Update START-trials: Late effects

START A



START B



Haviland et al. Lancet Oncol 2013

AGO 2014

RT nach brusterhaltender Operation (BEO) beim invasiven Karzinom

	Oxford / AGO LoE / GR		
➢ Homogene perkutane RT der verbliebenen Brust (WBI)	1a	A	++
➢ Normo-/standardfraktionierte WBI	1a	A	+°
➢ Hypofraktionierte WBI /+/- sequentieller Boost)	1a	A	++°
➢ Boost-Radiotherapie (verstärkt die lokale Tumorkontrolle)	1a	A	+
➢ Dosis-Wirkungsbeziehung unabhängig vom Patientenalter	1b		
➢ Absoluter Benefit abhängig vom Alter der Patientin	1b		
➢ Boost-RT bei nodal negativen, endokrin beeinflussbaren, komplett resezierten Tumoren	3a	C	+/-
➢ Intraoperative Radiotherapie (IORT/IOERT)			
➢ Als Boost-RT vor WBI	2a	B	+
➢ Als alleinige Radiotherapie			
➢ IORT mit 50 kV (pT1, N0, G1-2, kein lobular-invasives Karzinom, R0, Alter>50 J, kein extensives DCIS, IORT während der ersten Operation, HR+)	1b	B	+*
➢ IOERT	1b	B	-*
➢ Brachytherapie als alleinige Radiotherapie			
➢ Interstitielle Brachytherapie	1b	B	+/-*
➢ Intrakavitäre Ballon-Technik	1b	C	-*

° Empfehlungsgrad (GR) abweichend von dem der aktuellen DEGRO Leitlinie 2013/14 *Studienteilnahme empfohlen

DEGRO 2013

Comments and conclusion of the DEGRO panel

- Normofractionated WBI plus sequential boost remains standard.
- Hypofractionated WBI with single doses up to 2.7 Gy in 15–16 fractions to total doses of 40–42 Gy is an option for older women with pT1–2 pN0 tumors who need no chemotherapy. The additional use of a sequential boost is possible.
- Hypofractionated WBI plus boost either by SIB or by hypofractionated sequential application is discouraged outside clinical trials.

Sedlmayer et al. Strahlenther Onkol 2013

S3 Leitlinie Mamma-Ca. 2012

Hypofraktionierung

Empfehlungsgrad **B**	c.	Bei älteren Patientinnen ohne lokoregionären Lymphknotenbefall mit < 5 cm großen Tumoren, die keine Chemotherapie benötigen, können alternativ zur konventionell fraktionierten Strahlenbehandlung für die perkutane Homogenbestrahlung der Brust auch hypofraktionierte Schemata eingesetzt werden (z. B. 5 x 2,666 Gy pro Woche bis 40 Gy).
Level of Evidence **1a**		(Goldhirsch, A et al. 2011; Harnett, A 2010; NCCN 2011; NICE 2009; Smith, BD et al. 2011a; Whelan, TJ et al. 2010)

Die ältere Mammakarzinompatientin

Benötigt die ältere Patienten eine
adjuvante Strahlentherapien
nach brusterhaltender Operation?

Summary of results: No RT vs. RT in low risk patients (T1N0, ER+)

Reference	n	local recurrence		p	OS
		Tam	Tam+RT		
Fyles et al. NEJM 2004	611	12.2% @8y.	3.6% @8y	<0.001	n.s
Hughes et al. JCO 2013	636	17.0% @10y.	7.0% @10y.	<0.001	n.s
Pötter et al. IJROBP 2007	831	9.5% @6y.	0.5% @6y.	<0.001	n.s
Blamey et al. EJC 2013	204	7.0% @10y.	0.0% @10y.	<0.05	n.s

Radiotherapy after breast-conserving surgery, generally with axillary clearance (BCS±RT) in all women

(15 years median follow up) EBCTCG Lancet 2011

TAM

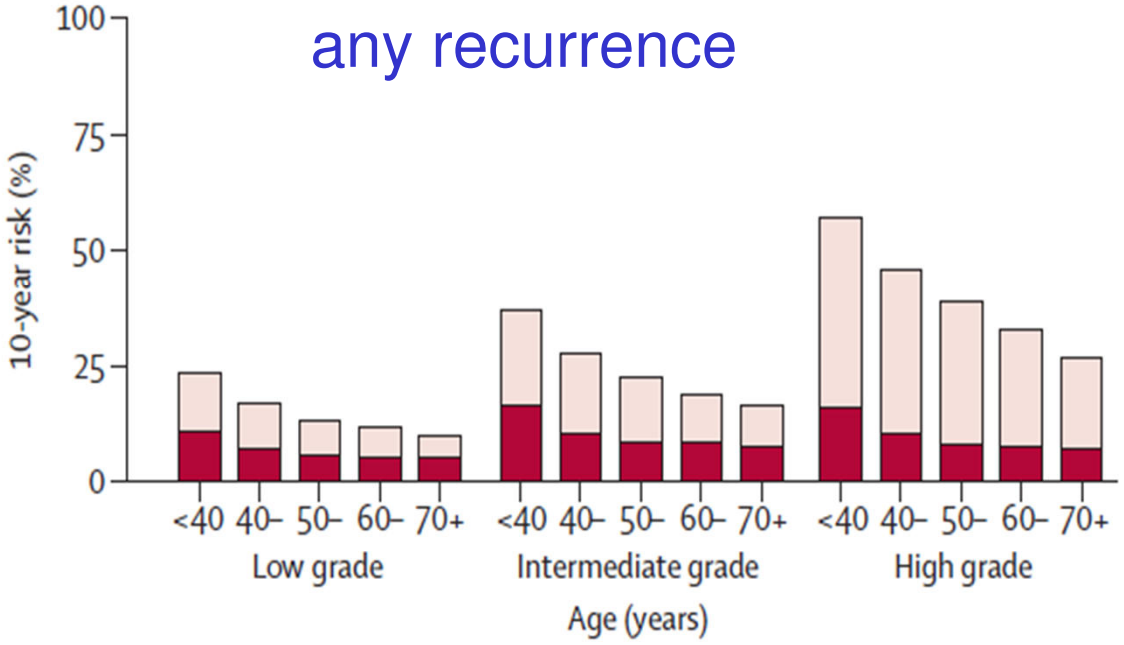
TAM+RT

Benefit from RT

ER+ TAM-: n=1656
ER+ TAM+: n=3100
>70 years: n~1900

pT1pN0, ER+, TAM

any recurrence



Absolute reduction in 10-year risk of recurrence with radiotherapy (%)

	Low grade					Intermediate grade					High grade				
	Age (years)					Age (years)					Age (years)				
	<40	40	50	60	70+	<40	40	50	60	70+	<40	40	50	60	70+
T1 (1-20mm) tumours															
Lumpectomy, ER+tam-	21	21	17	14	11	28	31	27	23	19	46	53	50	44	38
Lumpectomy, ER+tam+	12	10	8	6	5	21	18	15	12	9	41	37	31	25	20

Verzicht auf Strahlentherapie nach brusterhaltender Operation

Welche Patienten kommen in Frage?

Radiatio im Alter nach BEO

	Oxford / AGO LoE / GR		
➢ Verzicht auf Radiotherapie in low risk, wenn endokrine Therapie durchgeführt wird*	1b	A	+

Lokalrezidiv erhöht, kein Einfluss auf OS, Verminderung der Toxizität

*** ≥ 70 Jahre, pT1 , pN0, rez. pos, G1-2, HER2neu negativ, Resektionsrand >1 mm**

AGO-online März 2014

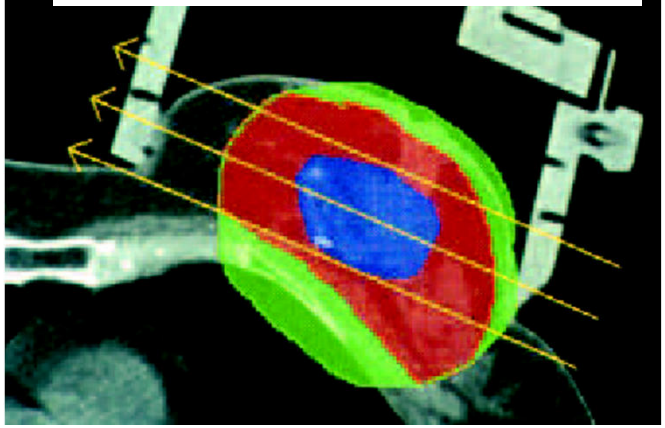
DEGRO panel:

- Chronological age alone is not an appropriate criterion for decision against or in favor of adjuvant treatment.
- No subgroup of elderly patients has yet been identified that did not profit from RT in terms of local control.
- The DEGRO breast cancer expert panel explicitly discourages determination of a certain age for the omission of postoperative RT in healthy elderly women with low risk breast cancer.
- In frail elderly women omission of postoperative RT should be individually decided on the basis of geriatric assessment.

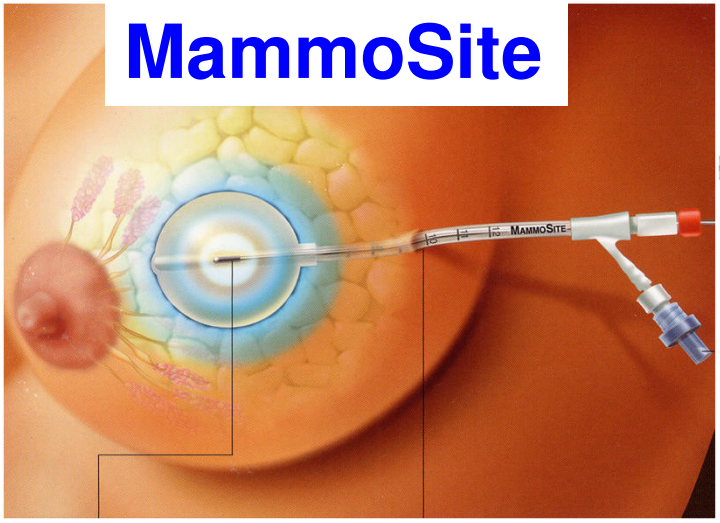
Sedlmayer et al.
Strahlenther Onkol, Okt. 2013

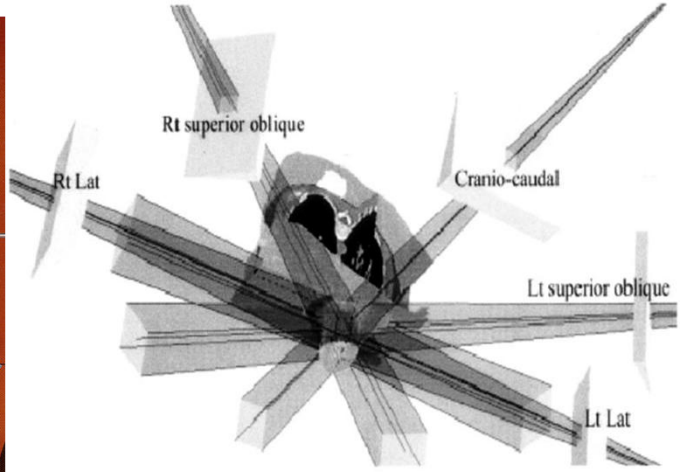
Techniken der partiellen Brustbestrahlung

Brachytherapie

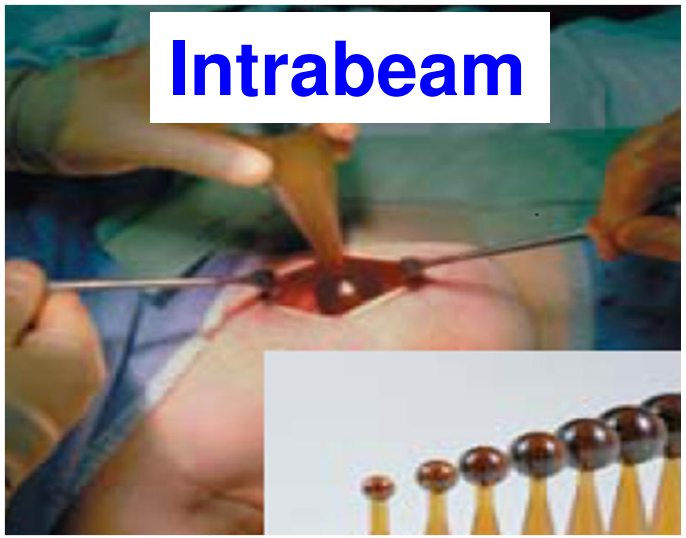


MammoSite

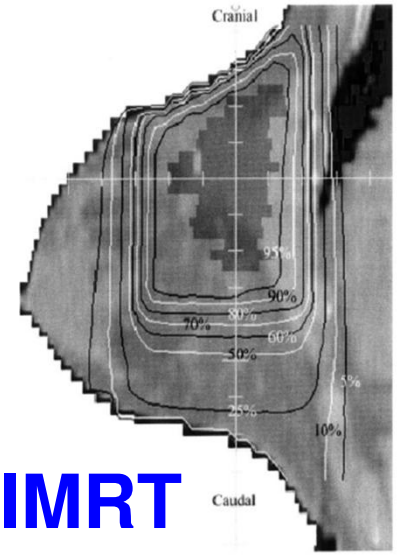




Intrabeam



Elektronen



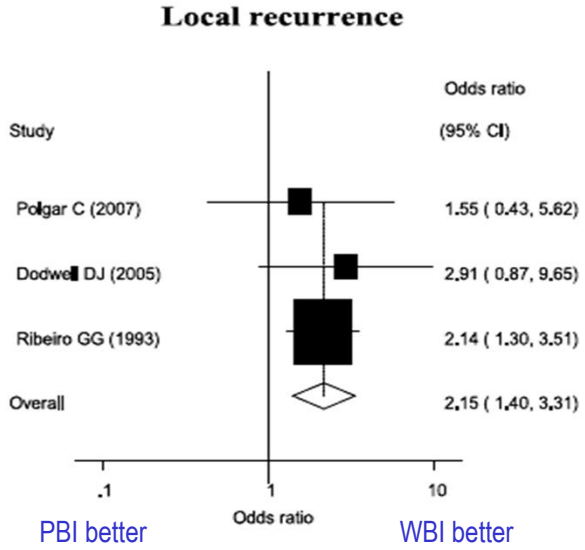
3D / IMRT

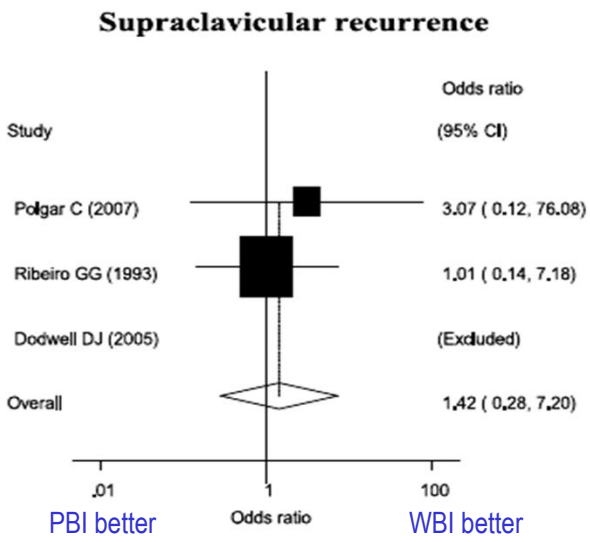
APBRT vs. RT der gesamten Brust (WBI)

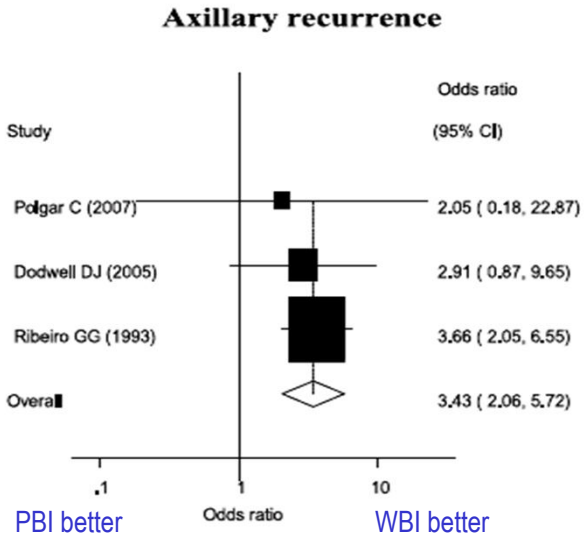
Vergleich der potentiellen Wirksamkeit der Dosierungen

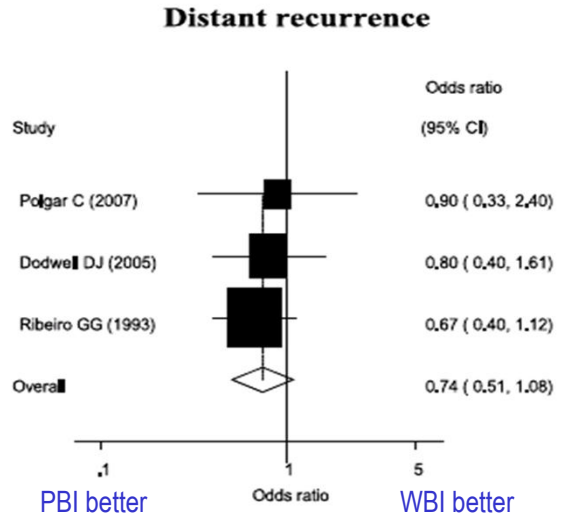
Gesamt-dosis	Einzel-dosis	**Tumorwirkung** $\alpha/\beta=10$	Repop. korr.	**Späteffekte** $\alpha/\beta=3$
Standard WBI				
66 Gy	2 Gy	66 Gy	66 Gy	66 Gy
HDR-AL / MammoSite / 3D / IMRT				
38 Gy	3,8 Gy	44 Gy	52 Gy	52 Gy
LDR-AL				
55 Gy	LDR	54 Gy	60 Gy	60 Gy
Intrabeam				
5 Gy	5 Gy	6,3 Gy	15,1 Gy	8 Gy
IORT mit Elektronen				
21 Gy	21 Gy	54 Gy	63 Gy	101 Gy

Partial breast irradiation (PBI) or whole breast radiotherapy (WBI) for early breast cancer: A meta-analysis of randomized controlled trials



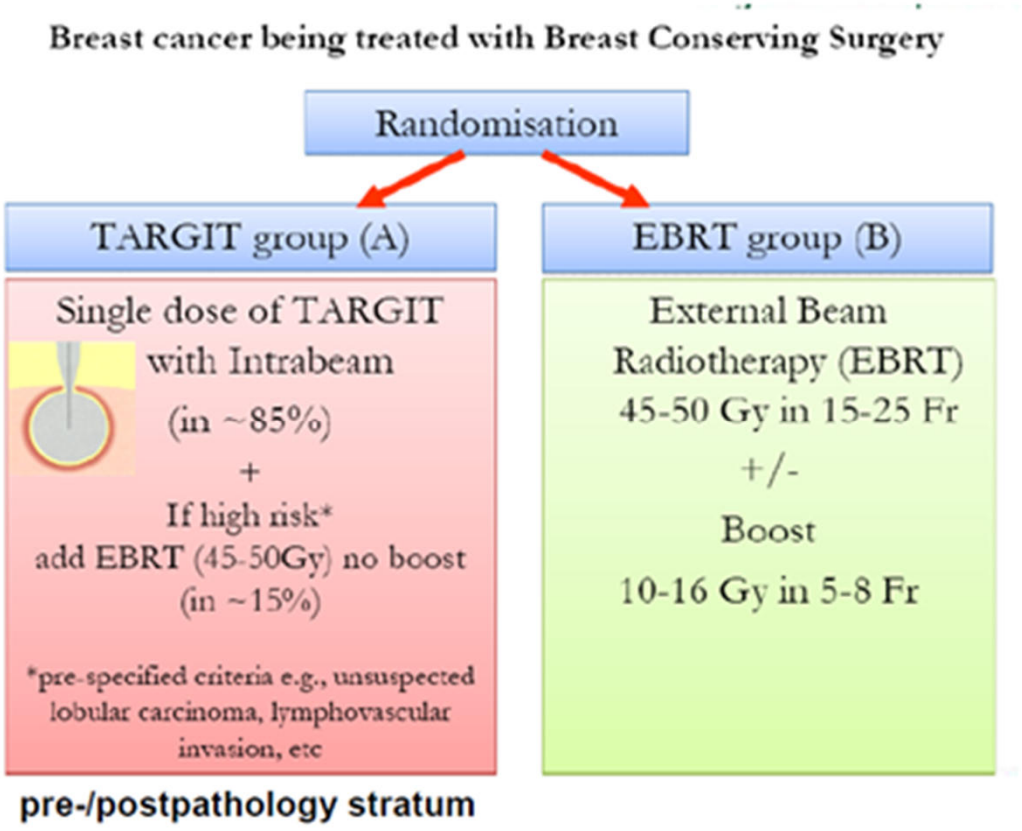






Valachis et al. Breast 2010

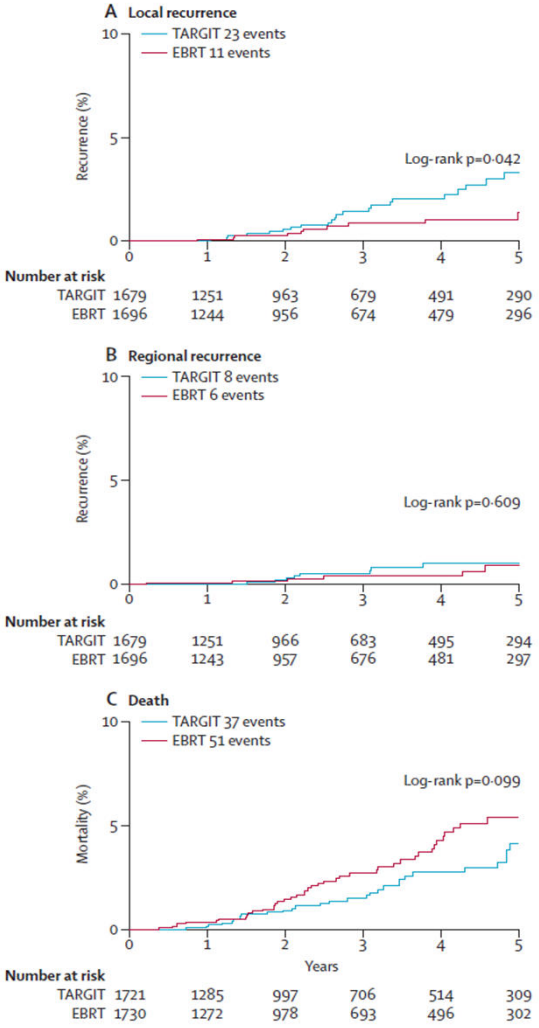
Partial breast irradiation (IORT) vs. whole breast radiotherapy
TARGIT randomized trial



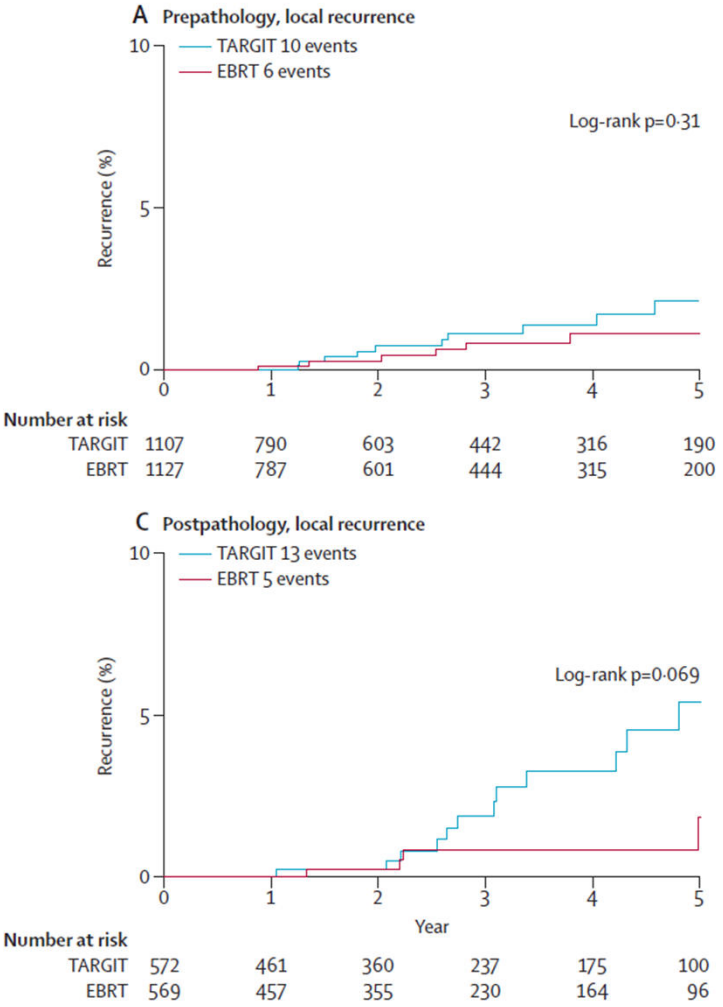
	Targeted intraoperative radiotherapy (n=1113)	External beam radiotherapy (n=1119)
Age (years)		
<45	17/1113 (2%)	10/1119 (1%)
45–54	212/1113 (19%)	167/1119 (15%)
55–64	443/1113 (40%)	464/1119 (41%)
65–74	355/1113 (32%)	381/1119 (34%)
>74	86/1113 (8%)	97/1119 (9%)
Pathological tumour size (cm)		
<1	381/1056 (36%)	388/1061 (37%)
1–2	531/1056 (50%)	519/1061 (49%)
>2	144/1056 (14%)	154/1061 (15%)
Unknown	57/1113 (5%)	58/1119 (5%)
Tumour grade		
1	341/1040 (33%)	374/1048 (36%)
2	540/1040 (52%)	514/1048 (49%)
3	159/1040 (15%)	160/1048 (15%)
Unknown	73/1113 (7%)	71/1119 (6%)
Nodes involved		
0	866/1059 (82%)	898/1070 (84%)
1–3	155/1059 (15%)	149/1070 (14%)
>3	38/1059 (4%)	23/1070 (2%)
Unknown	54/1113 (5%)	49/1119 (4%)
Hormone receptors		
Oestrogen-receptor positive	962/1063 (90%)	981/1060 (93%)
Oestrogen-receptor negative	101/1063 (10%)	79/1060 (7%)
Oestrogen-receptor status unknown	50/1113 (4%)	59/1119 (5%)
HER2 (ERBB2) receptor status		
Positive	132/991 (13%)	132/1004 (13%)
Negative	859/991 (87%)	872/1004 (87%)
Not done	31/1113 (3%)	33/1119 (3%)
Unknown	91/1113 (8%)	82/1119 (7%)
Adjuvant therapy		
Hormone therapy	727/1113 (65%)	753/1119 (67%)
Chemotherapy	116/1113 (10%)	141/1119 (13%)
Other	48/1113 (4%)	41/1119 (4%)
Unknown	100/1113 (9%)	89/1119 (8%)

Partial breast irradiation (IORT) vs. whole breast radiotherapy: TARGIT randomized trial

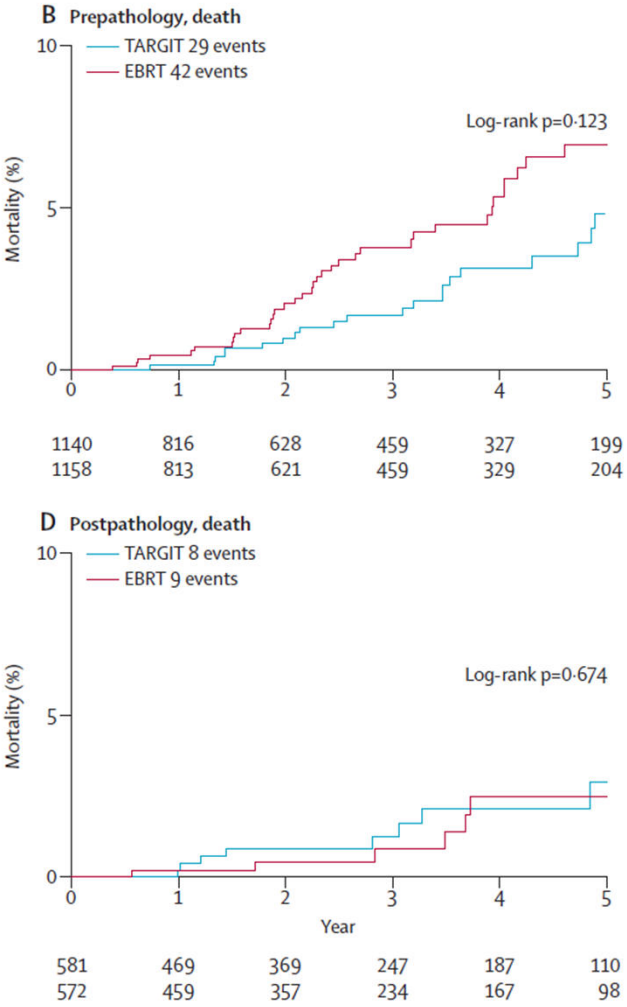
all patients



subgroups



subgroups

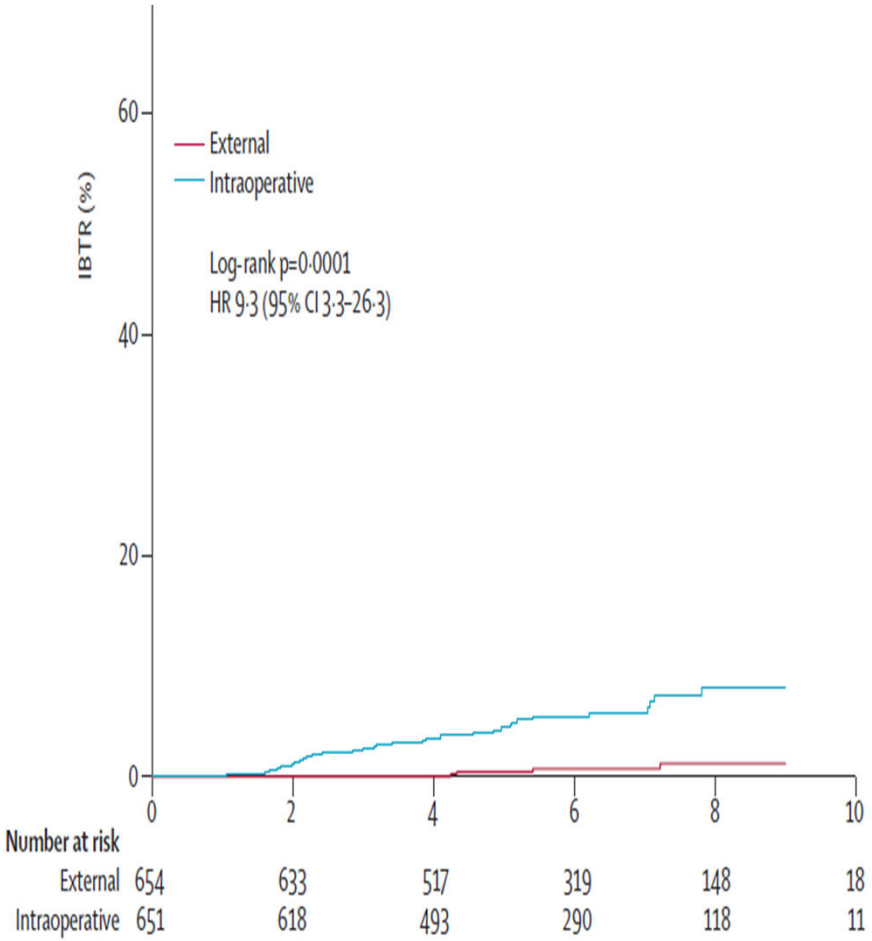


No data on efficacy by age

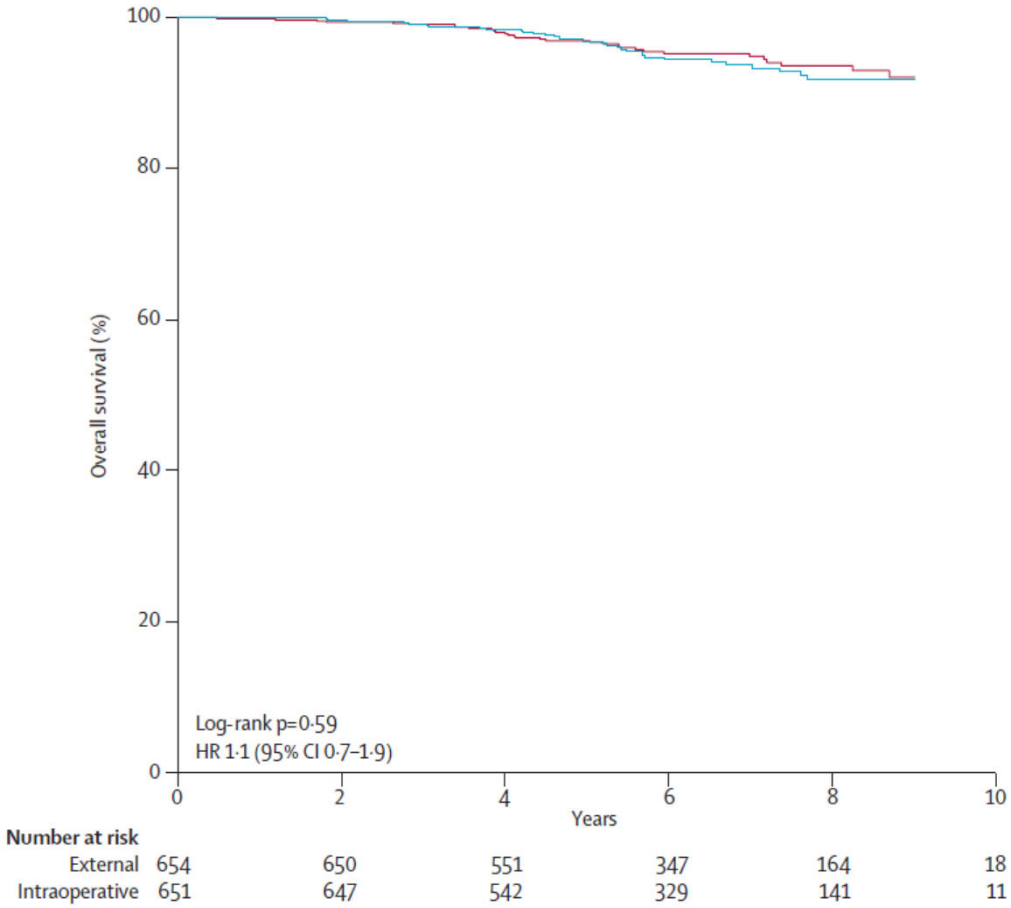
Vaidya et al. Lancet 2013

Partial breast irradiation (IOERT 21 Gy) vs. whole breast radiotherapy (WBI 50 Gy / 2 Gy)
ELIOT randomized trial (n=1305)

In breast recurrence



Overall survival



Veronesi et al. Lancet Oncol 2013

Partial breast irradiation (IOERT 21 Gy) vs. whole breast radiotherapy (WBI 50 Gy / 2 Gy)
ELIOT randomized trial (n=1305)

	Patients (n/N)	IBTR 5-year event rate (95% CI)	Log-rank p value*
Total	35/651	4·4% (2·7–6·1)	..
Age			
48–49 years	0/44	0	..
50–59 years	21/286	5·6% (2·7–8·5)	..
60–69 years	10/259	3·1% (0·8–5·4)	..
≥70 years	4/62	7·2% (0·4–14·1)	0·11
Histology			
Ductal	28/524	4·5% (2·6–6·5)	..
Lobular	3/53	4·6% (0·0–10·8)	..
Ductal and lobular	2/17	6·3% (0·0–18·1)	..
Other	2/53	2·1% (0·0– 6·1)	0·69
Pathological size			
≤1 cm	5/199	1·9% (0·0–4·0)	..
1–1·5 cm	13/243	4·2% (1·5–6·9)	..
1·5-2·0 cm	7/120	4·7% (0·7–8·8)	..
>2·0 cm	10/83	10·9% (3·7–18·1)	0·006
Number of positive nodes			
None	21/478	3·5% (1·7–5·3)	..
1–3	10/138	5·3% (1·5–9·2)	..
≥4	4/31	15·0% (1·4–28·7)	0·06
Overall p value	..	..	

	Patients (n/N)	IBTR 5-year event rate (95% CI)	Log-rank p value*
Tumour grade			
G1	5/196	1·1% (0·0–2·7)	..
G2	15/305	3·8% (1·5–6·1)	..
G3	15/129	11·9% (5·7–18·2)	0·0003
Oestrogen receptor			
Absent	8/63	14·9% (5·2–24·5)	..
Present	21/583	3·3% (1·8– 4·9)	0·004
Overall p value	..	..	
Progesterone receptor			
Absent	12/158	7·4% (2·9–11·8)	..
Present	23/487	3·5% (1·7– 5·2)	0·17
Proliferative index (Ki-67)			
<14%	8/263	1·8% (0·0–3·5)	..
14–20%	5/138	1·5% (0·0–3·6)	..
>20%	22/244	9·1% (5·1–13·1)	0·002
Molecular subtype			
Luminal A	7/256	1·4% (0·0–3·0)	..
Luminal B	20/327	4·9% (2·4–7·4)	..
HER2-positive (non-luminal)	1/20	5·9% (0·0–17·1)	..
Triple negative	7/43	18·9% (6·1–31·7)	0·001
Characteristics suggesting subsequent whole breast irradiation			
No	14/452	1·5% (0·3–2·7)	..
Yes†	21/199	11·3% (6·4–16·1)	<0·0001

IBTR=ipsilateral breast tumour recurrence. *Overall p value. †Tumour larger than 2·0 cm, or four or more positive nodes, grade 3, or triple negative.

Multivariate: Risk for IBTR (suggesting WBI)

Factor	HR	95% CL
>2 cm tumor	2.24	1.03 - 4.87
> 3 positive LN	2.61	0.91 - 7.50
G3	2.18	1.00 - 4.79
triple-negative	2.40	0.94 – 6.10

Veronesi et al. Lancet Oncol 2013

S3 Leitlinie Mamma-Ca. 2012

Teilbrustbestrahlung

RT-3	**Radiotherapie unter Beschränkung auf Teilbereiche der Brust (Teilbrustbestrahlung, PBI) als alleinige Bestrahlungsform einschließlich alleinige intraoperative Radiotherapie (IORT)**
Empfehlungsgrad **A**	Die Teilbrustbestrahlung als alleinige intra- oder postoperative Bestrahlungsbehandlung stellt keinen Therapiestandard dar.
Level of Evidence **3b**	(NCCN 2006; NCCN 2007)

Akzeleriert Partielle Brustbestrahlung (IORT, Brachytherapie)

Mögliche Indikationen außerhalb von klinischen Studien

RT nach brusterhaltender Operation (BEO) beim invasiven Karzinom

	Oxford / AGO LoE	GR	
➢ Intraoperative Radiotherapie (IORT/IOERT)			
➢ Als Boost-RT vor WBI	2a	B	+
➢ Als alleinige Radiotherapie			
➢ IORT mit 50 kV (pT1, N0, G1-2, kein lobular-invasives Karzinom, R0, Alter>50 J, kein extensives DCIS, IORT während der ersten Operation, HR+)	1b	B	+*
➢ IOERT	1b	B	-*
➢ Brachytherapie als alleinige Radiotherapie			
➢ Interstitielle Brachytherapie	1b	B	+/-*
➢ Intrakavitäre Ballon-Technik	1b	C	-*

° Empfehlungsgrad (GR) abweichend von dem der aktuellen DEGRO Leitlinie 2013/14 *Studienteilnahme empfohlen

AGO-online März 2014

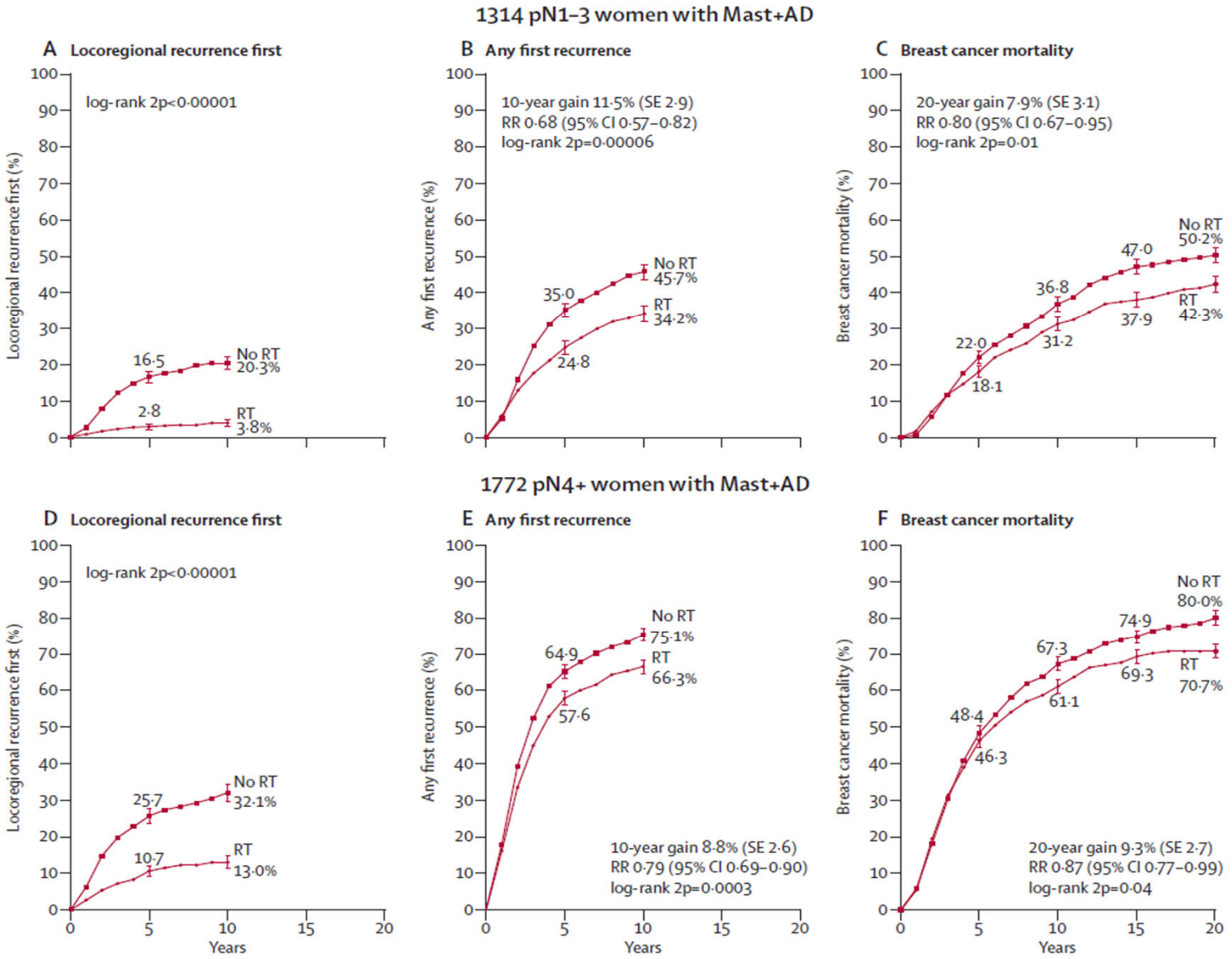
DEGRO panel:

- age >70 years
- tumor size <2 cm
- invasive ductal carcinoma
- negative axillary nodes
- free surgical margins
- luminal A (ER+ and PR+, G1/2, Her2neu negative)
- absence of EIC

The patient has to be informed about a modest reduction of in-breast tumor control rates.
Meticulous follow-up and documentation of outcome in the framework of a certified breast cancer center are mandatory.

Sedlmayer et al.
Strahlenther Onkol, Okt. 2013

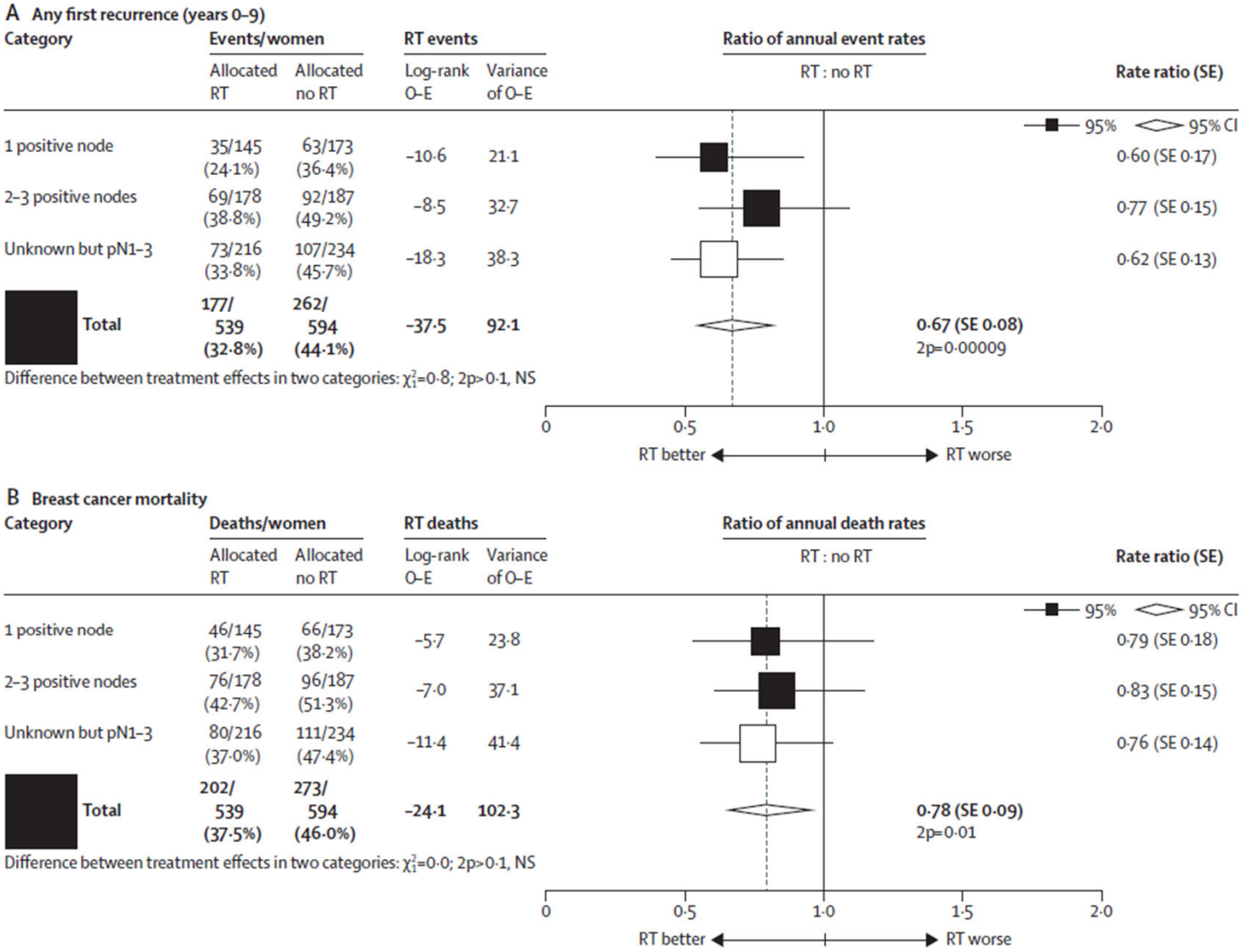
Adjuvant radiotherapy after mastectomy – EBCTCG update 2014



Early Breast Cancer Trialists' Collaborative Group, Lancet 2014

Adjuvant radiotherapy after mastectomy – EBCTCG update 2014

Adjuvant RT also in case of 1 positive nodes also beneficial



Early Breast Cancer Trialists' Collaborative Group, Lancet 2014

S3 Leitlinie Mamma-Ca. 2012

Bestrahlung nach Mastektomie

RT-4	Radiotherapie der Brustwand nach Mastektomie
	a. Die postoperative Radiotherapie der Brustwand nach Mastektomie senkt das Risiko eines lokoregionalen Rezidivs.
Level of Evidence 1a	(Clarke, M et al. 2005; EBMG 2006; NCCN 2011; NHMRC 2001; NICE 2009; NZGG 2009; Peto, R 2006; Shafiq, J et al. 2007; SIGN 2005; Whelan, T et al. 2007)
Level of Evidence 1a	b. Bei Patientinnen mit hohem Lokalrezidivrisiko wird auch das Gesamtüberleben verbessert.
Empfehlungsgrad A	c. Bei folgenden Situationen ist daher die nachfolgende Strahlentherapie der Brustwand nach Mastektomie indiziert: - T3/T4
Level of Evidence 1a	(NCCN 2011; NICE 2009; NZGG 2009)
Empfehlungsgrad B	- pT3 pN0 R0 nur bei Vorliegen von sonstigen Risikofaktoren (Lymphgefäßinvasion, Grading G3, „close resection margin", Prämenopausalstatus, Alter < 50 Jahre)
Level of Evidence 2b	(Floyd, SR et al. 2009; Kunkler, I 2010; McCammon, R et al. 2008; Rowell, NP 2009; Russell, NS et al. 2009)
Empfehlungsgrad A	- R1-/R2-Resektion und fehlender Möglichkeit der sanierenden Nachresektion
Level of Evidence 1a	(NCCN 2011; NICE 2009; NZGG 2009)
Empfehlungsgrad A	- pN+ (> 3 Lymphknoten)
Level of Evidence 1a	(NCCN 2011; NICE 2009; NZGG 2009)

Empfehlungsgrad A	d. Nach primärer (neoadjuvanter) systemischer Therapie soll sich die Indikation zur Radiotherapie nach der prätherapeutischen T- und N-Kategorie richten, unabhängig vom Ausmaß des Ansprechens auf die primäre systemische Therapie.
Level of Evidence 2a	(Buchholz, TA et al. 2002; Buchholz, TA et al. 2008; Buchholz, TA 2009; Garg, AK et al. 2007; Goldhirsch, A et al. 2009; Huang, EH et al. 2006; Kaufmann, M et al. 2003; Kaufmann, M et al. 2010; NCCN 2007; NCCN 2011)

- pT4
- pT3 pN+
- pT3pN0 wenn G3,L1,<50 J.
- R1/R2
- >3 befallene LK

Cave: 1-3 befallen LK fehlt

Pooled analysis of the German neo-adjuvant chemotherapy trials

pCR rates in different breast cancer phenotypes

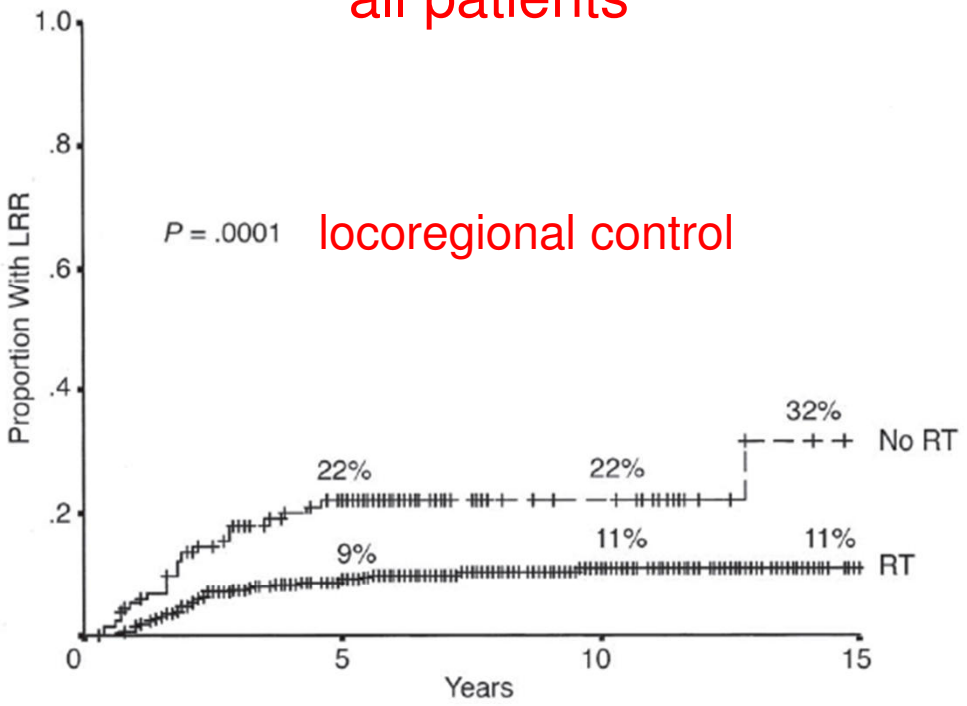
Characteristics	*N* without pCR (%)	*N* with pCR (%)	Crude OR (95% CI)	*P* value
Grading				<0.001
1	94 (93%)	7 (7%)	1.00 (reference)	
2	1558 (85%)	285 (15%)	2.37 (1.08–5.17)	
3	969 (70%)	419 (30%)	5.77 (2.65–12.59)	
Hormone receptor (HR) status				<0.001
HR +[a]	1870 (87%)	280 (13%)	1.00 (reference)	
HR −	751 (64%)	431 (36%)	3.79 (3.18–4.52)	
HER2 status				<0.001
HER2 +[b,c]	694 (68%)	321 (32%)	1.00 (reference)	
HER2 −	1927 (83%)	390 (17%)	0.48 (0.39–0.57)	
HER2/HR status				<0.001
HER2−/HR+	1435 (91%)	140 (9%)	1.00 (reference)	
HER2+/HR+[c]	435 (76%)	140 (24%)	3.14 (2.40–4.09)	
HER2+/HR−[c]	259 (59%)	181 (41%)	6.78 (5.16–8.90)	
HER2−/HR−	492 (66%)	250 (34%)	5.33 (4.23–6.73)	

3332 women included in 7 German neoadjuvant trials

von Minckwitz et al. Breast Cancer Res Treat (2011)

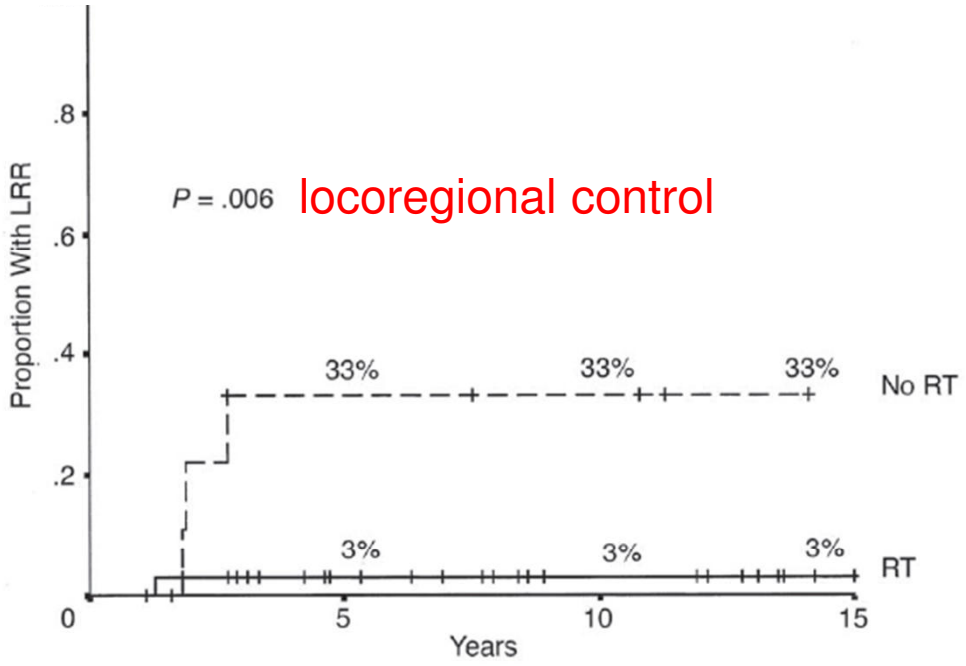
Neoadj. CHX → mastectomy +/- radiotherapy (not random.)

all patients



	No. Patients	No. Events
No RT	134	28
RT	542	50

patients with pCR after CHX



	No. Patients	No. Events
No RT	11	3
RT	35	1

LRR multivariate

Factor	Hazard Ratio	95% CI	*P*
No radiation	4.68	2.70 to 8.13	< .0001
≥ 20% sampled nodes positive	3.58	2.11 to 6.08	< .0001
Stage ≥ IIIB	2.38	1.42 to 4.02	.001
No tamoxifen	2.19	1.19 to 4.06	.012
Minimal or worse clinical response to neoadjuvant chemotherapy	1.88	1.10 to 3.23	.021
Estrogen receptor–negative	1.69	1.04 to 2.76	.033

Abbreviation: LRR, local-regional recurrence.

Huang et al. JCO 2004

Inflammatory breast cancer with pCR after neoadj. CHX and mastectomy (n=106)

92% anthracycline-based chemotherapy, 38% also taxane. ;72 with postmastectomy RT, 34 no RT

Locoregional recurrence

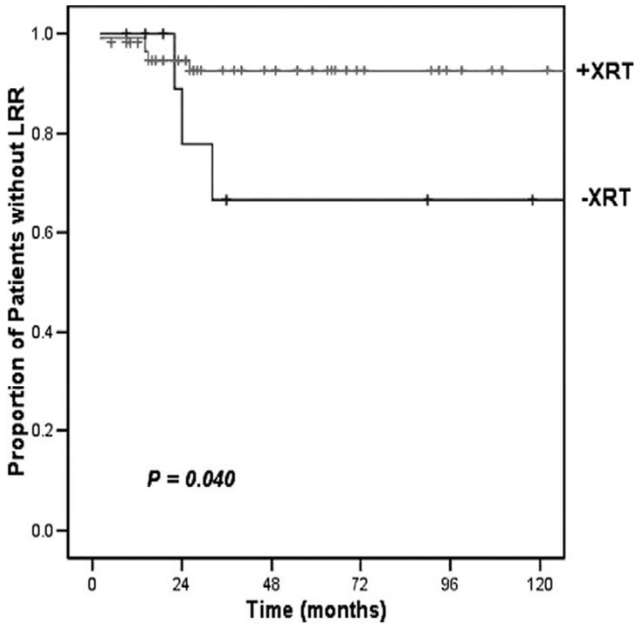


Fig. 1. Freedom from local-regional recurrence (LRR) in patients presenting with clinical Stage III breast cancer treated with neoadjuvant chemotherapy and mastectomy with or without radiation therapy (+XRT, $n = 62$ and −XRT, $n = 12$ respectively).

Distant metastasis

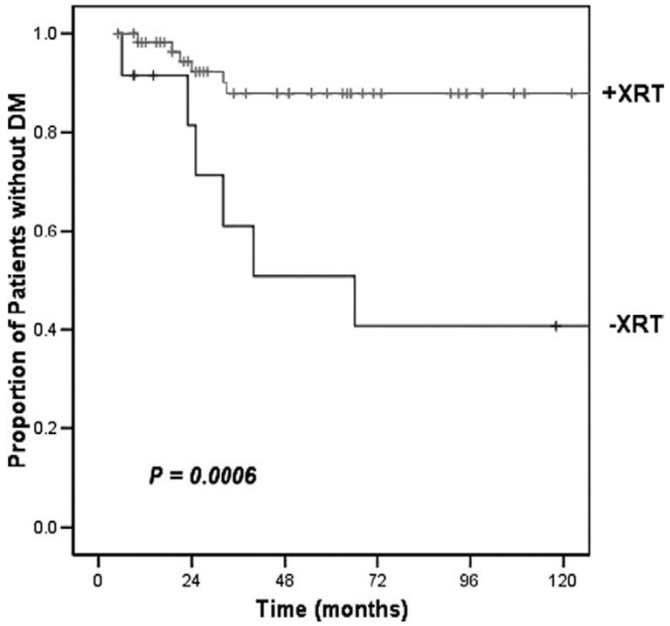


Fig. 2. Freedom from distant metastases (DM) in patients with clinical Stage III breast cancer treated with neoadjuvant chemotherapy and mastectomy with or without radiation therapy (+XRT and −XRT, respectively).

Overall survival

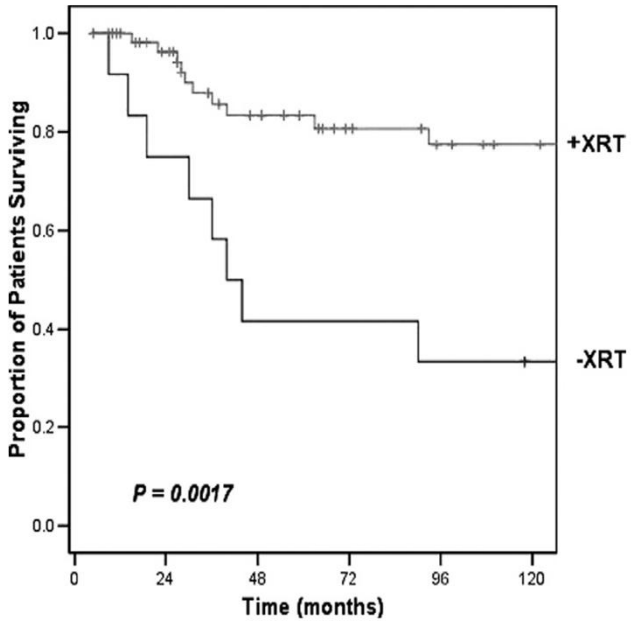


Fig. 3. Overall survival in patients with Stage III breast cancer treated with neoadjuvant chemotherapy and mastectomy with or without radiation therapy (+XRT and −XRT, respectively).

McGuire et al. IJROBP 2007

S3 Leitlinie Mamma-Ca. 2012

RT bei primär nicht operablen Brustkrebs

RT-6	Radiotherapie bei lokal weit fortgeschrittenem Tumor und bei primärer Inoperabilität
Empfehlungsgrad **A**	a. Für Patientinnen mit primär inoperablen bzw. inflammatorischen Karzinomen wird eine primäre Systemtherapie, gefolgt von Operation und postoperativer Strahlentherapie empfohlen.
Level of Evidence **1b**	(Kaufmann, M et al. 2003; Kaufmann, M et al. 2010; NCCN 2011; NICE 2009
	b. Wird durch die Systemtherapie keine Operabilität erreicht, ist eine Strahlentherapie – eventuell auch in Kombination mit simultaner Systemtherapie – indiziert.
GCP	(Kaufmann, M et al. 2003; Kaufmann, M et al. 2010; NCCN 2007; NCCN 2011; Shenkier, T et al. 2004; Truong, PT et al. 2004)

RT nach neoadjuvanter Systemtherapie

Empfehlungsgrad **A**	d. Nach primärer (neoadjuvanter) systemischer Therapie soll sich die Indikation zur Radiotherapie nach der prätherapeutischen T- und N-Kategorie richten, unabhängig vom Ausmaß des Ansprechens auf die primäre systemische Therapie.
Level of Evidence **2a**	(Buchholz, TA et al. 2002; Buchholz, TA et al. 2008; Buchholz, TA 2009; Garg, AK et al. 2007; Goldhirsch, A et al. 2009; Huang, EH et al. 2006; Kaufmann, M et al. 2003; Kaufmann, M et al. 2010; NCCN 2007; NCCN 2011)

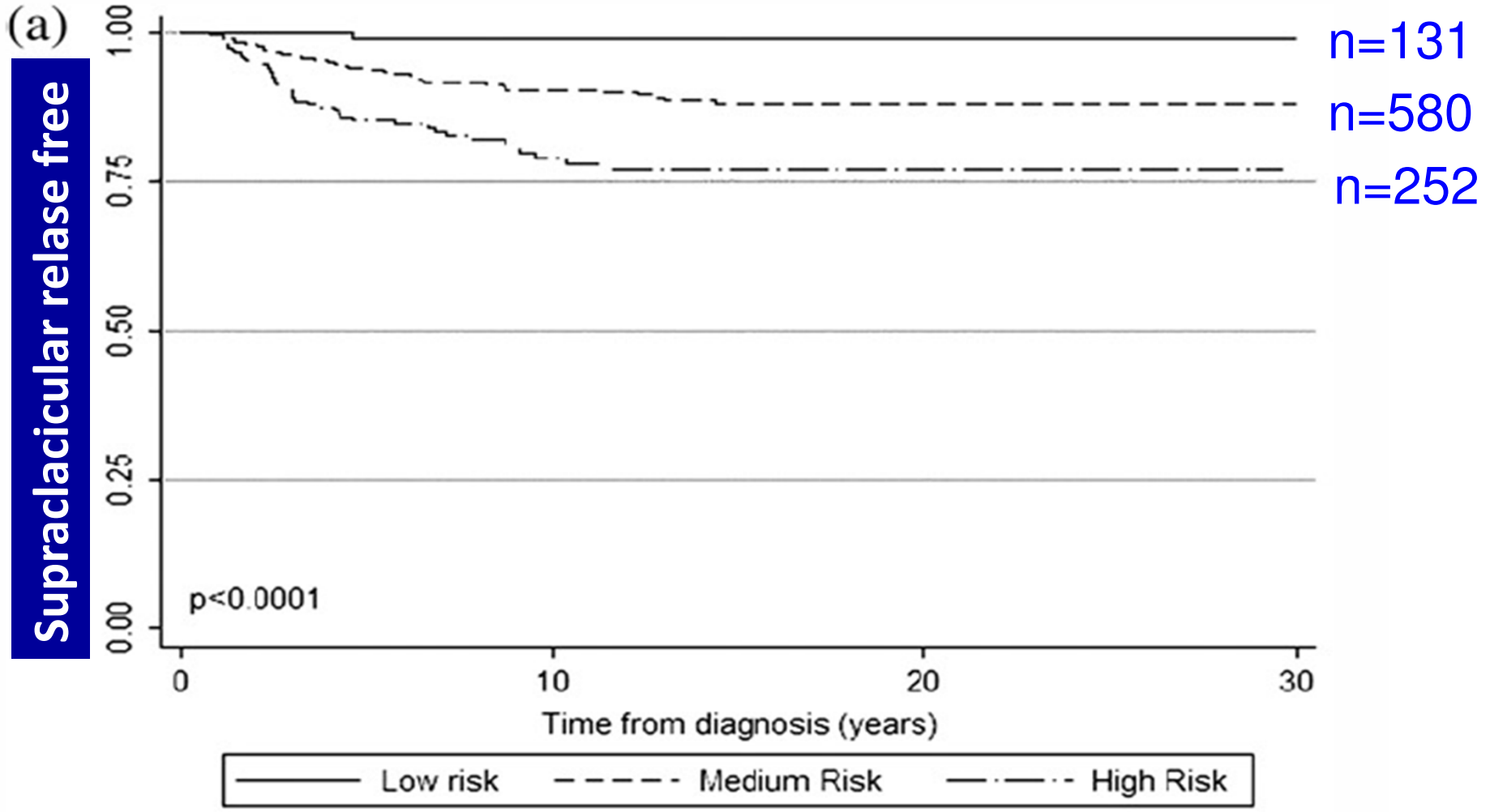
Supraklavikulärer Lymphknotenbefall in Abhängigkeit vom axillären Lymphknotenbefall

Axilla	Supraklavikulär	
N0	0/149	0%
N+	23/125	18%
1-3 N+		1-4%
>3 N+	17/102	17%

nach Recht et al. JCO 2001

Risk of supraclavicular recurrence in patients with 1-3 pos. axillary LN

no supraclavicular radiotherapy



n=131

n=580

n=252

Yates et al. IJROBP 2011

Risk of supraclavicular recurrence in patients with 1-3 pos. axillary LN

no supraclavicular radiotherapy

Hazard according to risk group

Risk Group	Number (%)	5-y SCFR (%)	10-y SCFR (%)	HR (95% CI)	*p* Value
Low	131 (14)	0.8	0.8	1.0	<0.001
Intermediate	580 (60)	6.0	9.6	13.5 (1.9–97.9)	
High	252 (26)	14.6	21.0	30.3 (4.2–220.3)	

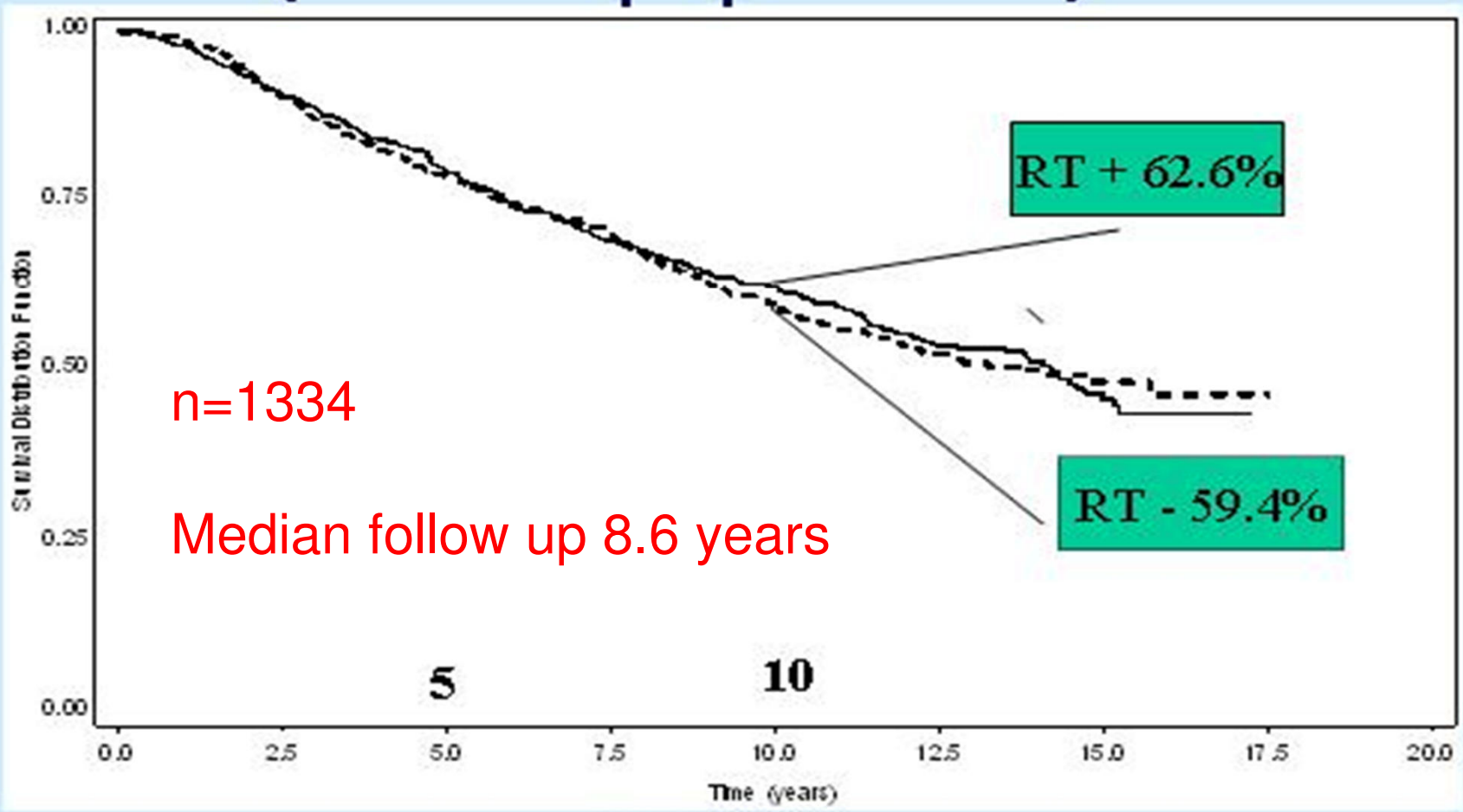
Low = G1 plus 1-3 positive LN

Intermediate = G2 plus1-2 positive LN; **or** G3 plus 1 positive LN

High = G3 plus 2-3 positive LN; **or** G2 plus 3 positive LN

Yates et al. IJROBP 2011

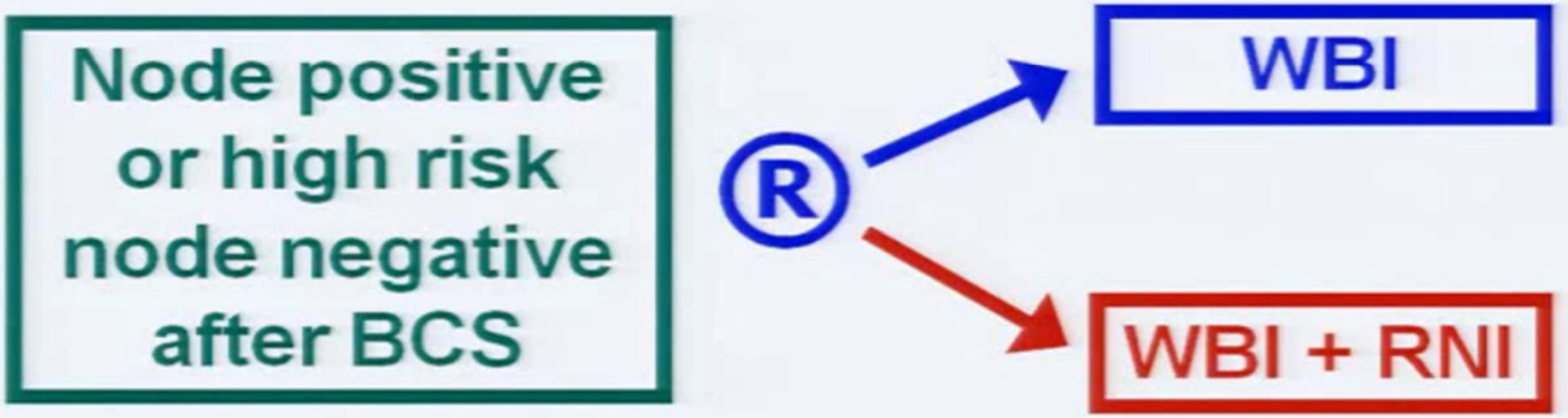
IMPACT OF IMC- RT ON 10-yr OVERALL SURVIVAL (Whole population)



ASTRO 2009

Romestaing et al. ASTRO 2009

MA.20 trial: breast RT vs. breast RT + axillary/supraclavI IMC RT

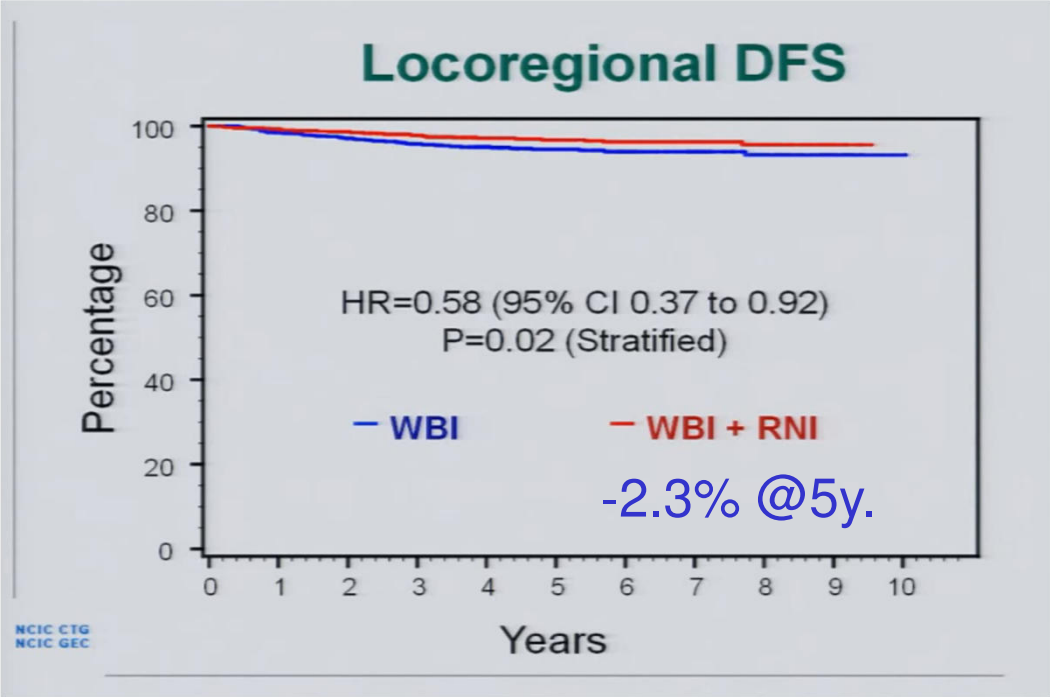


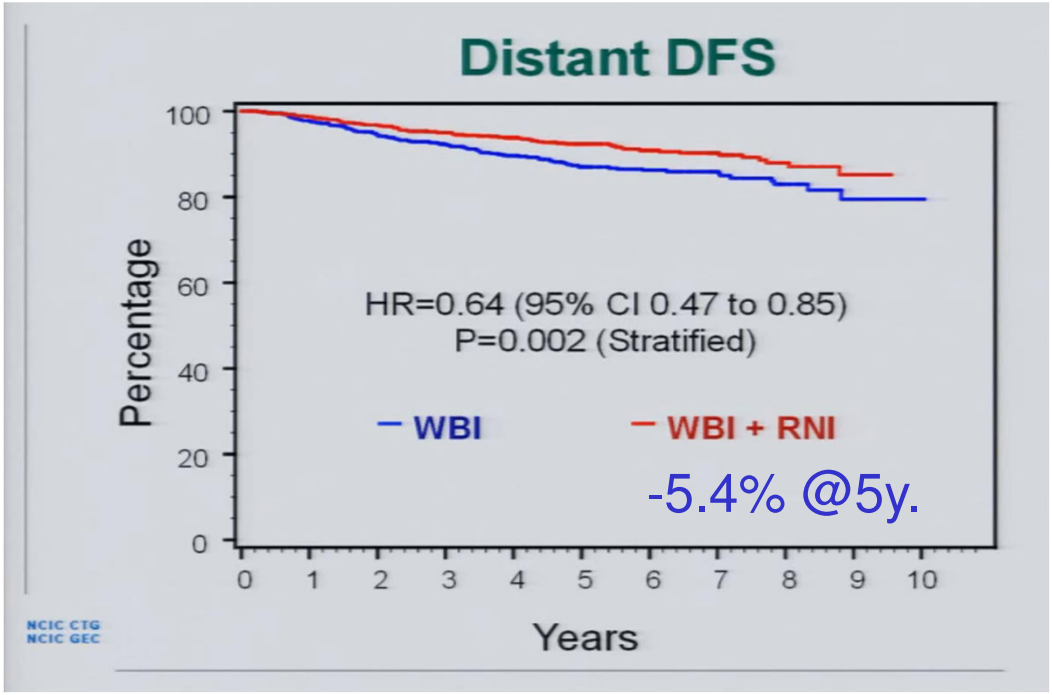
Stratification

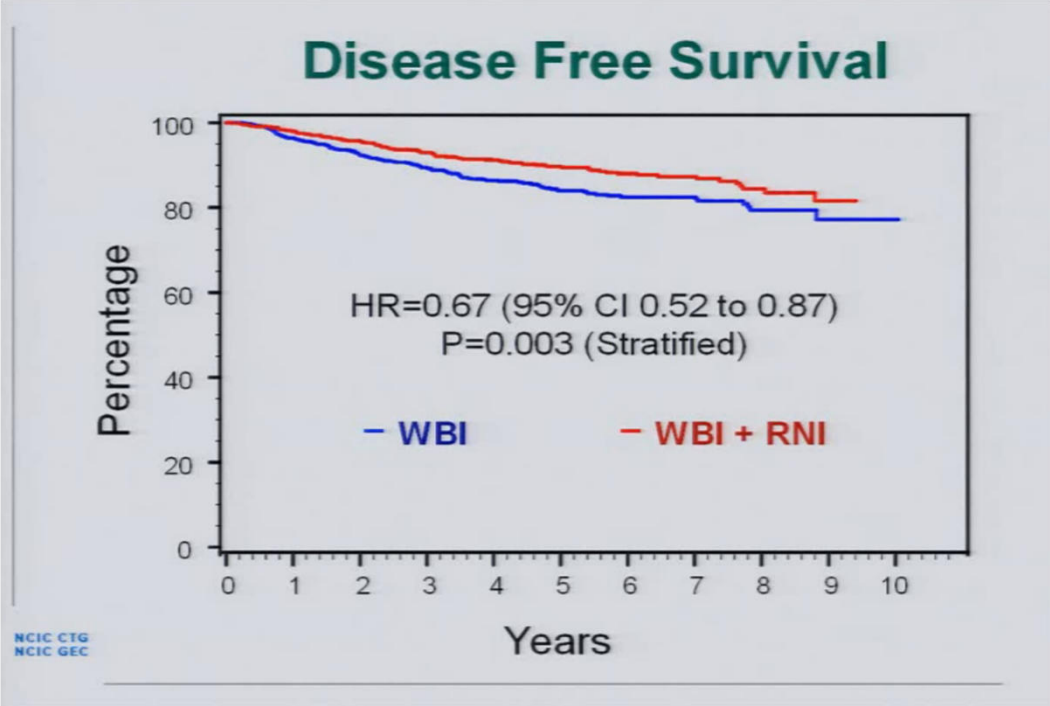
- Axillary nodes removed (<10, ≥10)
- Positive axillary nodes (0, 1-3, >3)
- Chemotherapy (anthracycline, other, none)
- Endocrine therapy (yes, no)

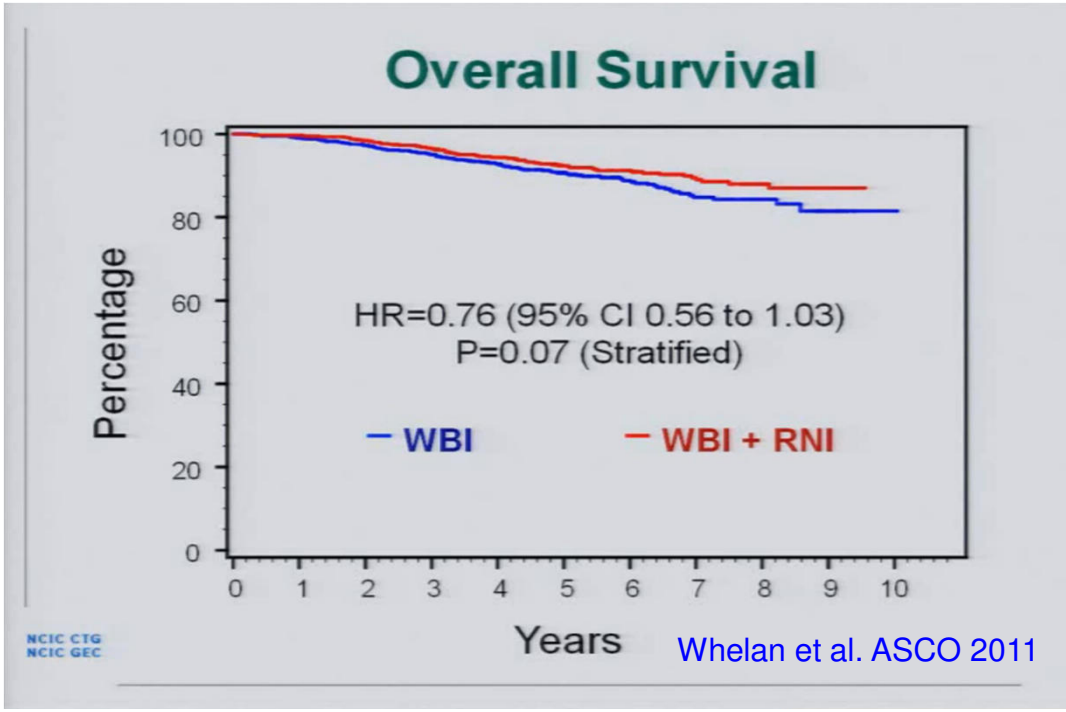
NCIC CTG
INCC GEC

Whelan et al. ASCO 2011









Whelan et al. ASCO 2011

EORTC 22922/10925

Study Design

pN+ axillary nodes
or pN- central
or medial tumour

RANDOM

- No IM-MS Irradiation
- IM-MS irradiation (50Gy)

ENDPOINTS

Main: Overall survival

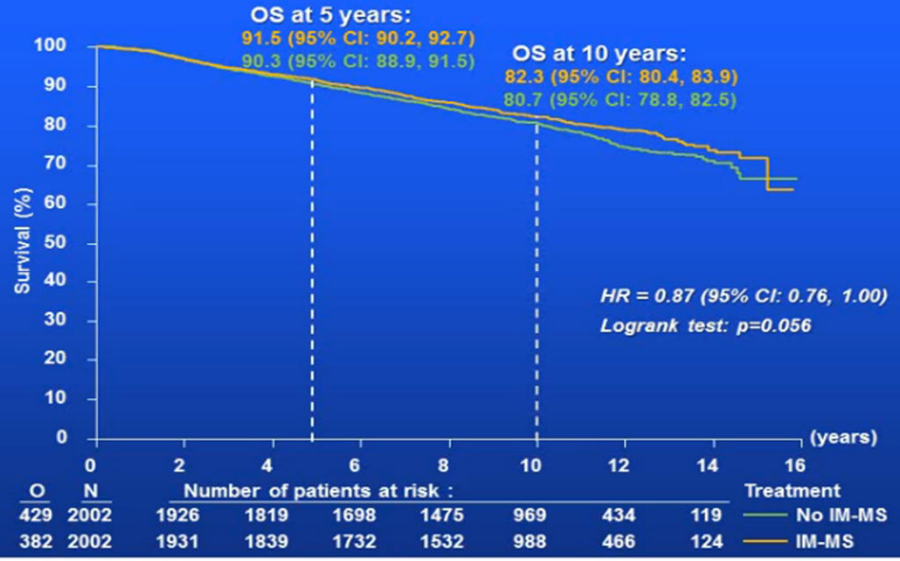
Secondary: Disease -free survival
Metastases-free survival
Cause of death

EORTC *The future of cancer therapy*

ECCO, Amsterdam 2013

EORTC 22922/10925

Overall Survival (ITT)

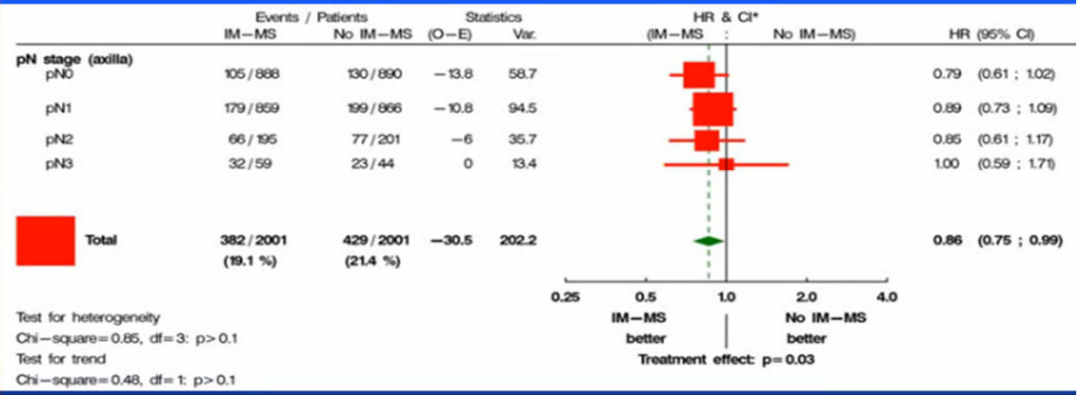


EORTC The future of cancer therapy

EORTC 22922/10925

Overall Survival (ITT)

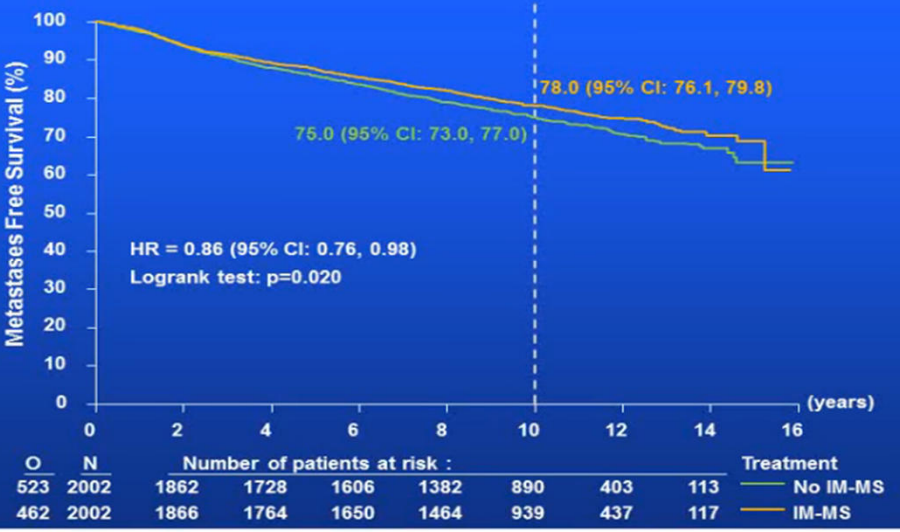
Influence of pathological N-stage



EORTC The future of cancer therapy

EORTC 22922/10925

Metastases-Free Survival (ITT)

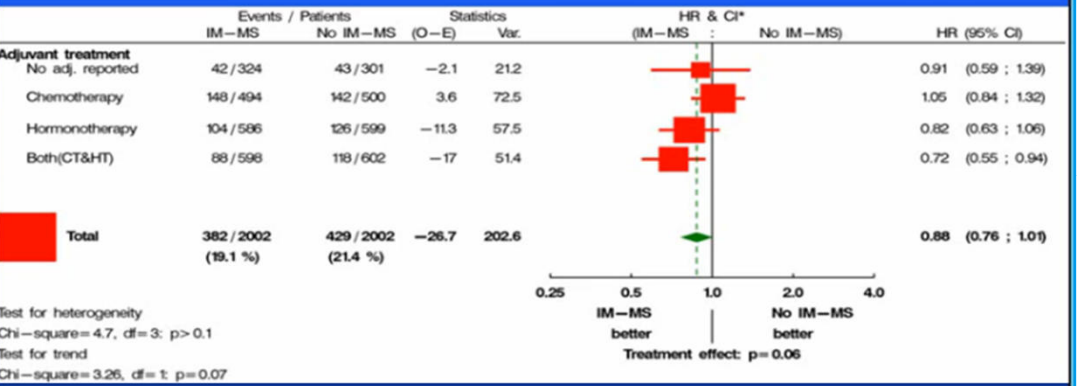


EORTC The future of cancer therapy

EORTC 22922/10925

Overall Survival (ITT)

Influence of use of adjuvant systemic therapy



EORTC The future of cancer therapy

ECCO, Amsterdam 2013

Meta-analysis: whole breast (WBI)/chest wall (CW) RT vs. WBI/CWI + regional lymph nodes

N+ or medial/central tumor location

Overall Survival

Comparison I: (MS+IM)+(WBI/CWI) vs. (WBI/CWI)

MA.20 [16]: n=1832; HR 0.76 (95% CL 0.56 - 1.03)

EORTC [17]: n=4004; HR 0.87 (95% CL 0.76 - 1.00)

Subtotal*: n=5836; HR 0.85 (95% CL 0.75 - 0.96) p=0.011

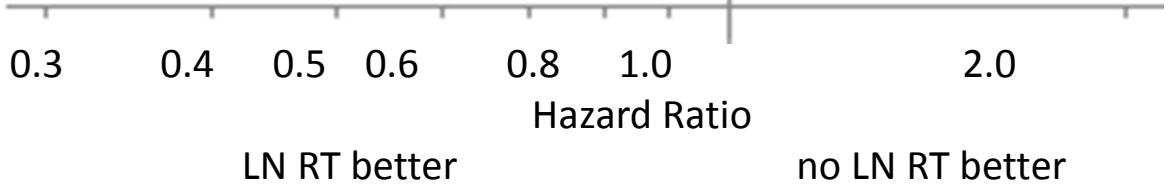
Comparison II: IM+(WBI/CWI+MS) vs. (WBI/CWI+MS)

French [15]: n=1334; HR 0.94 (95% CL 0.79 - 1.11)

Subtotal: n=1334; HR 0.94 (95% CL 0.79 - 1.11) p=0.80

Comparison I+II

Total**: n=7170; HR 0.88 (95% CL 0.80 - 0.97) p=0.012



*= fixed effect model

** = random effect model

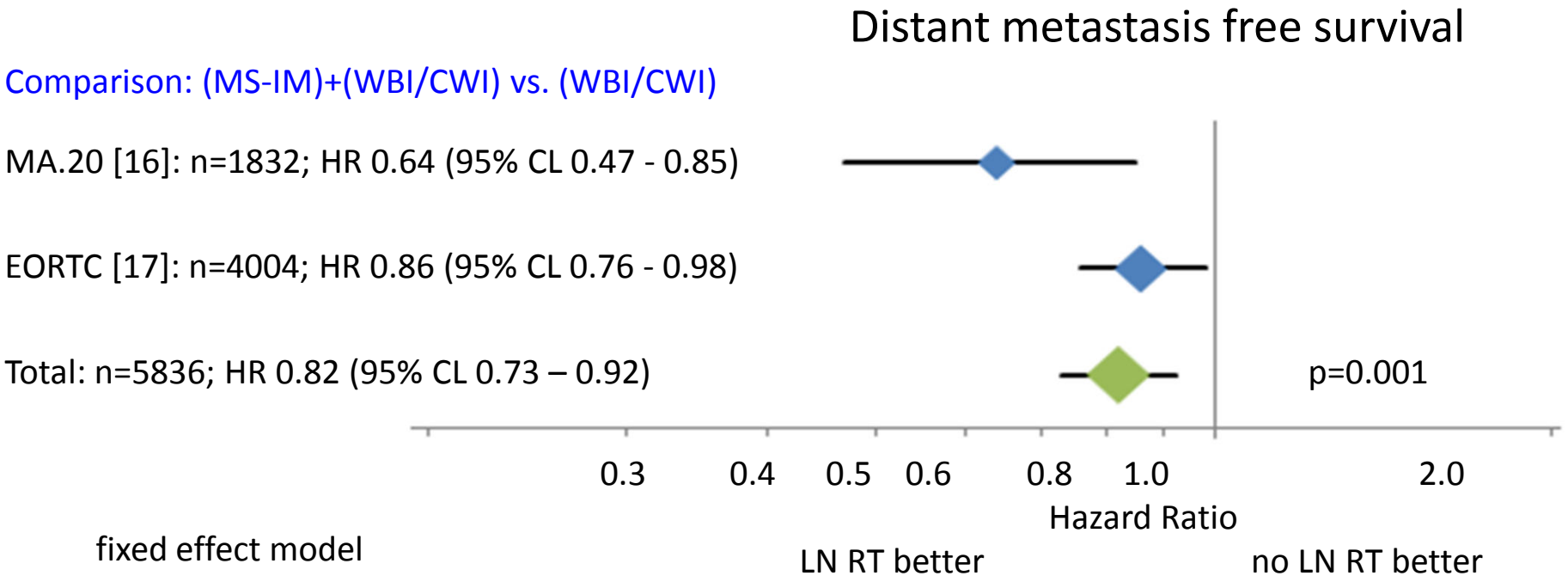
MS = medial supraclavicular LN

IM = internal mammary LN

W. Budach et al. Radiat Oncol 2013

Meta-analysis: whole breast (WBI)/chest wall (CW) RT vs. WBI/CWI + regional lymph nodes

N+ or medial/central tumor location



MS = medial supraclavicular LN
IM = internal mammary LN

W. Budach et al. Radiat Oncol 2013

Meta-analysis: whole breast (WBI)/chest wall (CW) RT vs. WBI/CWI + regional lymph nodes

Table 2 Late toxicity in breast cancer trials on regional radiotherapy

Trial late toxicity	MA.20 [16]			EORTC [17]			French [15]		
	MS-IM-	IM-IM+	p	MS-IM-	IM-IM+	p	MS+	IM-IM+	p
Lung									
Grade 2	0.2%	1.3	0.01	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Grade >2	0%	0%	n.a.	n.s.					
Any grade n.a	n.a.	n.a.	n.a.	1.3%	4.3%	<0.0001	n.a.	n.a.	n.a.
Lymphedema									
Grade 2	3.7%	6.8%	0.004	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Grade >2	0.4%	0.4%	n.s.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Any grade (arm)	n.a.	n.a.	n.a.	3.6%	3.8%	n.s.	n.a.	n.a.	n.a.
Cardiac									
Any grade	n.a.	n.a.	n.a.	1.4%	1.6%	n.s.	1.7%	2.2%	n.s
Total late									
Any grade	n.a.	n.a.	n.a.	21.8%	25.5%	0.006	n.a.	n.a.	n.a.
Grade >2	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	2.3%	3.1%	n.s.

Late toxicitiy.
n.a. = not available; n.s. = not significant; MS-IM-: no radiotherapy of the medial supraclavicular and internal mammary lymph nodes; MS-IM+: radiotherapy of the medial supraclavicular and internal mammary lymph nodes; MS+: radiotherapy of the medial supraclavicular lymph nodes.

W. Budach et al. Radiat Oncol 2013

Concepts of radiotherapy in randomized trials on post-mastectomy RT

trial chest wall supracl./ax. Parasternal boost systemic. treat.

code and study name	irradiation	(AF) irradiation	(IMC) irradiation	to scar (S)	therapy
Mastectomy with axillary clearance					
62B Berlin-Buch ABC	55 Gy (u Gy/f) c	55 Gy (u Gy/f) c	55 Gy (u Gy/f) c	None	None
64B Oslo X-ray	25-41 Gy (1.3-2.1 Gy/f) o	36 Gy (1.8 Gy/f) o	25-41 Gy (1.3-2.1 Gy/f) o	None	Ovarian irradiation
64E Oslo Co-60	None	50 Gy de (2.5 Gy/f) c	50 Gy de (2.5 Gy/f) c	None	Ovarian irradiation
69A Heidelberg XRT	None	65 Gy (2.2-2.7 Gy/f) c	65 Gy (2.2-2.7 Gy/f) c	None	None
71B Stockholm A	45 Gy (1.8 Gy/f) c or e	45 Gy de (1.8 Gy/f) c	45 Gy (1.8 Gy/f) c or e	None	None
71D SASIB	0-45 Gy (4.5 Gy/f) o or c	45-60 Gy (2-4.5 Gy/f) c	40-60 Gy (2-4 Gy/f) c or e	None	None
73C Mayo 70-56-32	0-50 Gy (2.1 Gy/f) m	50 Gy de (2.1 Gy/f) m	50 Gy de (2.1 Gy/f) m	None	CFP vs not
73E INT Milan 1	None	40-45 Gy (1.8-2 Gy/f) c or m	40-45 Gy (1.8-2 Gy/f) c or m	None	None
74D DFCI Boston	45 Gy (2.3 Gy/f) c or m	45 Gy (2.3 Gy/f) c or m	None	None	Either AC 6 vs AC 12 cycles, or CMF vs M
74Q Piedmont OA	0-45 Gy (1.5 Gy/f) u	45 Gy (1.5-2.8 Gy/f) u	45 Gy (1.5-2.8 Gy/f) u	None	Mel vs CMF
76A SECSG 1	50 Gy (2 Gy/f) m	50 Gy (2 Gy/f) m	50 Gy (2 Gy/f) m	None	CMF
76C Glasgow	37.8 Gy (2.5 Gy/f) o	37.8 Gy (2.5 Gy/f) o	37.8 Gy (2.5 Gy/f) o	None	CMF
77J MD Ander. 7730B	45-50 Gy (1.8-1.9 Gy/f) c	45-50 Gy (1.8-1.9 Gy/f) c	45-50 Gy (1.8-1.9 Gy/f) c	12 Gy (u Gy/f) u	BCG+FAC vs FAC
78A S Swedish BCG	38 Gy (1.9 Gy/f) e,o,m or c	48-60 Gy (2.4 Gy/f) c or m	48 Gy (2.4 Gy/f) e, c or m	None	Premen: C; Postmen: tamoxifen
78B Toronto-Edmont.	None	40 Gy de (2.5 Gy/f) c	40 Gy de (2.5 Gy/f) c	None	CMF+ovarian irradiation+P±BCG
78G BCCA Vancouver	40 Gy (2.5 Gy/f) c or m	37.5 Gy de (2.3 Gy/f) c or m	37.5 Gy (2.3 Gy/f) c or m	None	CMF+ovarian irradiation+P vs CMF
78Q Düsseldorf U.	40 Gy (2 Gy/f) c	40 Gy (2 Gy/f) c	40 Gy (2 Gy/f) c	None	LMF
79F Coimbra	36 Gy (3 Gy/f) o or m	39-45 Gy (3.3-3.8 Gy/f) m	39 Gy (3.3 Gy/f) m	None	AC
79G Metaxas Athens	45-60 Gy (2 Gy/f) m	50 Gy (2 Gy/f) m	50 Gy (2 Gy/f) m	None	Various
80S Helsinki	45 Gy (3 Gy/f) c	45 Gy (3 Gy/f) c	30 Gy (3 Gy/f) c	None	CAFt
80W NSABC Israel	46-50 Gy (2 Gy/f) c or m	46-50 Gy (2 Gy/f) c or m	40 Gy (2 Gy/f) c or m	None	CMF
82B Danish BCG 82b pre	48-50 Gy (2-2.2 Gy/f) e	48-50 Gy (2-2.2 Gy/f) m	48-50 Gy (2-2.2 Gy/f) e	None	CMF
82C Danish BCG 82c post	48-50 Gy (2-2.2 Gy/f) e	48-50 Gy (2-2.2 Gy/f) m	48-50 Gy (2-2.2 Gy/f) e	None	Tamoxifen
82Q ECOG EST3181	46 Gy (2 Gy/f) c or m	46-50 Gy (2 Gy/f) c or m	46 Gy (2 Gy/f) c, m or e	None	CAF+H+tamoxifen
84A GBSG 03 Germany	50 Gy (2 Gy/f) m	50 Gy (2 Gy/f) m	44 Gy (1.8 Gy/f) m	None	CMF
Mastectomy with axillary sampling					
73A Wessex	46 Gy (2.3 Gy/f) c	55 Gy (2.5 Gy/f) c	46 Gy (2.3 Gy/f) c	None	None
74B Edinburgh I	45 Gy md (4.5 Gy/f) m	42.5 Gy md (4.3 Gy/f) m	None	None	None
85F Nottingham	45 Gy (3 Gy/f) u	45 Gy (3 Gy/f) u	None	None	Various
86C CRC UK	Various	Various	Various	Various	None required
Mastectomy alone					
61H NSABP B-03	None	35-45 Gy (1.8-2.3 Gy/f) o or c	35-45 Gy (1.8-2.3 Gy/f) o or c	None	None
70A Manchester RBS1	30-37 Gy (2-2.5 Gy/f) o	37-40 Gy (2.5-2.7 Gy/f) o or m	37-40 Gy (2.5-2.7 Gy/f) o or m	None	Ovarian ablation
70B Kings/Cambridge	28.5-46 Gy (1.5-3.2 Gy/f) o or s	28.5-46 Gy (1.5-3.2 Gy/f) o or s	28.5-46 Gy (1.5-3.2 Gy/f) o or s	None	None
71C NSABP B-04	50 Gy (2 Gy/f) s	45-50 Gy de (1.8-2.0 Gy/f) s	45 Gy de (1.8 Gy/f) s	None	None
78D Scottish D	37-45 Gy (2.3-3.7 Gy/f) o or m	38.4-45.9 Gy (2.3-3.8 Gy/f) o or m	40-45 Gy (2.3-2.7 Gy/f) o or m	None	Tamoxifen vs not
85Z Tokyo CIH PS	None	42-48 Gy (2-3 Gy/f) u	42-48 Gy (2-3 Gy/f) u	None	CMF
88U Tokyo CIH CZ	None	42-48 Gy (2-3 Gy/f) u	42-48 Gy (2-3 Gy/f) u	None	CMF

EBCTCG 2005

Breast conserving surgery

Comments and conclusions of the DEGRO panel

- Data from the MA-20 and EORTC studies suggest that *all* node-positive patients profit from comprehensive RNI including SCN and IMN.
- The respective contribution of RNI by site (SCN vs. IMN) on improved outcome cannot be distinguished, axillary nodes of level I and II were partly included in the control arms using WBI/CWI.
- Full publication of the MA-20 and the EORTC studies is pending; several important details or subgroup analyses are not yet available.

Sautter-Bihl et al. Strahlenther Onkol 2014

Mastectomy

Summary of the DEGRO expert panel

- PMRT including the chest wall and regional lymphatics is mandatory following mastectomy in patients with T4 tumors or (any) positive lymph nodes or R1/R2 resection. Radiotherapy to the IMC in node-positive patients should be strongly considered.
- PMRT should be strongly considered in T3 N0 patients with two or more risk factors (see ◘ Table 1).

Wenz et al. Strahlenther Onkol 2014

Radiotherapie der übrigen lokoregionalen Lymphabflussregionen

	Oxford / AGO LoE	GR	
➢ **RT der supra-/infraklavikulären Lymphregion:**			
➢ Level III befallen	1	B	+
➢ Sofern RT der Axilla erfolgt	3b	B	+
➢ pN1a	1	A	+/-
➢ pN2a	1	A	++
➢ (p)N3a-c	1	A	++
➢ Nach NACT (wenn prätherap. LK-Status positiv)*	3	C	+/-
➢ **RT der Axilla:**			
➢ Nach Axillaclearing der Level I + II	3b	D	-
➢ SNB -	4	D	-
➢ Bei Kontraindikation oder Ablehnung eines suffizienten Axillaclearing	2a[a]	B	+/-
➢ **RT der Mammaria-interna-Lymphabflussregion**	1	B	+/-

Der jeweilige Anteil der RNI pro erfasster RT-Region (SCN vs. IMN) am verbesserten Outcome kann nicht differenziert werden

**beachte Risiko-Nutzen-Relation der RT

[a]AMAROS trial

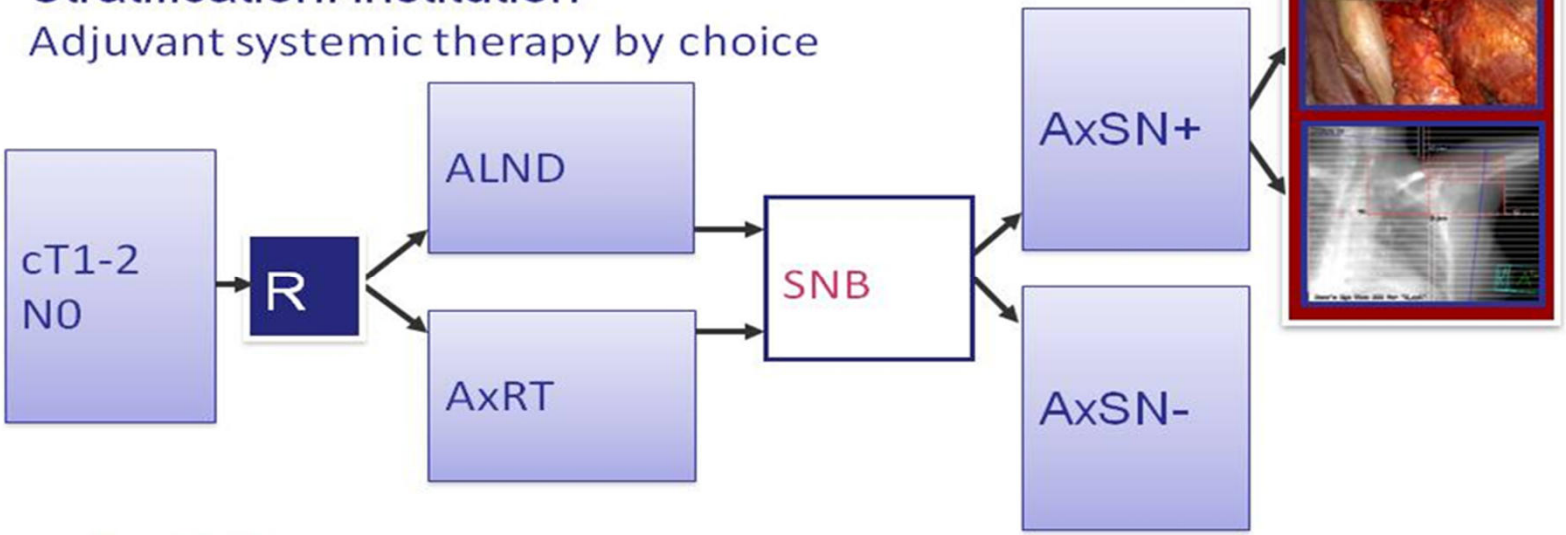
(3/2014)

Trial design

EORTC

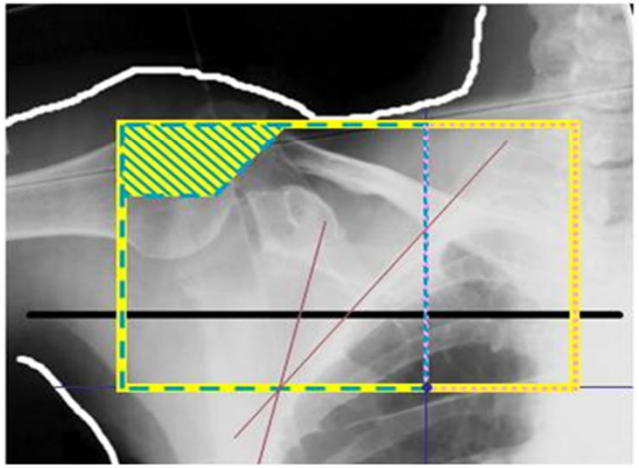
Stratification: institution

Adjuvant systemic therapy by choice



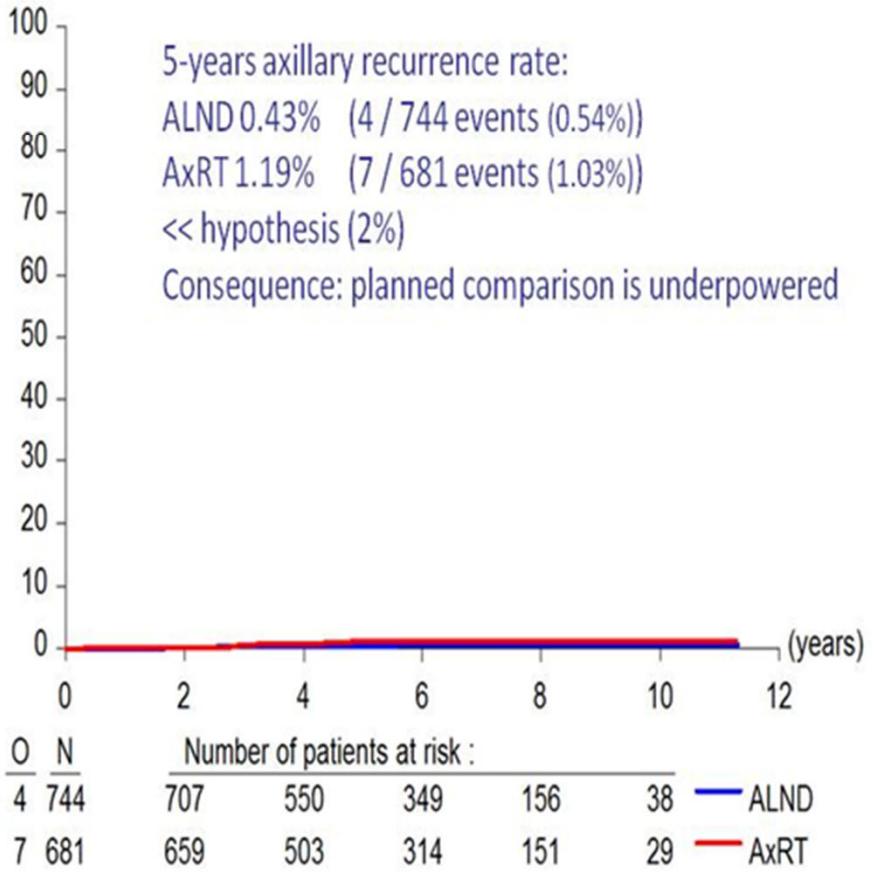
AxRT

- Timing:
  Start < 12 weeks after SNB
- Extent:
  level I + II + III + medial SC
- Dose & schedule:
  25 x 2 Gy or equivalent

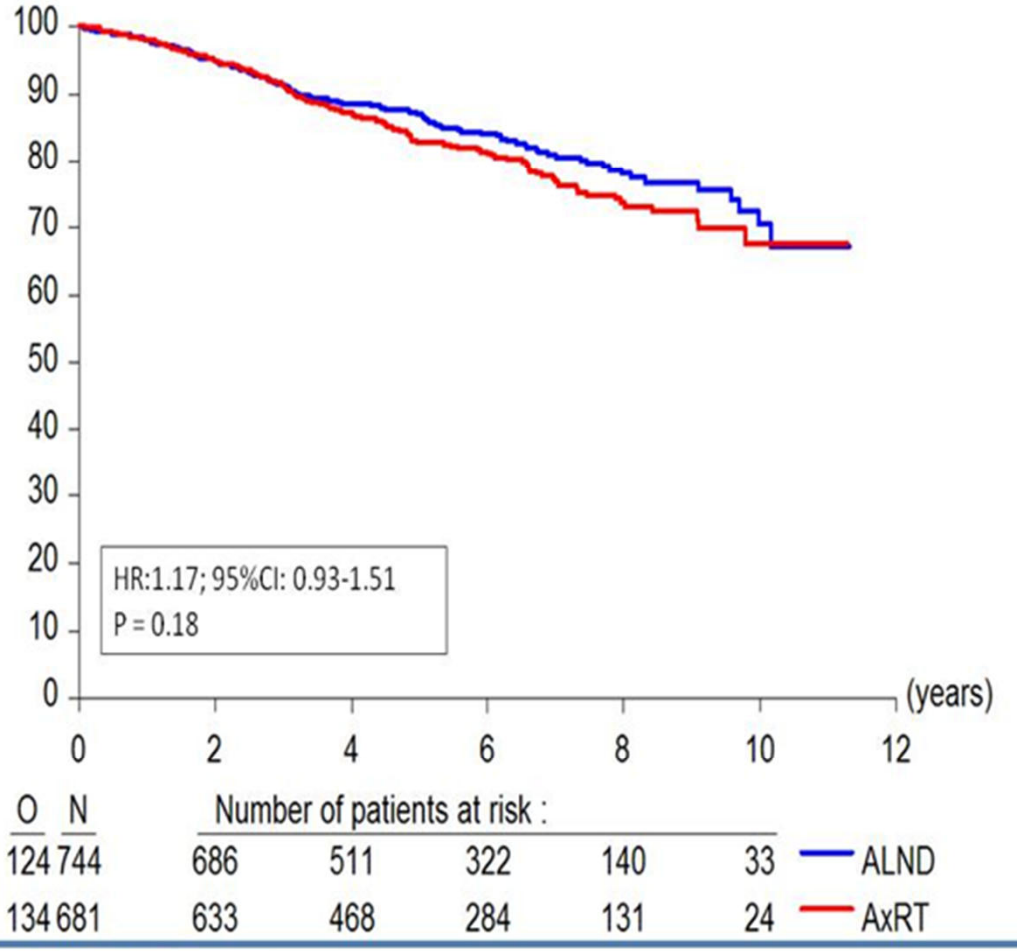


AMAROS

Axillary recurrence rate



Disease-free survival



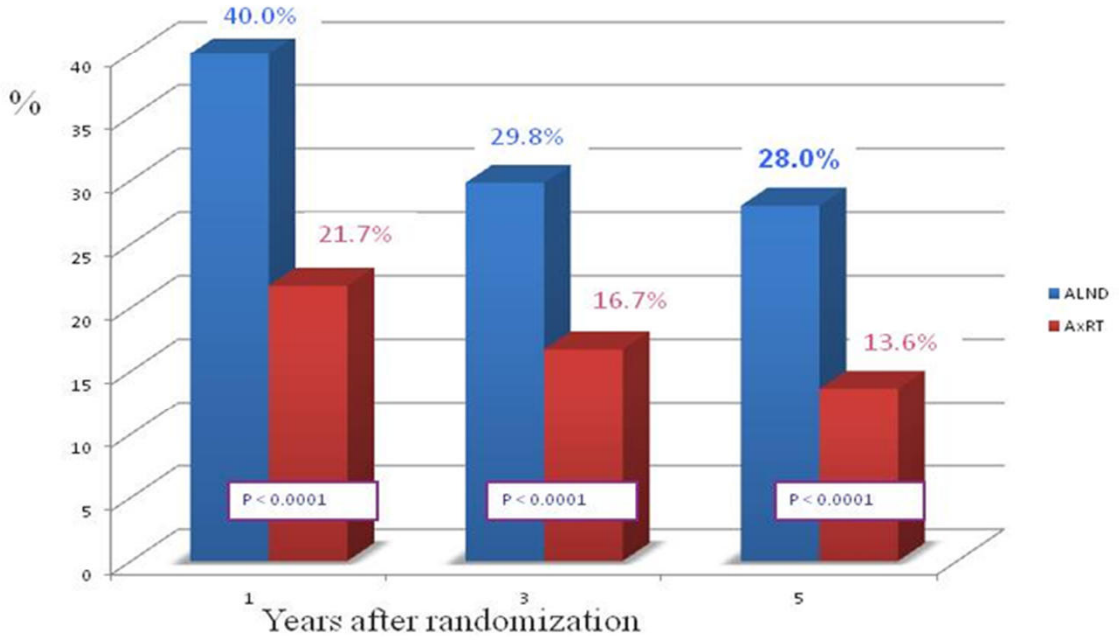
EORTC

AMAROS

Presented By Emiel J. Rutgers, MD, PhD at 2013 ASCO Annual Meeting

Lymphedema:

clinical observation and/or treatment

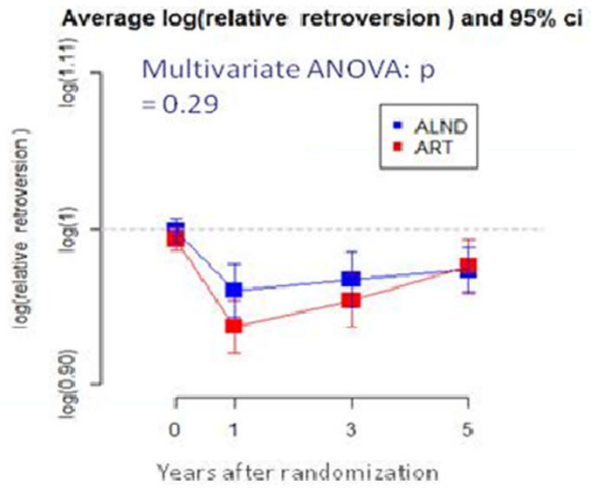


Shoulder function

Results:

No significant differences in all 4 excursions

Trend towards impaired movement after AxRT in first year only



EORTC

AMAROS

Presented By Emiel J. Rutgers, MD, PhD at 2013 ASCO Annual Meeting

Conclusion

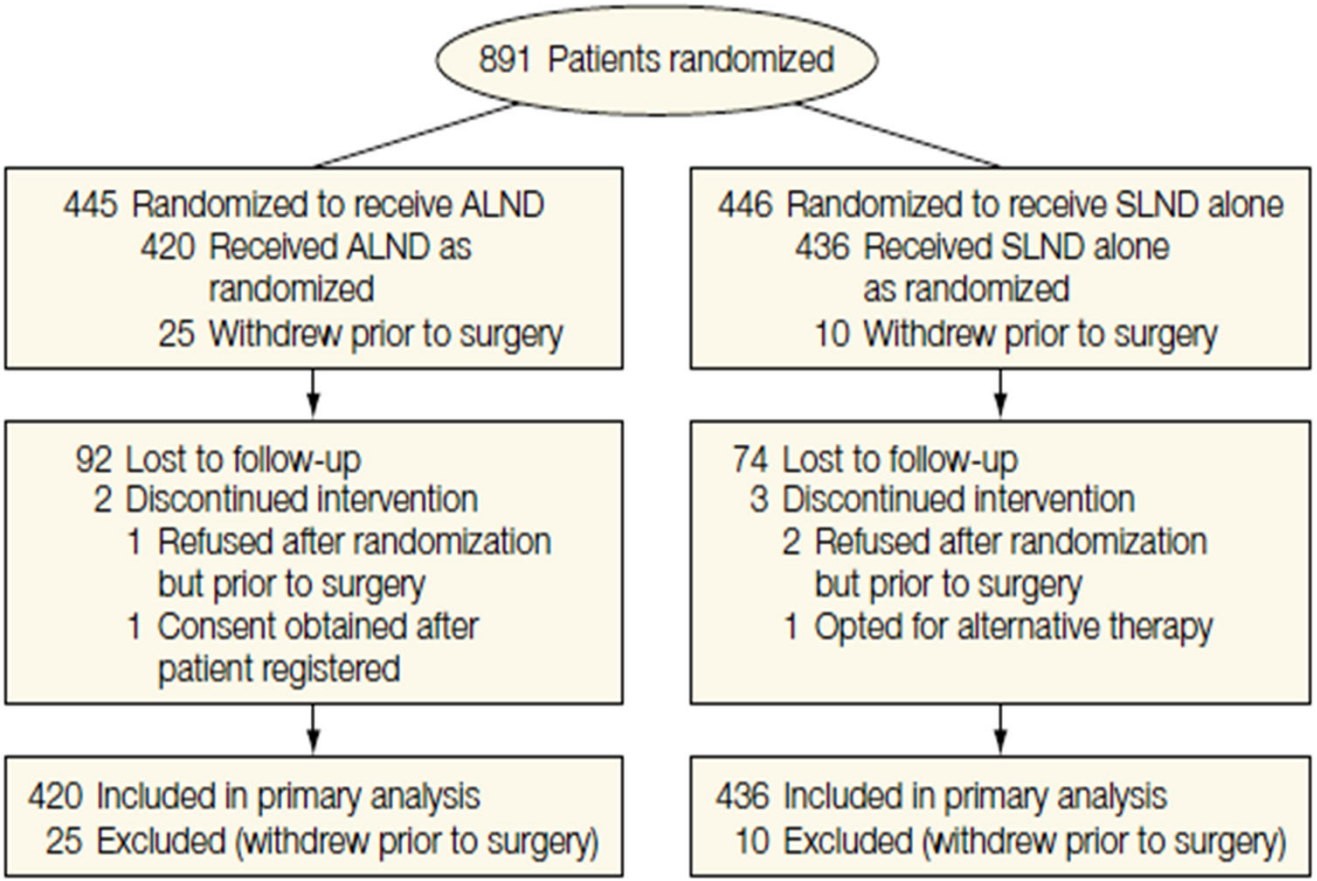
Both ALND and AxRT provide excellent and comparable locoregional control in AxSN+ patients

Significantly less lymphedema after AxRT

AxRT can be considered standard

Management of the axilla: pos SNB: lymph node dissection vs. no LN-dissection

All patients received tangential radiotherapy to the breast



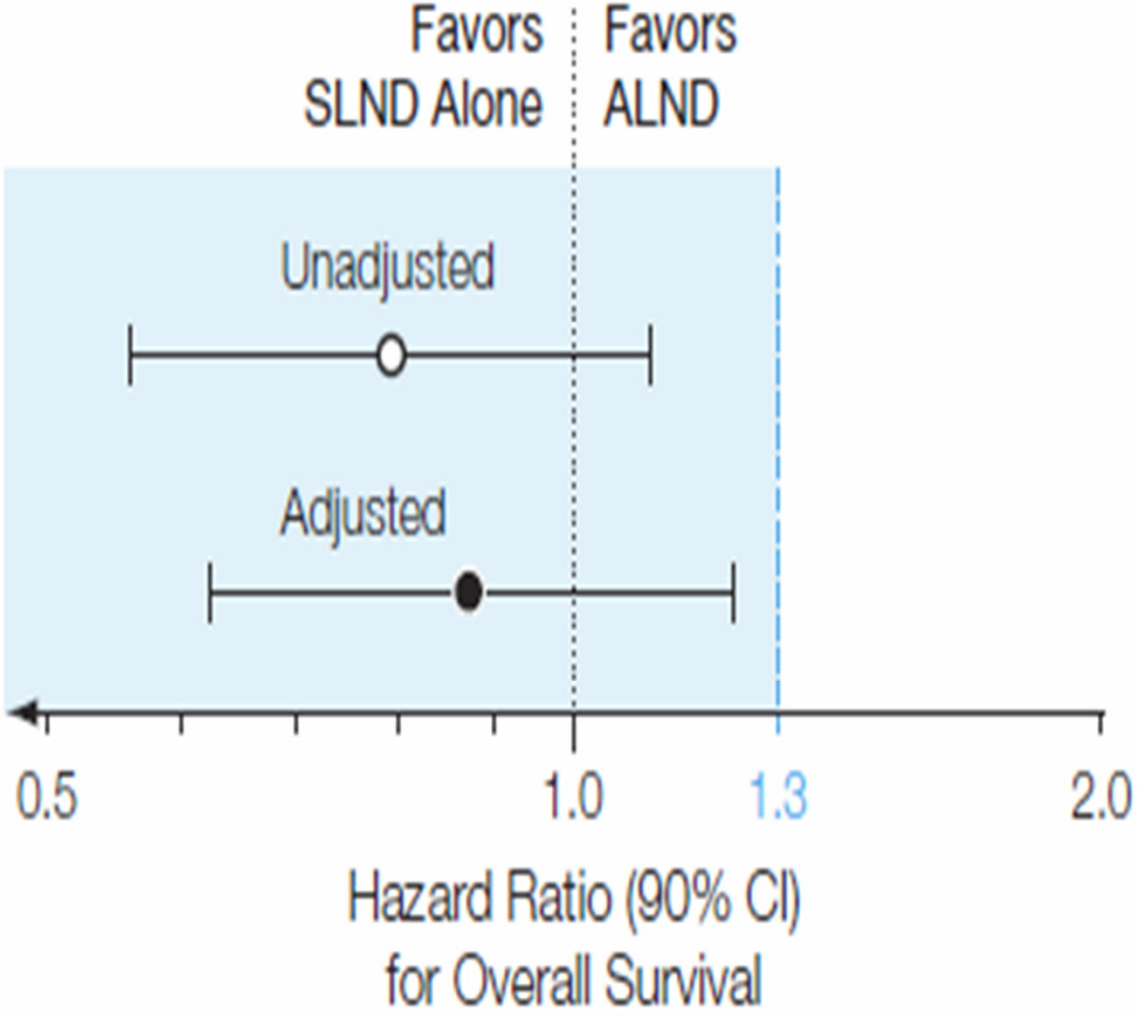
Characteristic	No. (%) ALND (n = 420)	No. (%) SLND Alone (n = 436)
Age, median (range), y	56 (24-92)	54 (25-90)
Missing	7	10
Clinical T stage		
T1	284 (67.9)	303 (70.6)
T2	134 (32.1)	126 (29.4)
Missing	2	7
Tumor size, median (range), cm	1.7 (0.4-7.0)	1.6 (0.0-5.0)
Missing	6	14
Receptor status		
ER+/PR+	256 (66.8)	270 (68.9)
ER+/PR–	61 (15.9)	54 (13.8)
ER–/PR+	3 (0.8)	4 (1.0)
ER–/PR–	63 (16.5)	64 (16.3)
Missing	37	44
Lymph node metastases		
0	4 (1.2)	29 (7.0)
1	199 (58.0)	295 (71.1)
2	68 (19.8)	76 (18.3)
3	25 (7.3)	11 (2.7)
≥4	47 (13.7)	4 (1.0)
Missing	77	21

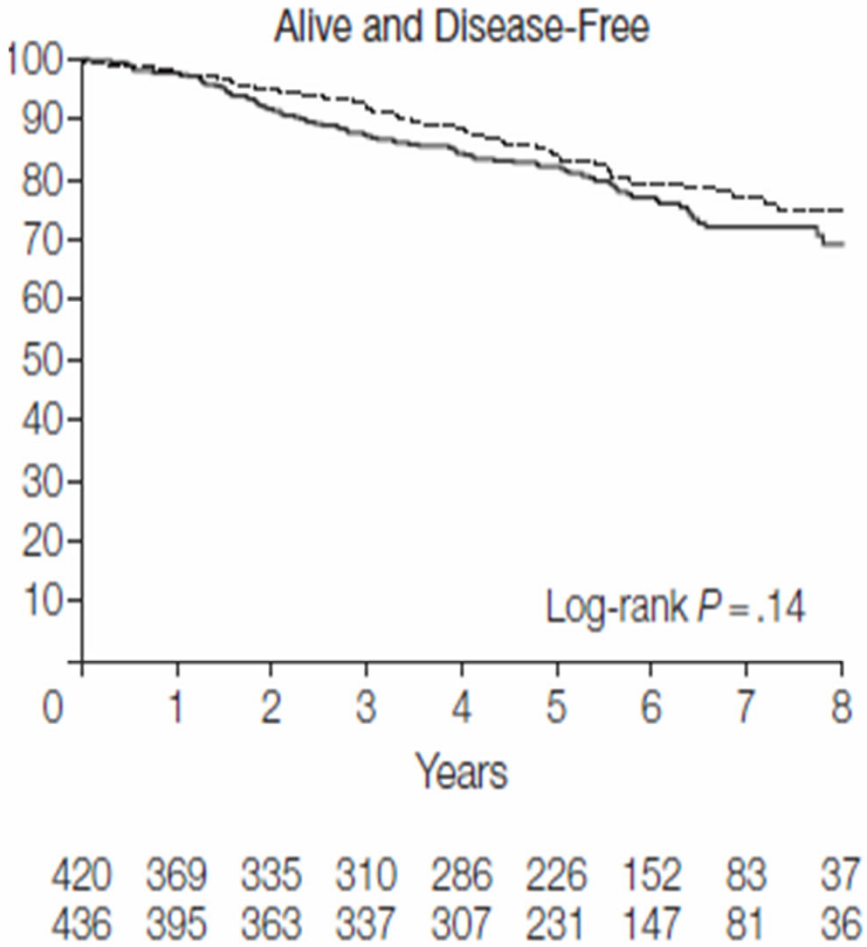
Giuliano et al. JAMA 2011

Z0011 trial

Management of the axilla: pos SNB: lymph node dissection vs. no LN-dissection

All patients received tangential radiotherapy to the breast





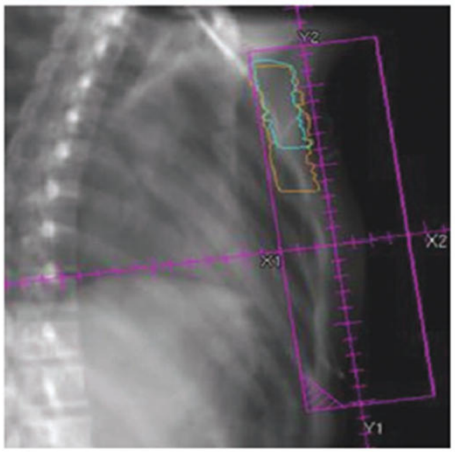
Giuliano et al. JAMA 2011

Z0011 trial

Management of the axilla: pos SNB: lymph node dissection vs. no LN-dissection

Use of RT in the Z001 trial (Data available in a subgroup)

High tangents
(supine)



Orange: level I axilla

Blue: level II axilla

Setton et al. Cancer 2012

positive nodes	**direct RT to nodes**	
	SLN-arm	**ALND-arm**
0	33% (1/3)	no data
1	10.6% (9/85)	7.3% (4/55)
2	24.0% (6/25)	15.8% (3/19)
3	100% (3/3)	33.0% (2/6)
≥4	100% (2/2)	78.6% (11/14)

SLN arm received more nodal RT ($p<0.001$)

Jagsi et al. ASCO Poster 2013

Guidelines Breast
Version 2014.1D

Radiotherapie der Axilla

	Oxford / AGO LoE	GR	
➢ Tumorresiduen nach axillärer Dissektion	2b	B	++
➢ Sentinel-Lymphknoten negativ	1	B	--
➢ Axilladissektion nicht indiziert (z.B. bei positivem SLN; siehe Kapitel op. Therapie)	2a	B	-
➢ Extrakapsuläre Tumoraussaat (ECS)	2b	B	--
➢ Axilläre Mikrometastasen oder isolierte Tumorzellen in regionalen Lymphknoten	3b	B	--
➢ Anstelle einer indizierten axillären Lymphonodektomie bei positivem SLN°	1	B	+/-

° AMAROS trial

(3/2014)

S3 Leitlinie Mamma-Ca. 2012

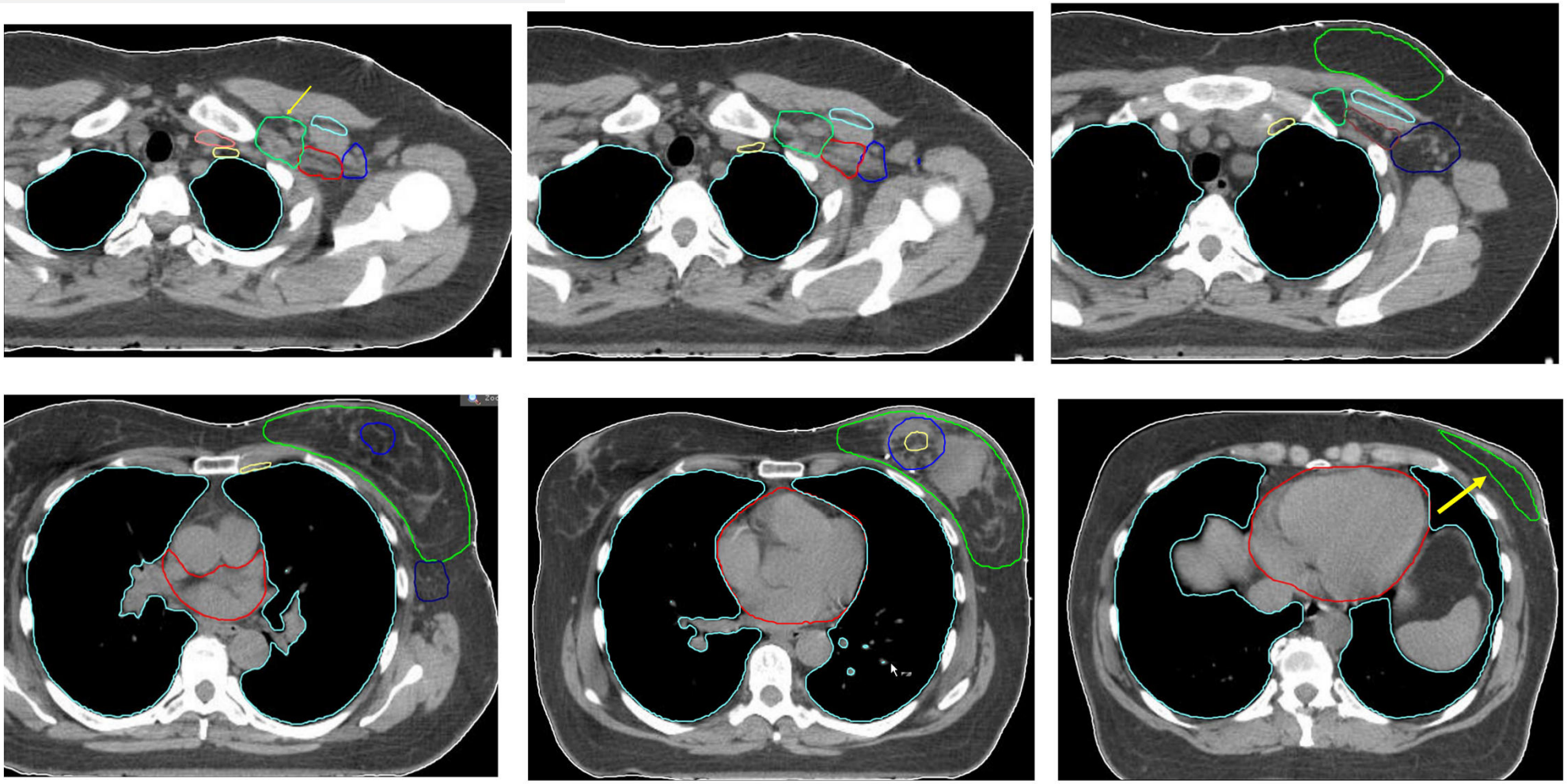
Bestrahlung des Lymphabflusses

RT-5	Radiotherapie des regionalen Lymphabflusses
Empfehlungsgrad A	a. Bei pN0-Situation soll eine Nachbestrahlung der regionalen Lymphabflussgebiete nicht durchgeführt werden.
Level of Evidence 3b	(NCCN 2011; NICE 2009)
	b. Eine Strahlentherapie der Axilla wird nur empfohlen bei:
Empfehlungsgrad A	- Resttumor in der Axilla
Level of Evidence 2b	(NCCN 2011; NICE 2009; NZGG 2009; SIGN 2005; Truong, PT et al. 2004; Truong, PT et al. 2005b)
Empfehlungsgrad A	- eindeutigem klinischem Befall und nicht erfolgter Axilladissektion.
Level of Evidence 3b	(NCCN 2011; NICE 2009; NZGG 2009)
Empfehlungsgrad A	c. Der Nutzen einer Strahlentherapie der regionalen Lymphabflusswege bei Nachweis isolierter Tumorzellen oder von Mikrometastasen in regionären Lymphknoten (pNmic) ist nicht belegt, sodass diese nicht durchgeführt werden soll.
Level of Evidence 3b	(de Boer, M et al. 2009; de Boer, M et al. 2010; Lupe, K et al. 2011; Tjan-Heijnen, VC et al. 2009; Truong, PT et al. 2008)
	d. Eine Strahlentherapie der Mammaria-interna-Lymphabflussregion soll nicht durchgeführt werden.
GCP	(NICE 2009; NZGG 2009)
	e. Eine Strahlentherapie der supra-/infraklavikulären Lymphabflusswege wird empfohlen bei:
Empfehlungsgrad B	- > 3 befallenen axillären Lymphknoten (> pN2a)
Level of Evidence 1b	(NICE 2009; NZGG 2009)
Empfehlungsgrad B	- Befall des Level III der Achselhöhle
Level of Evidence 3b	(NZGG 2009; SIGN 2005)
Empfehlungsgrad B	- bei Indikation zur Bestrahlung der Achselhöhle (Resttumor in der Axilla)
Level of Evidence 3b	(NZGG 2009; SIGN 2005)
Empfehlungsgrad B	f. Die Indikation zur Strahlentherapie der regionalen Lymphablusswege nach primärer systemischer Therapie ist abhängig zu machen von der prätherapeutischen Ausgangssituation und unabhängig vom Ansprechen der Tumormanifestationen auf die Systemtherapie.
Level of Evidence 3b	(Buchholz, TA et al. 2002; Garg, AK et al. 2007; Huang, EH et al. 2006; Kaufmann, M et al. 2010; McGuire, SE et al. 2007; NCCN 2011)
	g. Falls die Indikation zur Bestrahlung von Lymphabflussgebieten gestellt wird, erfolgt die Strahlentherapie mit ca. 50 Gy in konventioneller Fraktionierung (5 x 1,8 - 2,0 Gy/Woche). Bei der Bestrahlung der supraklavikulären Lymphabflussregion sollte eine Einzeldosis von 1,8 Gy bevorzugt werden.
GCP	

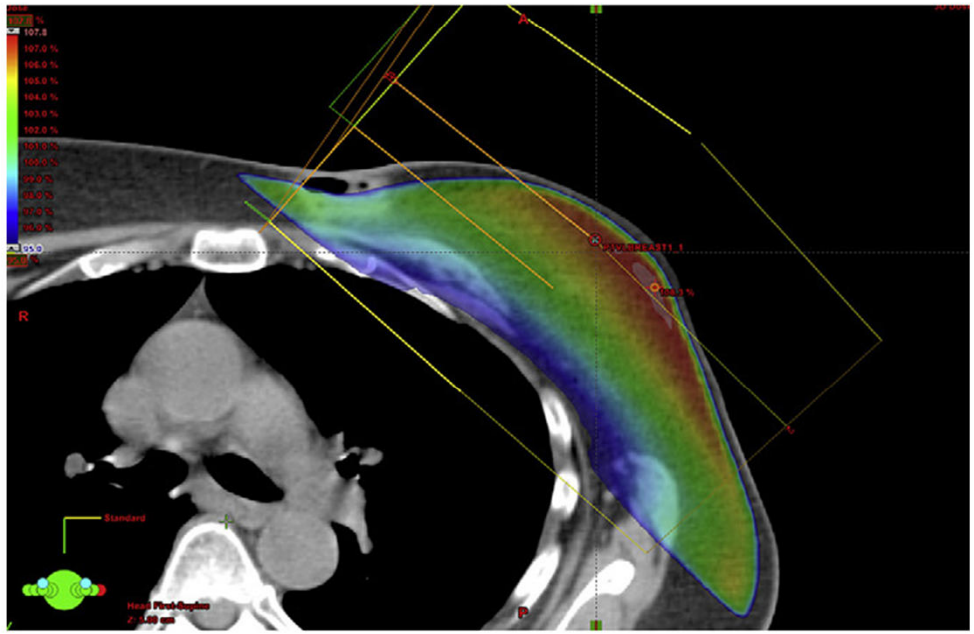
ESTRO delineation consensus guideline 2014 (submitted)

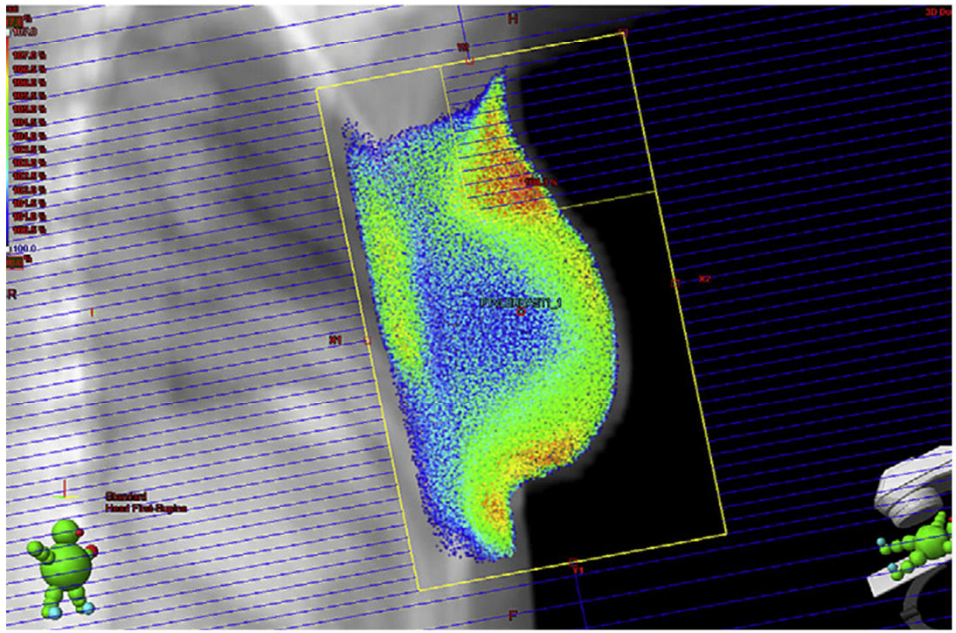
Breast cancer

level 3 - level 2 – Rotter - level 1



Radiation technique, dose homogeneity



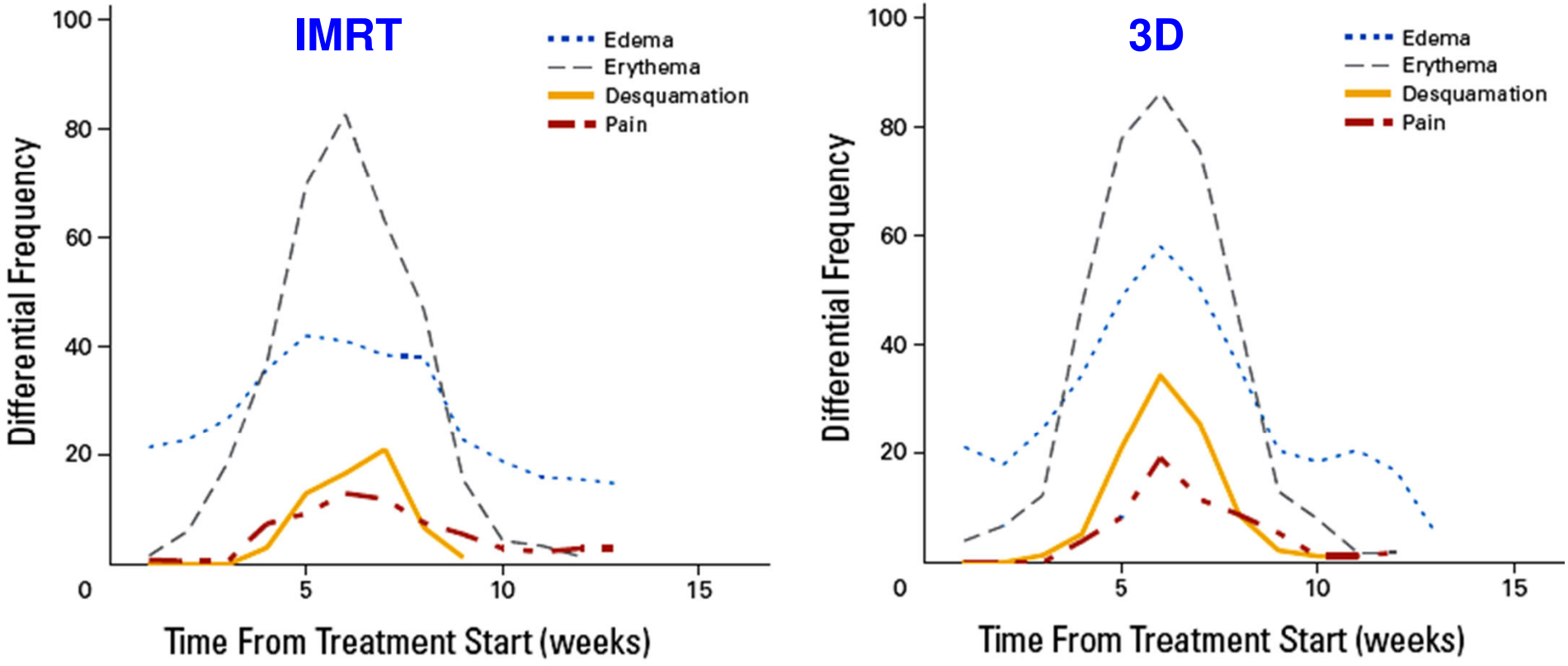


More late effects in case of large inhomogeneity?

- Cosmetic results in larger breasts?
- Heart
- Lung
- Secondary cancer

Random. trial „3D“ vs. IMRT treatment planning

Acute toxicity



358 patients randomized

Pignol et al. JCO 2008

Random. trial 2D vs. IMRT treatment planning

End point: clinician-assessed breast induration

(a little, quite a bit or very much)

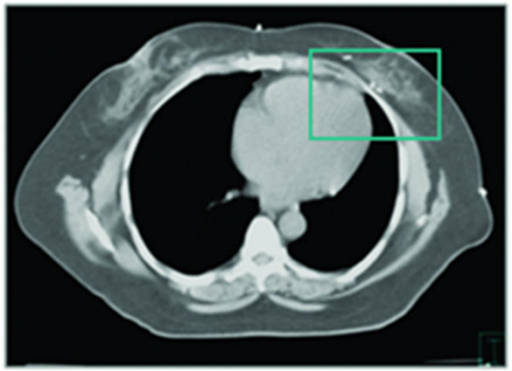
	Year 5 assessment		*P*-value
	Standard 2D	IMRT 3D	
Centre of the breast	37/117 (32%)	25/118 (21%)	0.02
Pectoral fold	34/118 (29%)	26/119 (22%)	0.006
Inframammary fold	28/116 (24%)	20/117 (17%)	0.009
Boost site	70/114 (61%)	43/115 (37%)	<0.001

306 patients randomized

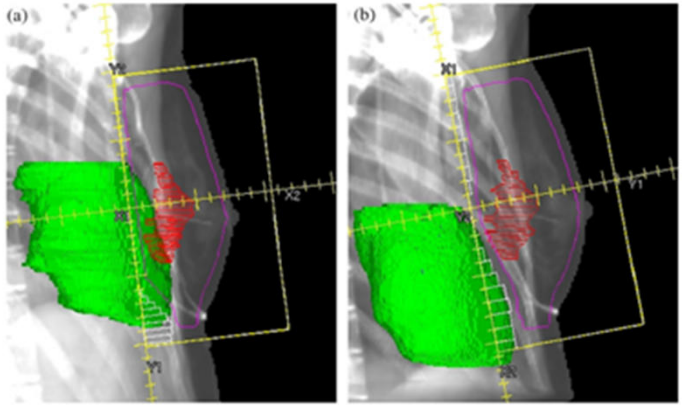
Donovana et al. Radiother Oncol 2007

RT with active breathing control in left sided breast cancer

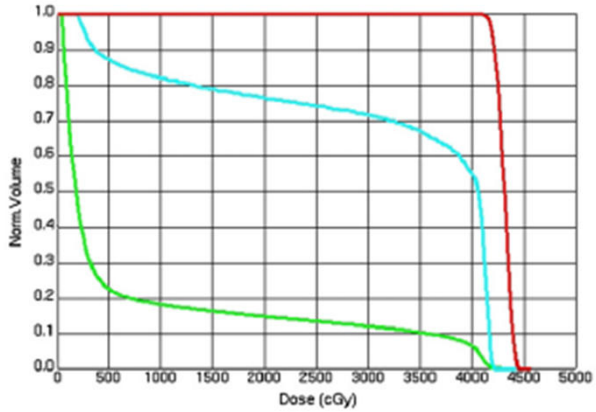
Free breathing



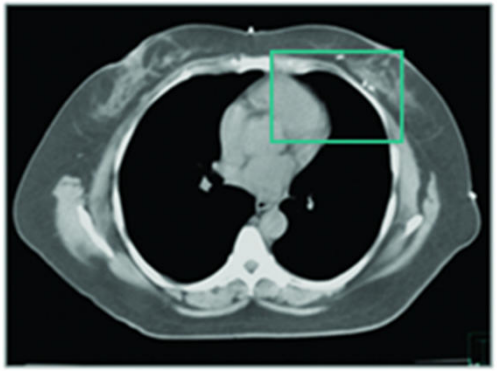
Free breathing



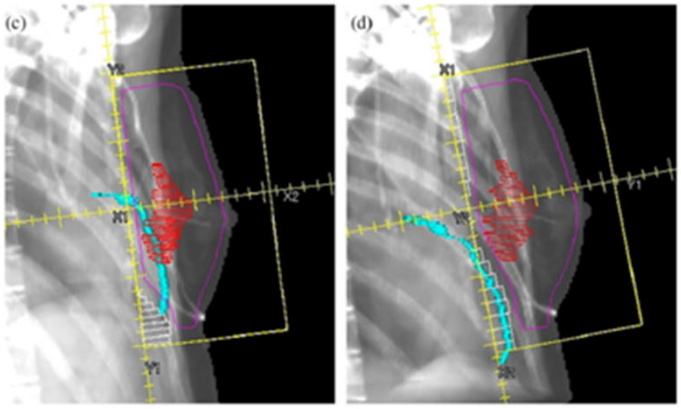
Free breathing



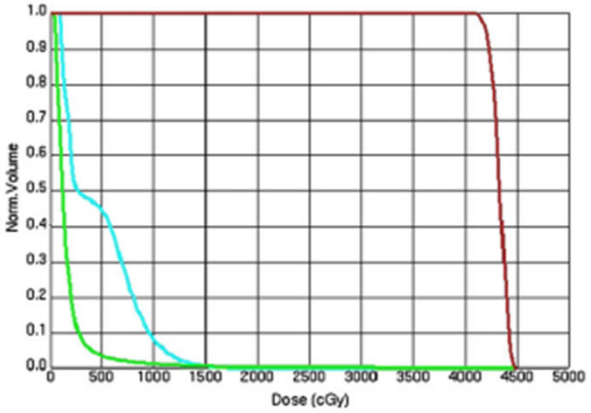
Inspirat. breath hold



Inspirat. breath hold



Inspirat. breath hold



Swanson et al. Am J Clin Oncol 2013

Wang et al. IJROBP 2012

Wang et al. IJROBP 2012

Non Breast Cancer Mortality: EBCTCG update 2006 (unpublished)

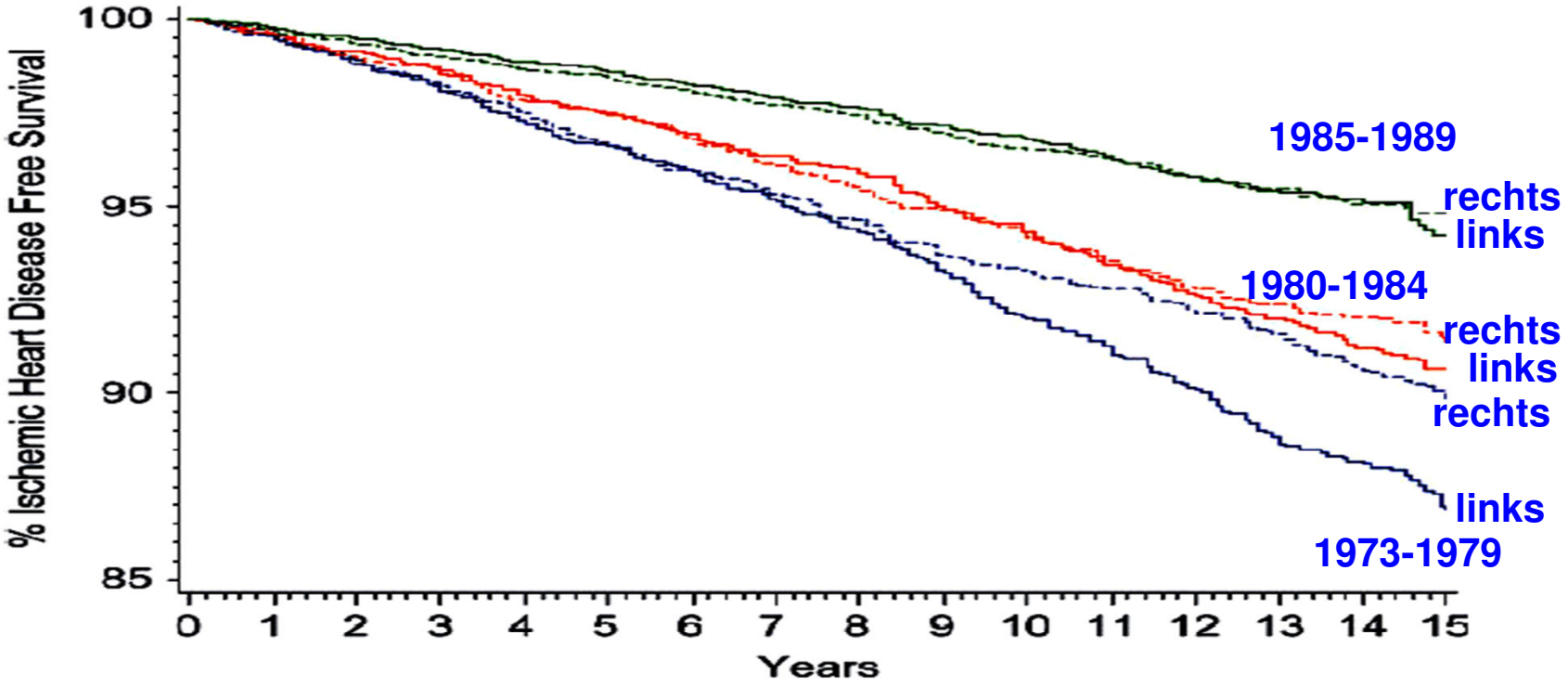
Cause of death	Total evets	Excess events	Ratio of rates (se)[a]	2p
Circulatory disease	1598	167	1.26 (0.06)	0.00001
Other causes	1615	43.4	1.06 (0.05)	NS
Respiratory disease	267	-1.4	0.99 (0.13)	NS
Other known causes	1122	-19.2	0.96 (0.06)	NS
Lung cancer	165	47.0	1.81 (0.22)	0.0002
Oesophagus cancer	23	11.8	2.89 (0.75)	0.01
Leukaemia	31	2.6	1.20 (0.41)	NS
Soft-tissue sarcoma	7	2.6	2.13 (1.14)	NS
Unspecified cause[b]	1610	103.8	1.16 (0.06)	0.005
Total	4823	314.2	1.16 (0.03)	<0.0001

[a] Ratio of annual event rates irradiated versus unirradiated

[b] Unspecified, but known not to be breast cancer

Technischen Weiterentwicklung der RT verbessert die Ergebnisse

Koronare Herzerkrankung nach RT in Abhängigkeit der bestrahlten Seite

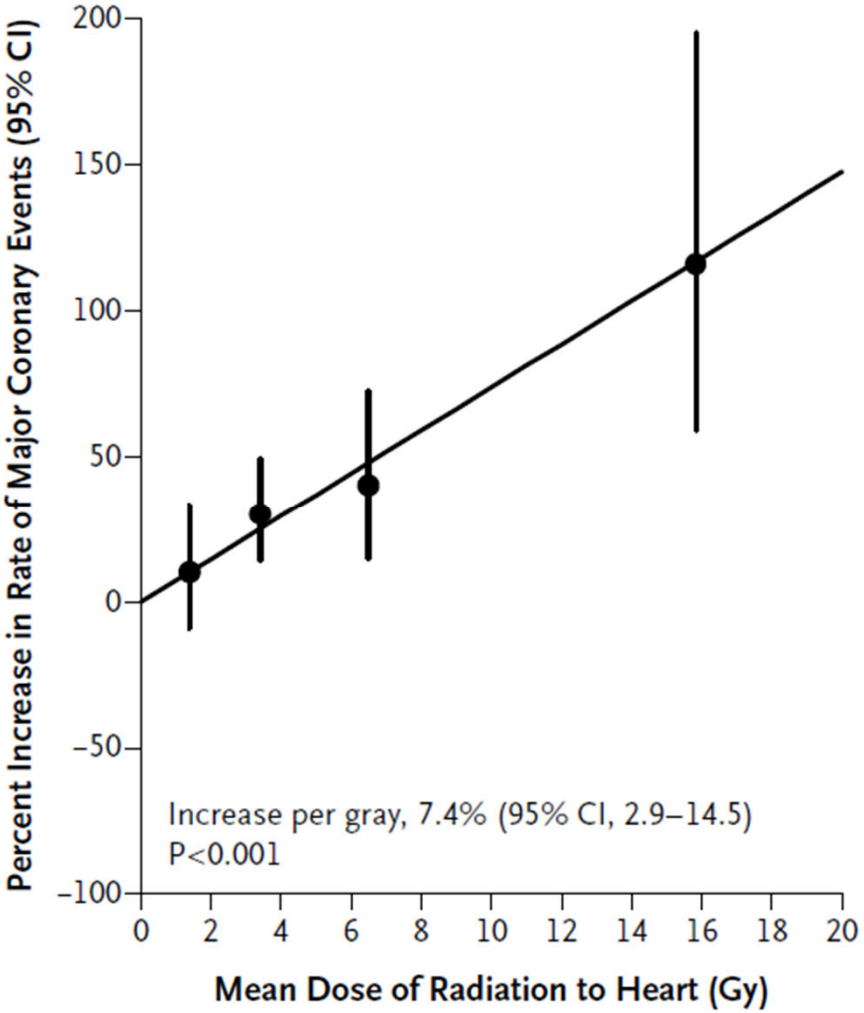


No. of patients at risk		0 year	3 year	6 year	9 year	12 year	15 year
1973-1979	Right	4201	3113	2241	1761	1453	1214
	Left	4451	3305	2384	1885	1523	1272
1980-1984	Right	3131	2539	2044	1676	1425	1232
	Left	3364	2748	2159	1788	1512	1287
1985-1989	Right	5953	5266	4553	4014	2770	507
	Left	6183	5457	4780	4194	2868	533

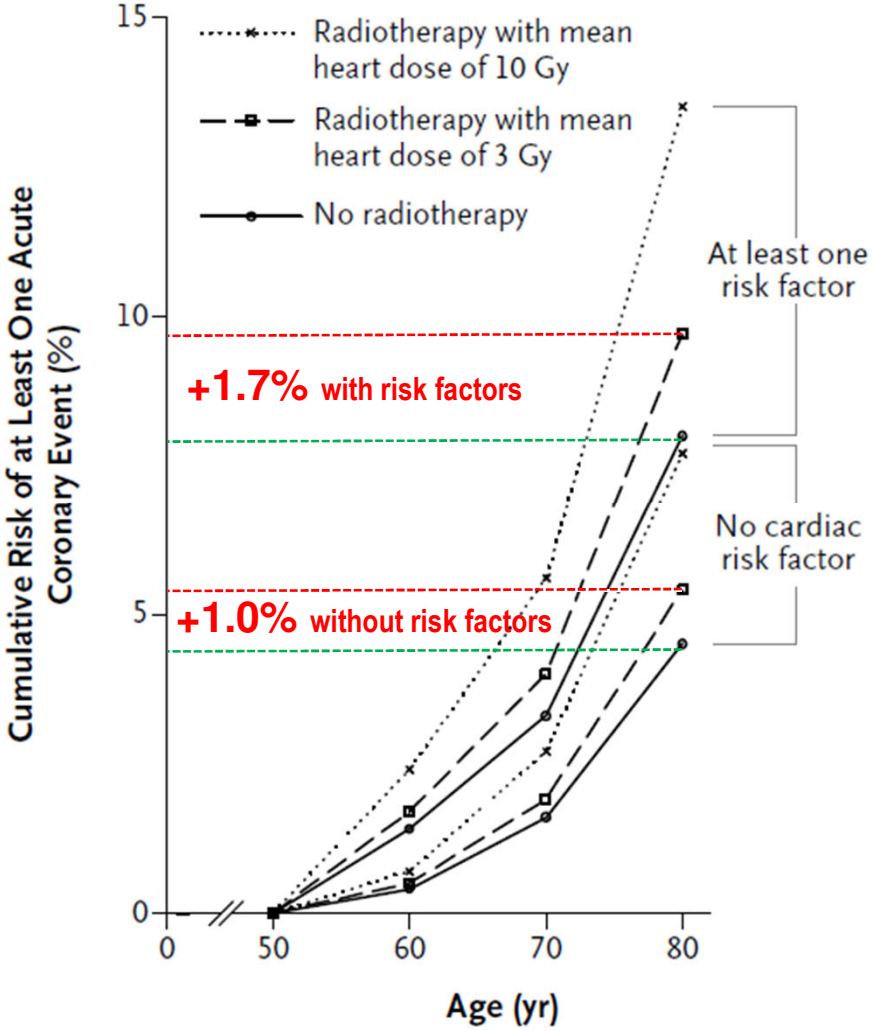
Giordano et al. Lancet 2005

Mean heart dose and risk of cardiac events

Relative Risk



Absolute Risk



Darby et al. NEJM 2013

Schlussfolgerung

- Überstreblichkeit durch RT nach 10 Jahren 0,7% und nach 20 Jahren 2,2%, wenn alle Patienten berücksichtigt werden *(auch mit parasternaler RT und der vor 1975 bestrahlten)*

- Mit 3-D Technik und ohne parasternale RT wird das Risiko von RT-induzierten Tumoren halbiert und die kardiale Übersterblichkeit weitgehend vermieden

- Die Übersterblichkeit wird dadurch um ca. 2/3 reduziert, d.h. auf ca. 0,7% nach 20 Jahren

Die Risken der RT sind im Verhältnis zum Nutzen klein

Adjuvante Therapien beim Brustkrebs

Radiotherapie

- Whole breast irradiation
- Boost irradiation
- Partial breast

Zytostatika

- Adriamycin / Epirubicin
- Cyclophosphamid
- Methotrexat
- 5-FU
- Paclitaxel / Docetaxel

Hormontherapie

- Tamoxifen
- Aromatase-Inhibitoren
- LHRH-Analoge

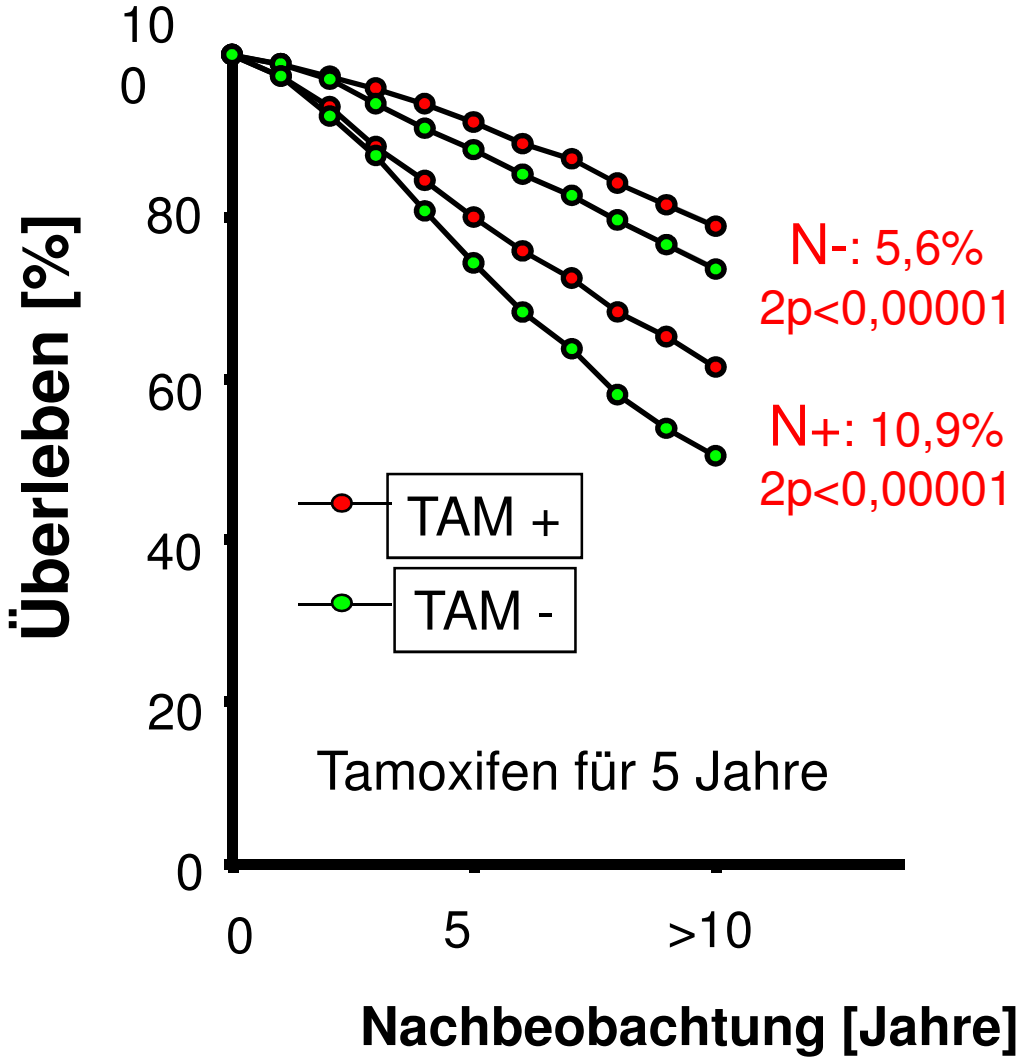
EGFR-Antagonisten

- Trastuzumab

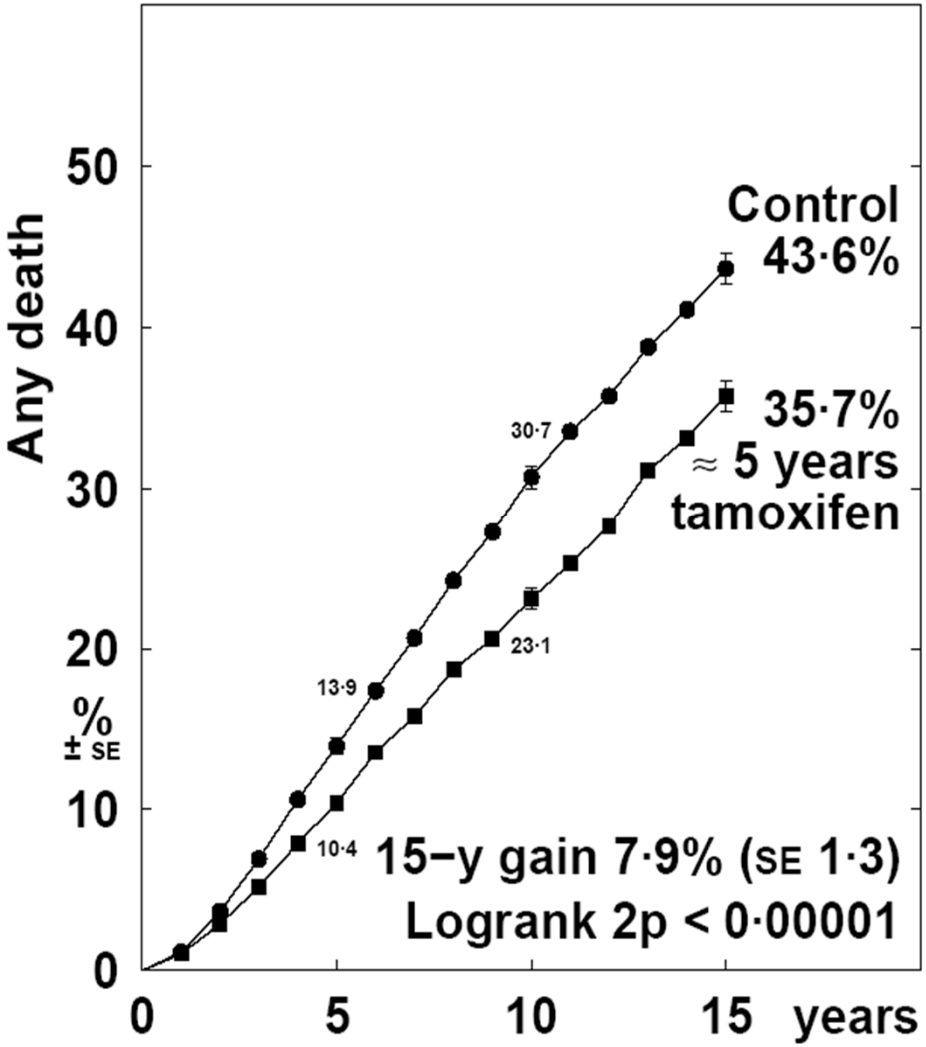
Tamoxifen adjuvant beim Mamma-Ca.

Rezeptor Status + oder unbekannt

Metaanalyse: n=7427, Lancet 1998



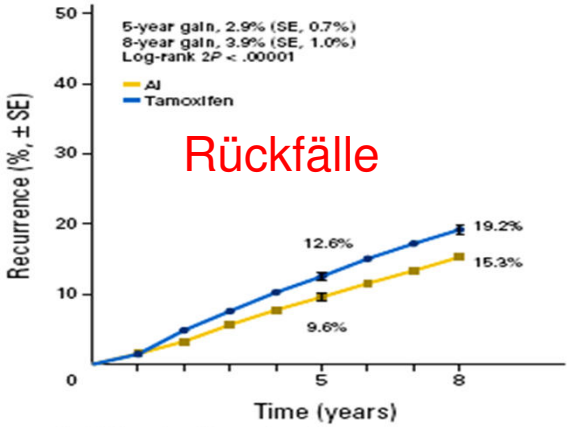
Metaanalyse: n=15017, Lancet 2005



Metaanalyse: 5 Jahre Tamoxifen vs. 5 Jahre Aromatasehemmer

Hormonrezeptorpositiver postmenopausaler Brustkrebs

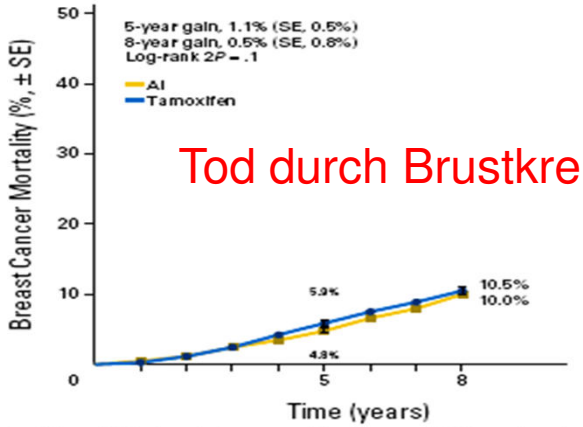
n= 19157



Rückfälle

Recurrence rates (% / year) and log-rank analyses

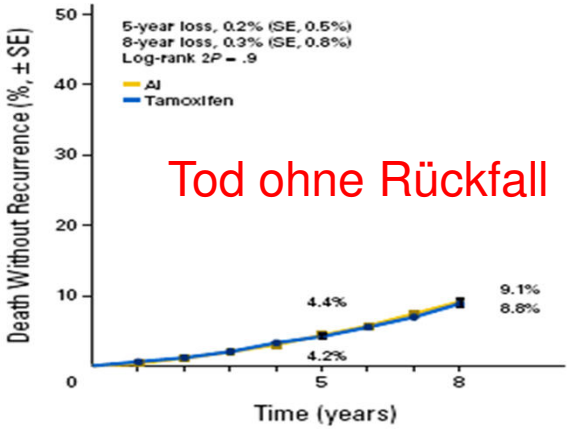
	Years 0–1	Years 2–4	Years 5+
AI	1.69 (163 / 9,647)	2.31 (261 / 11,297)	2.33 (160 / 6,879)
Tamoxifen	2.46 (234 / 9,510)	2.81 (307 / 10,938)	2.78 (180 / 6,478)
Rate ratio, from	0.67 (SE, 0.08)	0.81 (SE, 0.06)	0.83 (SE, 0.10)
(O–E) / V	-38.4 / 96.6	-29.5 / 137.9	-15.7 / 83.0



Tod durch Brustkrebs

Death rates (%/year: total rate—rate in women without recurrence) & log-rank analyse

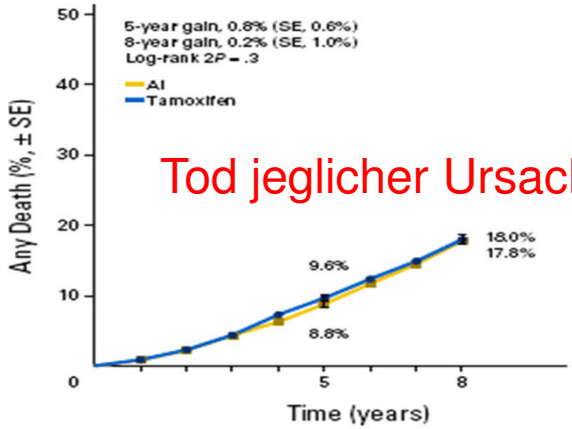
	Years 0–1	Years 2–4	Years 5+
AI	0.59 (SE, 0.06)	1.26 (SE, 0.10)	1.78 (SE, 0.16)
Tamoxifen	0.57 (SE, 0.06)	1.60 (SE, 0.12)	1.79 (SE, 0.16)
Rate ratio, from	1.01 (SE, 0.19)	0.77 (SE, 0.10)	1.01 (SE, 0.13)
(O–E) / V	0.2 / 27.5	-20.5 / 80.2	0.4 / 61.5



Tod ohne Rückfall

Death rates (% / year) and log-rank analyses

	Years 0–1	Years 2–4	Years 5+
AI	0.54 (52 / 9,647)	1.10 (124 / 11,297)	1.60 (110 / 6,879)
Tamoxifen	0.59 (56 / 9,510)	1.02 (112 / 10,938)	1.62 (105 / 6,478)
Rate ratio, from	0.92 (SE, 0.19)	1.07 (SE, 0.14)	0.99 (SE, 0.14)
(O–E) / V	-2.1 / 26.8	4.1 / 58.3	-0.4 / 52.9



Tod jeglicher Ursache

Death rates (% / year) and log-rank analyses

	Years 0–1	Years 2–4	Years 5+
AI	1.12 (109 / 9,743)	2.31 (272 / 11,757)	3.29 (240 / 7,286)
Tamoxifen	1.15 (111 / 9,656)	2.57 (297 / 11,569)	3.26 (232 / 7,107)
Rate ratio, from	0.97 (SE, 0.13)	0.89 (SE, 0.08)	1.00 (SE, 0.09)
(O–E) / V	-1.9 / 54.3	-16.4 / 138.5	0.0 / 114.4

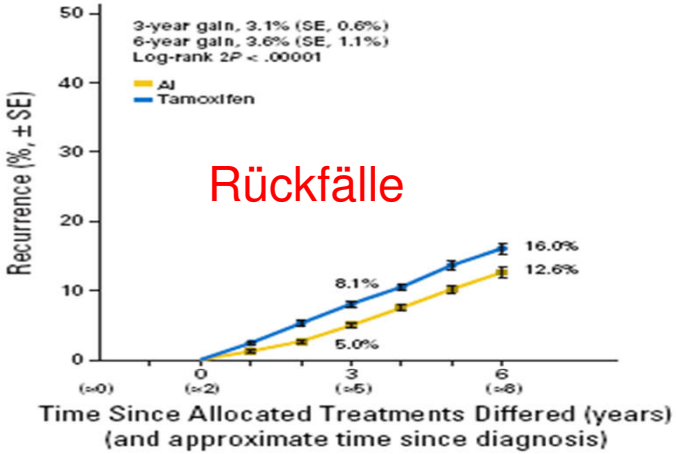
Dowsett et al. JCO 2010

Metaanalyse: 5 Jahre TAM vs. 2-3 TAM gefolgt von 2-3 Jahren Aromatasehemmern

Hormonrezeptorpositiver postmenopausaler Brustkrebs

n= 22096

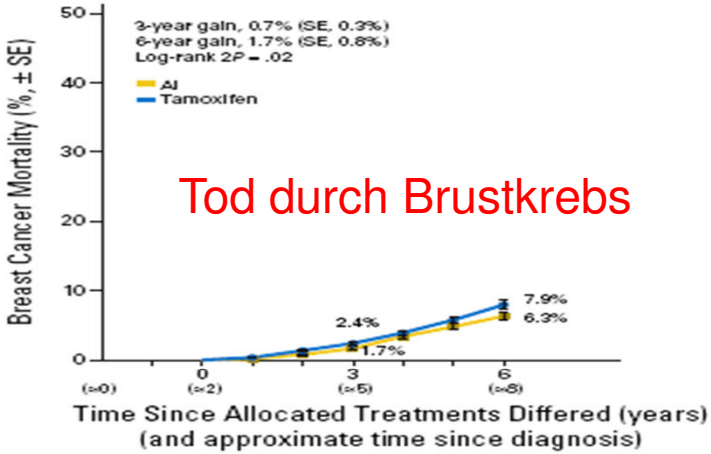
Rückfälle



Recurrence rates (% / year) and log-rank analyses

	Years 0–2 (≈2–4)	Years 2–4 (≈5–7)	Years 5+ (≈8+)
AI	1.68 (187 / 11,134)	2.78 (147 / 5,298)	3.21 (23 / 716)
Tamoxifen	2.76 (303 / 10,962)	2.99 (149 / 5,007)	3.87 (27 / 697)
Rate ratio, from	0.60 (SE, 0.07)	0.92 (SE, 0.11)	0.85 (SE, 0.27)
(O–E) / V	-61.0 / 118.4	-6.0 / 71.9	-2.0 / 12.1

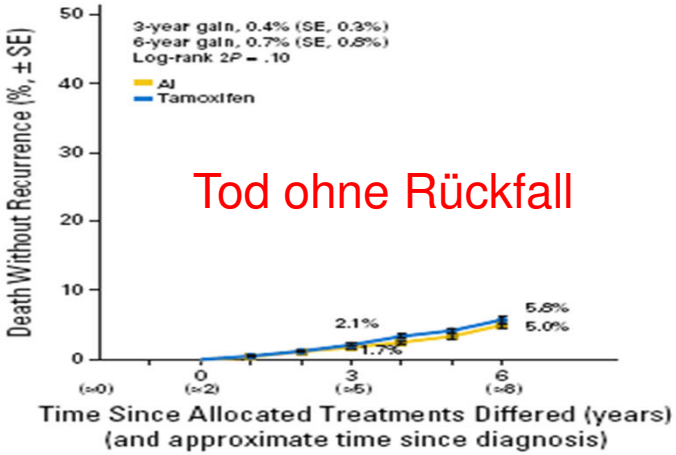
Tod durch Brustkrebs



Death rates (%/year: total rate—rate in women without recurrence) & log-rank analyses

	Years 0–2 (≈2–4)	Years 2–4 (≈5–7)	Years 5+ (≈8+)
AI	0.54 (SE, 0.07)	1.60 (SE, 0.17)	1.17 (SE, 0.39)
Tamoxifen	0.79 (SE, 0.08)	1.83 (SE, 0.18)	1.80 (SE, 0.48)
Rate ratio, from	0.68 (SE, 0.14)	0.88 (SE, 0.14)	0.65 (SE, 0.34)
(O–E) / V	-13.9 / 36.5	-5.8 / 45.5	-2.5 / 5.7

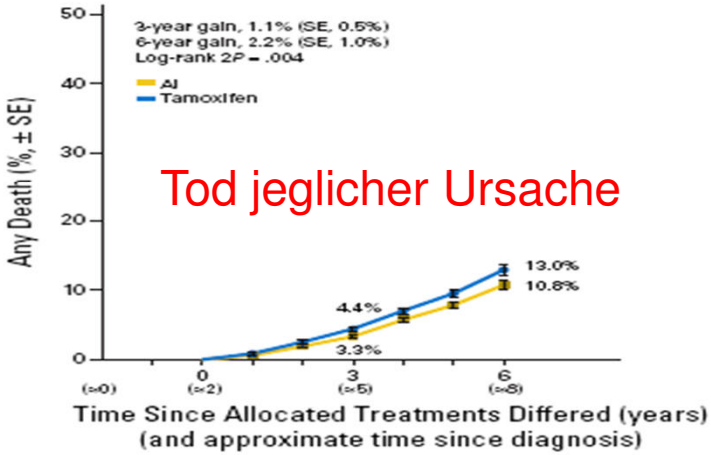
Tod ohne Rückfall



Death rates (% / year) and log-rank analyses

	Years 0–2 (≈2–4)	Years 2–4 (≈5–7)	Years 5+ (≈8+)
AI	0.57 (64 / 11,134)	1.04 (55 / 5,298)	1.12 (8 / 716)
Tamoxifen	0.70 (77 / 10,962)	1.22 (61 / 5,007)	1.58 (11 / 697)
Rate ratio, from	0.82 (SE, 0.15)	0.85 (SE, 0.17)	0.68 (SE, 0.38)
(O–E) / V	-7.0 / 35.0	-4.9 / 28.5	-1.8 / 4.7

Tod jeglicher Ursache



Death rates (% / year) and log-rank analyses

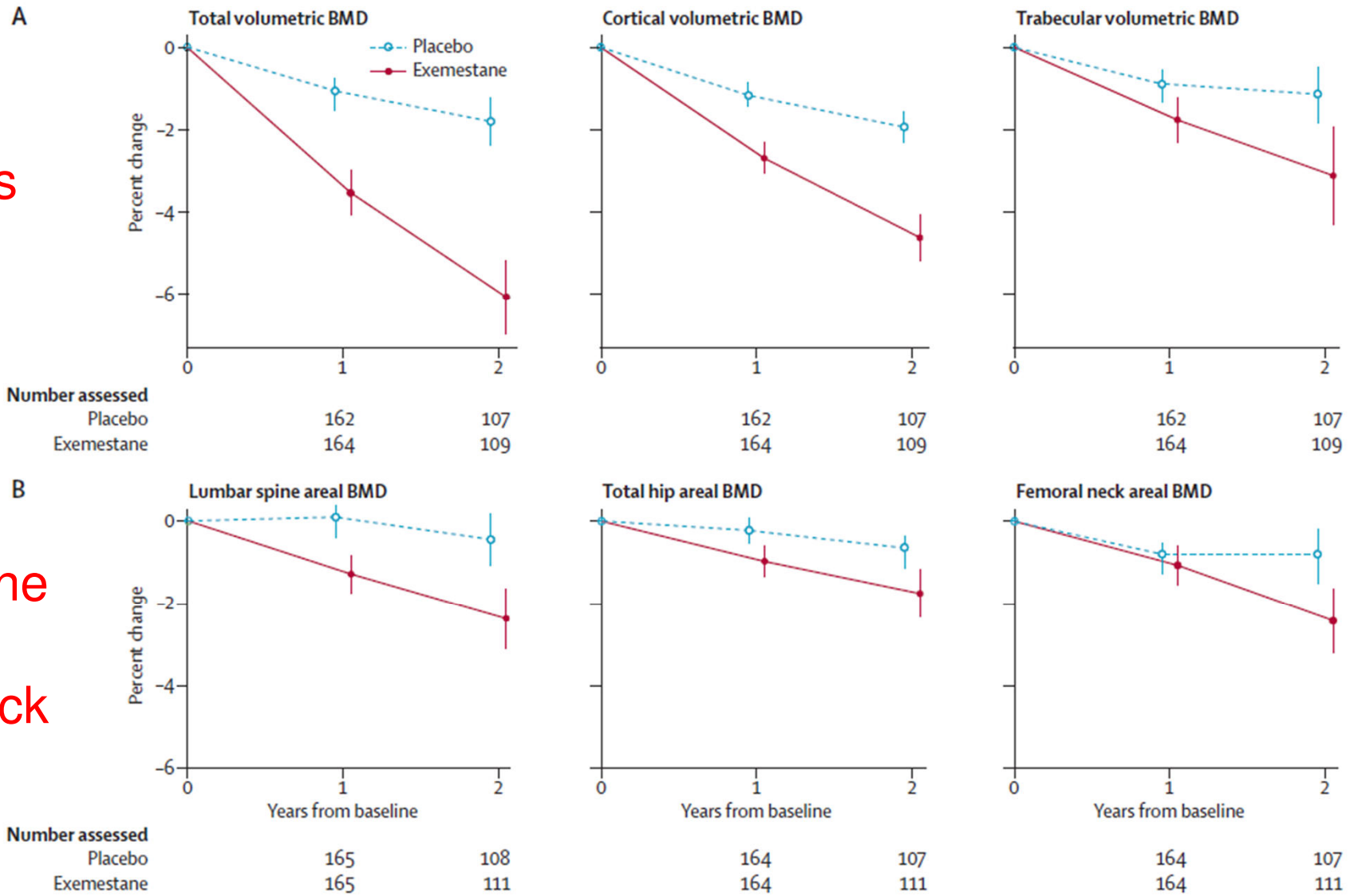
	Years 0–2 (≈2–4)	Years 2–4 (≈5–7)	Years 5+ (≈8+)
AI	1.11 (125 / 11,300)	2.59 (144 / 5,566)	2.20 (17 / 771)
Tamoxifen	1.47 (166 / 11,301)	2.95 (161 / 5,455)	3.22 (25 / 776)
Rate ratio, from	0.75 (SE, 0.10)	0.87 (SE, 0.11)	0.66 (SE, 0.25)
(O–E) / V	−20.9 / 71.5	−10.8 / 74.2	-4.3 / 10.3

Dowsett et al. JCO 2010

Effect of Exemestan on bone density (MAP.3 prevention trial)

distal radius

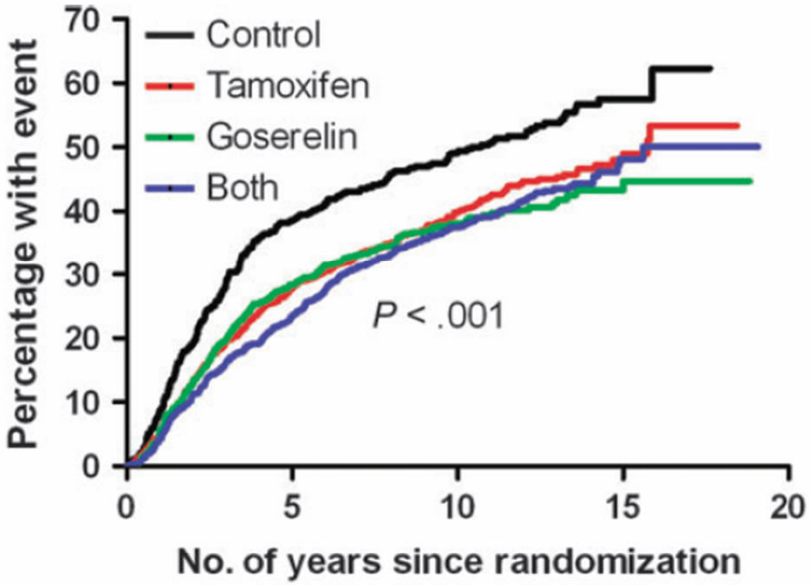
Lumbar spine
Hip
Femoral neck



Cheung et al. Lancet Oncology 2012

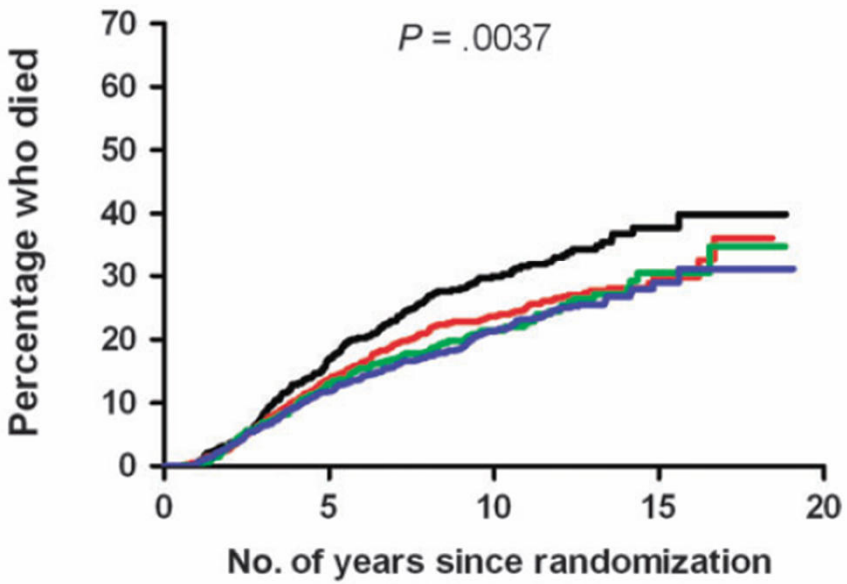
Breast-Ca. adjuvant: Nil vs. TAM vs. Goserelin vs. Both

DFS



No. at risk				
control	476	283	178	33
tamoxifen	879	613	367	53
goserelin	469	326	206	40
both	882	649	408	49

Overall survival



No. at risk				
control	476	382	242	44
tamoxifen	879	733	473	71
goserelin	469	395	262	45
both	882	747	500	62

2 years adjuvant treatment in premenopausal women

Hackshaw et al. JNCI 2009

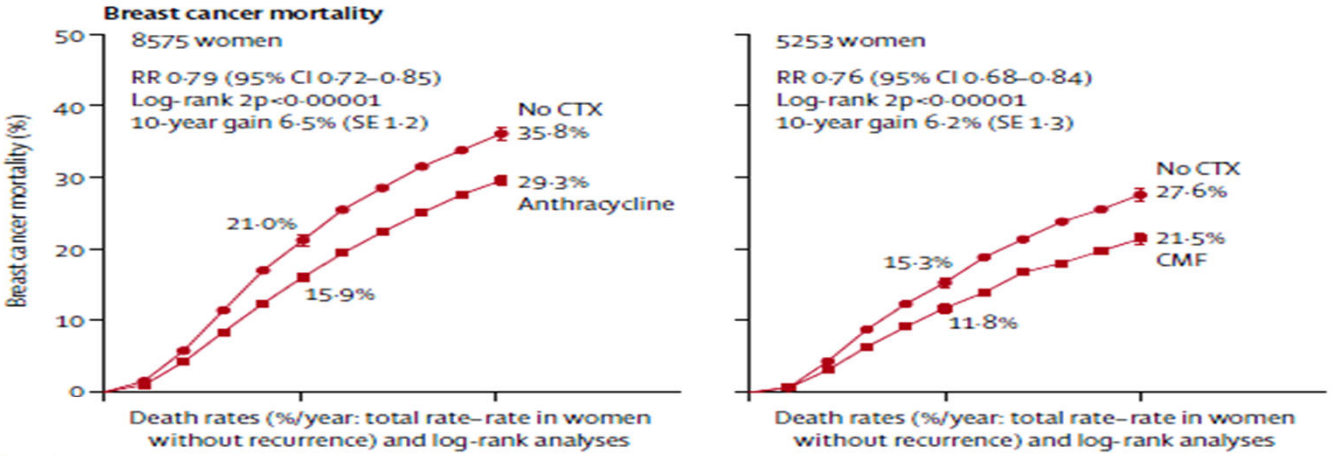
S3 Leitlinie Mamma-Ca. 2012

Sequenz RT und endokriner Therapie

RT-9	Therapiesequenz von endokriner System- und Radiotherapie
	Endokrine Therapieformen können simultan zur Radiotherapie oder sequenziell durchgeführt werden.
Level of Evidence **1a**	(Ahn, PH et al. 2005; Harris, EE et al. 2005; Hoeller, U et al. 2007; Pierce, LJ et al. 2005; Whelan, T et al. 2005)

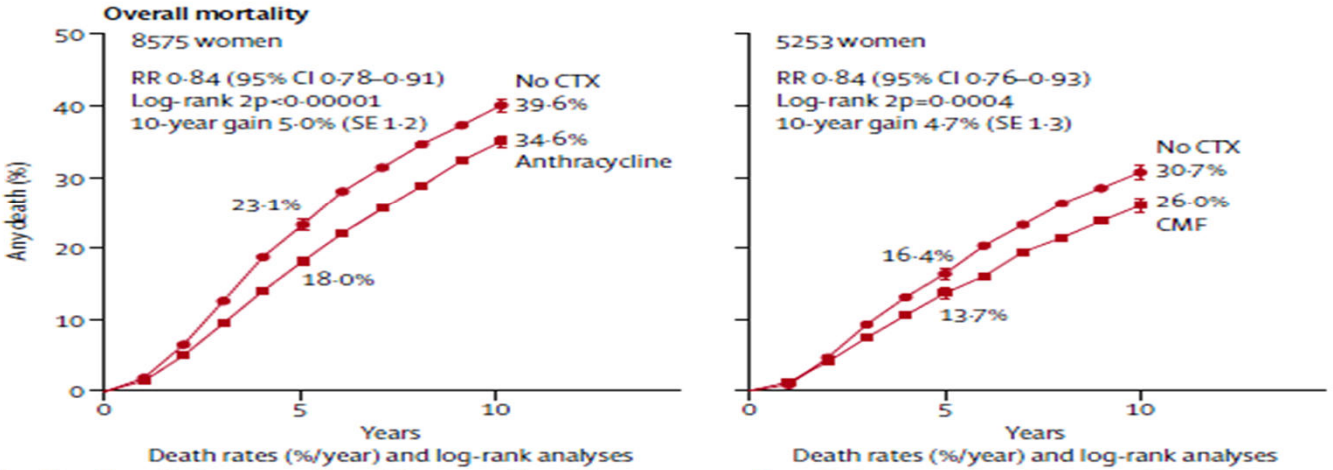
EBCTCB Meta-analysis

Adjuvant CMF/anthracycline vs. no adjuvant CHX



Allocation	Years 0–4	Years 5–9	Year 10+
CTX	3·38 SE 0·13	3·57 SE 0·16	2·83 SE 0·19
No CTX	4·77 SE 0·17	4·31 SE 0·21	2·98 SE 0·22
Rate ratio	0·73 SE 0·05	0·83 SE 0·07	0·92 SE 0·11
(O–E)/V	−97·5/307·0	−35·9/193·2	−6·7/81·0

Years 0–4	Years 5–9	Year 10+
2·51 SE 0·14	2·42 SE 0·16	1·80 SE 0·16
3·23 SE 0·17	3·14 SE 0·19	2·10 SE 0·18
0·75 SE 0·07	0·74 SE 0·08	0·82 SE 0·12
−43·5/151·3	−33·7/109·6	−11·9/59·1



Allocation	Years 0–4	Years 5–9	Year 10+
CTX	3·91 (811/20718)	4·62 (645/13 969)	4·39 (337/7680)
No CTX	5·25 (834/15 889)	4·93 (492/9975)	4·34 (259/5969)
Rate ratio	0·75 SE 0·05	0·92 SE 0·06	1·00 SE 0·09
(O–E)/V	−99·0/346·4	−19·1/234·6	−0·1/120·2

Years 0–4	Years 5–9	Year 10+
2·93 (357/12 167)	3·15 (286/9091)	3·14 (230/7318)
3·49 (410/11 756)	3·78 (326/8617)	3·39 (224/6612)
0·82 SE 0·07	0·81 SE 0·08	0·91 SE 0·10
−33·6/170·7	−28·5/137·2	−8·8/96·2

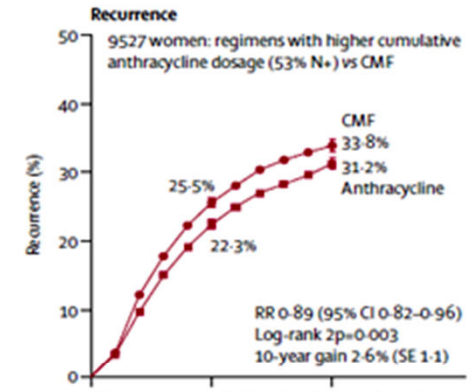
EBCTCG
Lancet 2012

EBCTCB Meta-analysis
Adjuvant CMF vs. anthracycline

Cumulative dosage
>240 mg/m² doxorubicin
or
360 mg/m² epirubicin
(eg. CAF or CEF)

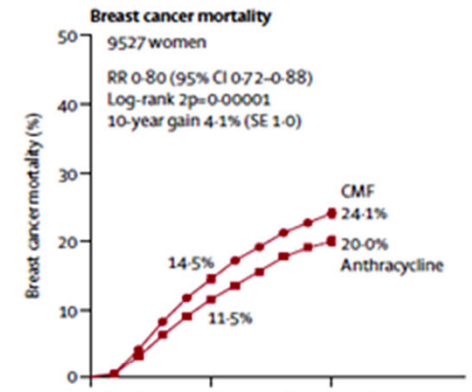
Standard 4xAC
Cumulative dosage
= 240 mg/m² doxorubicin

Regimens with
<60 mg/m² doxorubicin or
<90 mg/m² epirubicin
per cycle excluded



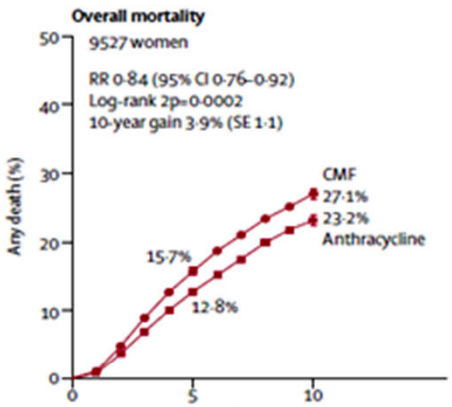
Recurrence rates (%/year) and log-rank analyses

Allocation	Years 0–4	Years 5–9	Year 10+
Anth	5·05 (989/19 575)	2·45 (238/9723)	1·64 (65/3973)
CMF	6·01 (1104/18 377)	2·57 (237/9236)	1·35 (54/4007)
Rate ratio	0·85 SE 0·04	1·00 SE 0·10	1·12 SE 0·21
(O–E)/V	−74·9/457·0	0·1/106·9	2·9/26·4



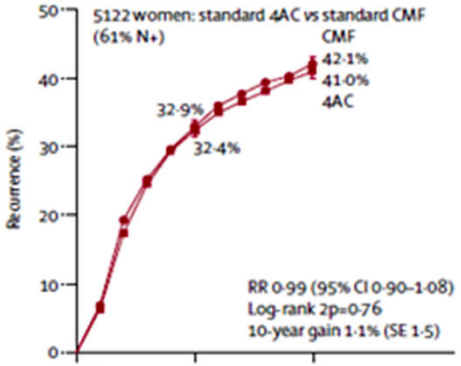
Death rates (%/year: total rate–rate in women without recurrence) and log-rank analyses

Allocation	Years 0–4	Years 5–9	Year 10+
Anth	2·39 SE 0·11	2·08 SE 0·14	0·91 SE 0·14
CMF	3·06 SE 0·12	2·50 SE 0·15	1·11 SE 0·16
Rate ratio	0·78 SE 0·06	0·84 SE 0·09	0·84 SE 0·20
(O–E)/V	−62·9/248·9	−19·3/111·5	−3·5/20·8



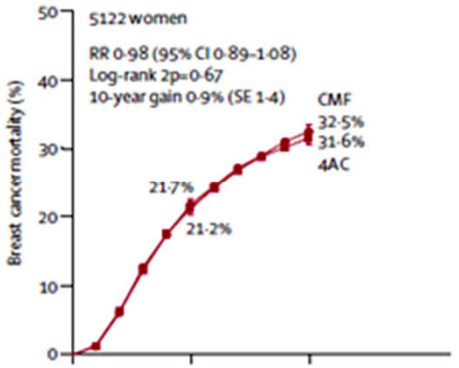
Death rates (%/year) and log-rank analyses

Allocation	Years 0–4	Years 5–9	Year 10+
Anth	2·67 (561/20 977)	2·60 (290/11 151)	1·99 (90/4528)
CMF	3·36 (669/19 894)	2·99 (319/10 661)	1·92 (87/4523)
Rate ratio	0·79 SE 0·05	0·88 SE 0·08	1·06 SE 0·16
(O–E)/V	−65·0/277·4	−17·8/137·2	2·5/40·9



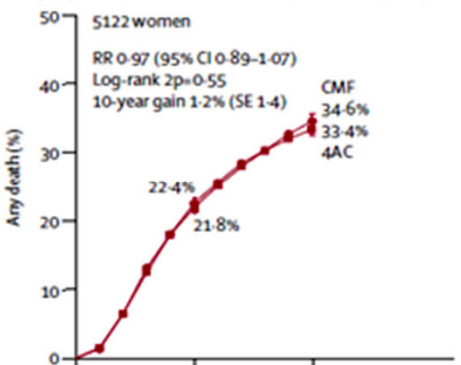
Recurrence rates (%/year) and log-rank analyses

Years 0–4	Years 5–9	Year 10+
7·97 (820/10 292)	2·86 (194/6795)	2·36 (100/4237)
8·21 (830/10 108)	2·99 (199/6658)	1·87 (76/4054)
0·98 SE 0·05	0·91 SE 0·10	1·28 SE 0·17
−8·7/355·5	−8·5/92·1	10·4/42·3



Death rates (%/year: total rate–rate in women without recurrence) and log-rank analyses

Years 0–4	Years 5–9	Year 10+
4·65 SE 0·20	2·94 SE 0·19	2·06 SE 0·20
4·81 SE 0·21	3·04 SE 0·20	1·96 SE 0·20
0·97 SE 0·06	0·97 SE 0·09	1·03 SE 0·15
−6·3/245·2	−3·7/111·6	1·5/48·9



Death rates (%/year) and log-rank analyses

Years 0–4	Years 5–9	Year 10+
4·81 (551/11 458)	3·33 (266/7994)	2·67 (141/5281)
5·00 (567/11 351)	3·48 (274/7883)	2·57 (131/5106)
0·97 SE 0·06	0·96 SE 0·09	1·01 SE 0·13
−8·1/254·9	−5·3/127·6	0·8/64·2

EBCTCG Lancet 2012

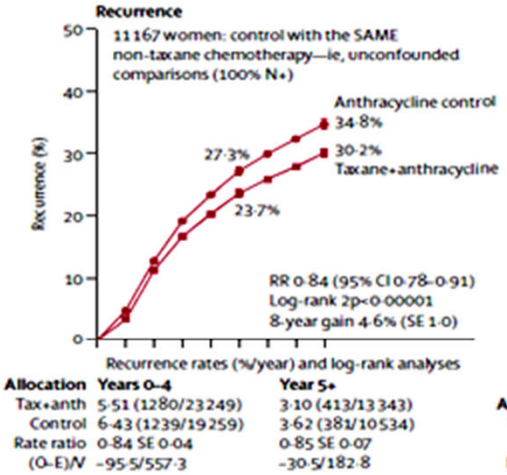
EBCTCB Meta-analysis

Adjuvant anthracycline vs. anthracycline + taxane

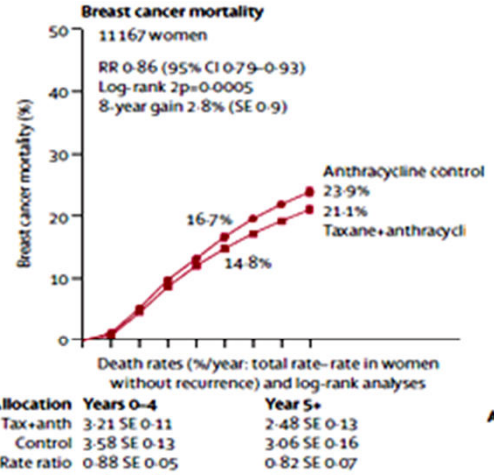
Anthracycline + Taxane

versus

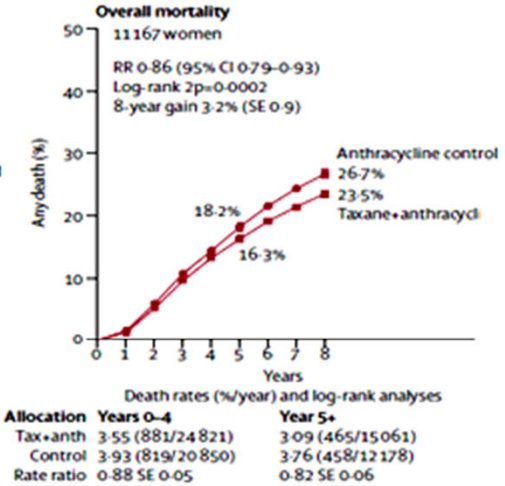
Anthracycline



Allocation	Years 0–4	Year 5+
Tax+anth	5·51 (1280/23 249)	3·10 (413/13 343)
Control	6·43 (1239/19 259)	3·62 (381/10 534)
Rate ratio	0·84 SE 0·04	0·85 SE 0·07
(O–E)/V	−95·5/557·3	−30·5/182·8



Allocation	Years 0–4	Year 5+
Tax+anth	3·21 SE 0·11	2·48 SE 0·13
Control	3·58 SE 0·13	3·06 SE 0·16
Rate ratio	0·88 SE 0·05	0·82 SE 0·07
(O–E)/V	−46·4/348·5	−33·3/172·3

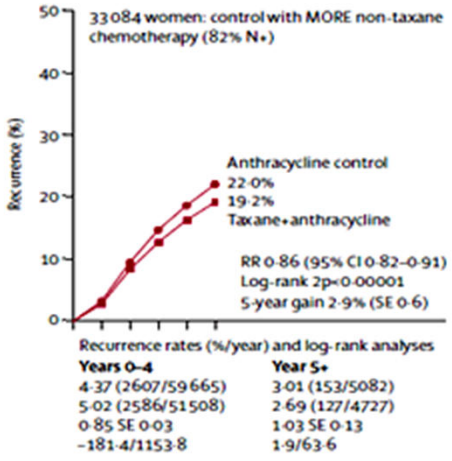


Allocation	Years 0–4	Year 5+
Tax+anth	3·55 (881/24 821)	3·09 (465/15 061)
Control	3·93 (819/20 850)	3·76 (458/12 178)
Rate ratio	0·88 SE 0·05	0·82 SE 0·06
(O–E)/V	−48·6/386·0	−41·3/213·4

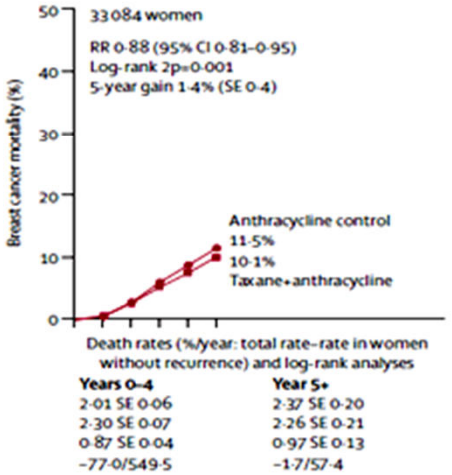
Anthracycline +Taxane

versus

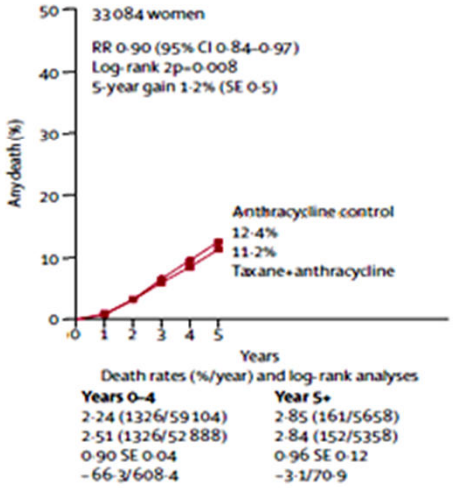
more Anthracycline



Years 0–4	Year 5+
4·37 (2607/59 665)	3·01 (153/5082)
5·02 (2586/51 508)	2·69 (127/4727)
0·85 SE 0·03	1·03 SE 0·13
−181·4/1153·8	1·9/63·6



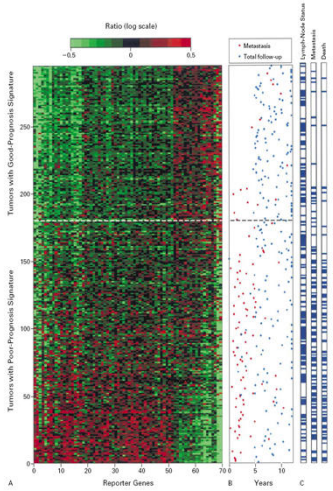
Years 0–4	Year 5+
2·01 SE 0·06	2·37 SE 0·20
2·30 SE 0·07	2·26 SE 0·21
0·87 SE 0·04	0·97 SE 0·13
−77·0/549·5	−1·7/57·4



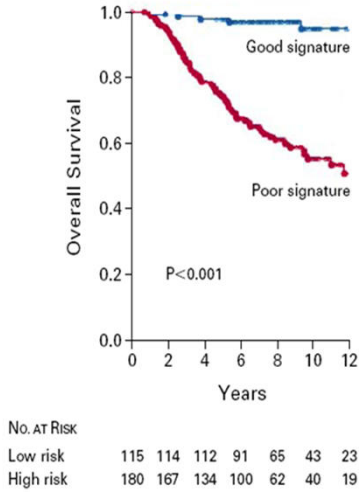
Years 0–4	Year 5+
2·24 (1326/59 104)	2·85 (161/5658)
2·51 (1326/52 888)	2·84 (152/5358)
0·90 SE 0·04	0·96 SE 0·12
−66·3/608·4	−3·1/70·9

EBCTCG Lancet 2012

Prospective Randomized Multicenter Trials Chemotherapy in N0 ?



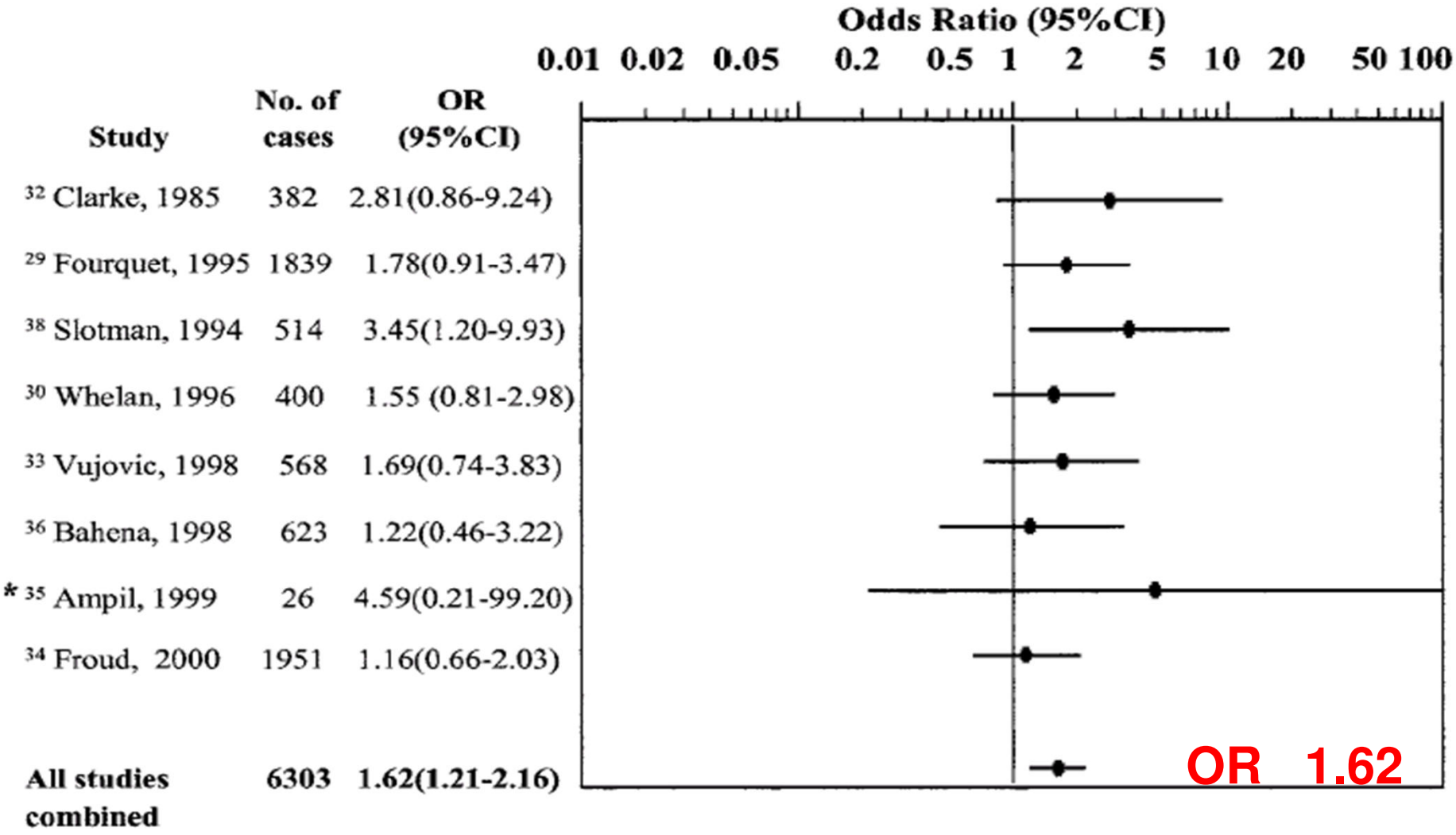
70 relevante genes



Van de Vijver et al. NEJM 2002

	MammaPrint® 70-Gene Profile	uPA /PAI-Test uPA/PAI-1	Oncotype DX® 21-Gene Recurrence Score
Tissue	Frozen or RNA preservative	Frozen	Paraffin embedded
% with "good risk"	~ 45%	~ 44%	~ 40-54%
Independent Factor	Yes – retrospective series	Yes – prospective phase III	Yes – retrospective phase III
Prospective Trial	MINDACT	Chemo N0 NNBC-3	TAILORx

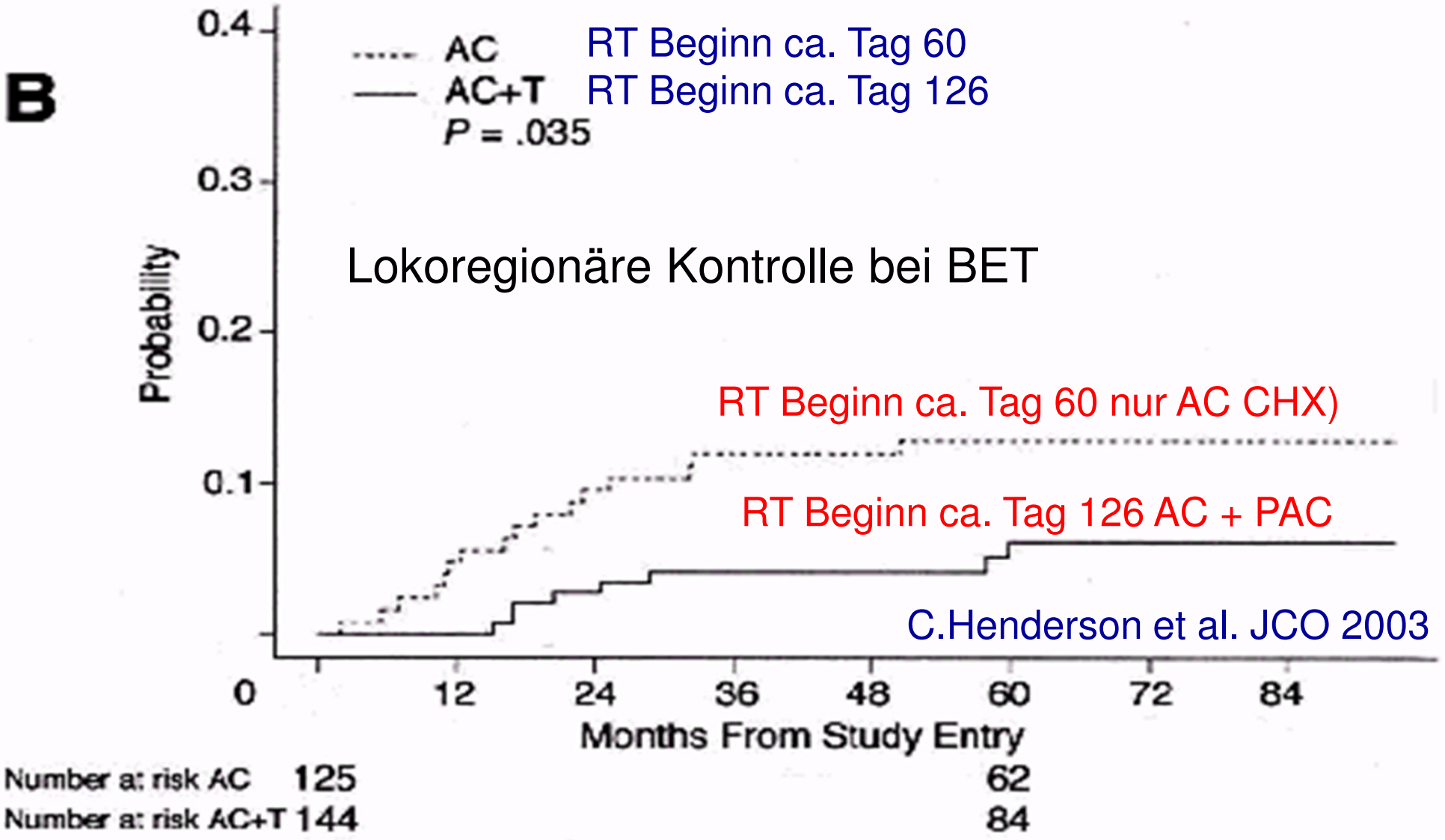
Meta-analysis: Early vs. late onset of RT



Local recurrences: >8 weeks better < 8 weeks better

Huang et al. JCO 2003

CALGB B 9344: 3xAC vs. 3x AC + 4x Paclitaxel



Lokoregionäre Kontrolle bei BET

RT Beginn ca. Tag 60 nur AC CHX)

RT Beginn ca. Tag 126 AC + PAC

C.Henderson et al. JCO 2003

S3 Leitlinie Mamma-Ca. 2012

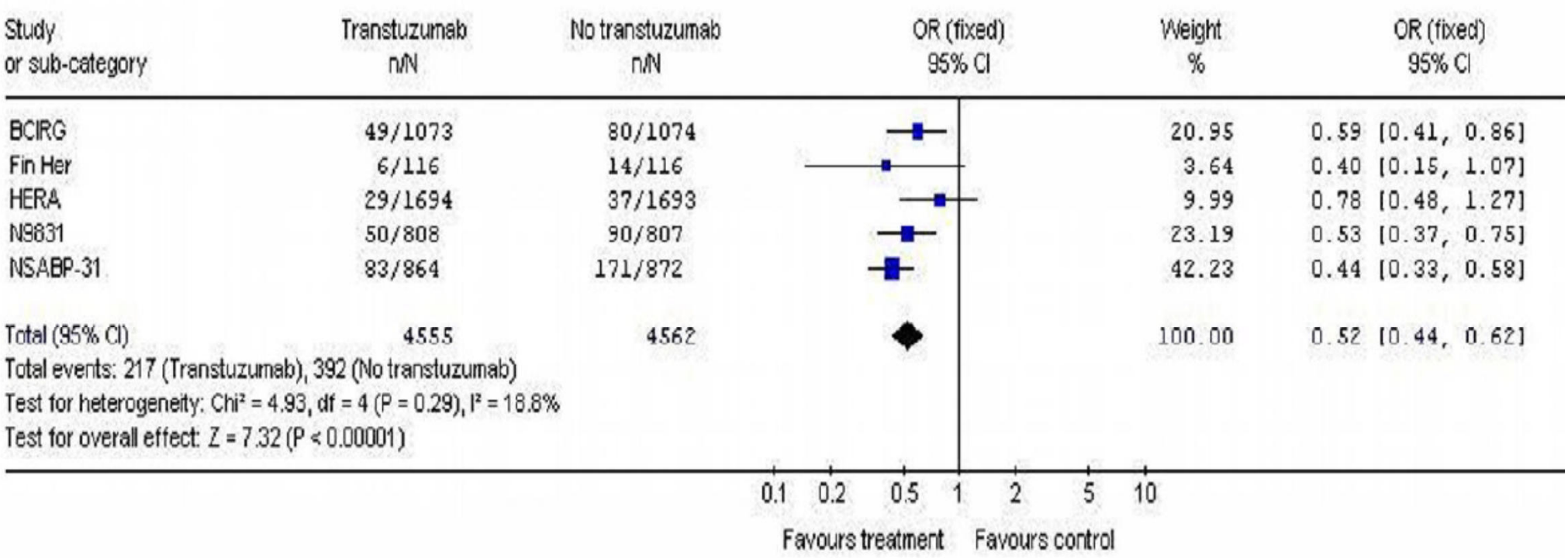
Sequenz RT und systemischer Chemotherapie

RT-7	Therapiesequenz von Chemo- und Radiotherapie
Empfehlungsgrad **B**	Die Überlegenheit einer speziellen zeitlichen Sequenz von Chemo- und Radiotherapie ist nicht ausreichend belegt. Grundsätzlich ist die Sequenz postoperativ von dem dominierenden Rezidivrisiko abhängig, zumal der optimale Zeitpunkt nicht ausreichend abgesichert ist.
Level of Evidence **1a**	(Cochrane: Hickey, BE et al. 2006; Kaufmann, M et al. 2010; NCCN 2011; NICE 2009; Poortmans, P 2007; Recht, A 2003; Recht, A 2010; Rouesse, J et al. 2006; Tsoutsou, PG et al. 2010)

Meta-analysis: Adjuvant trastuzumab

Gesamtüberleben

Review: Adjuvant Trastuzumab in the Treatment of HER-2-Positive Early Breast Cancer: A meta-analyses with 9117 patients. (Version 01)
Comparison: 01 Mortality Rate
Outcome: 01 Overall Survival

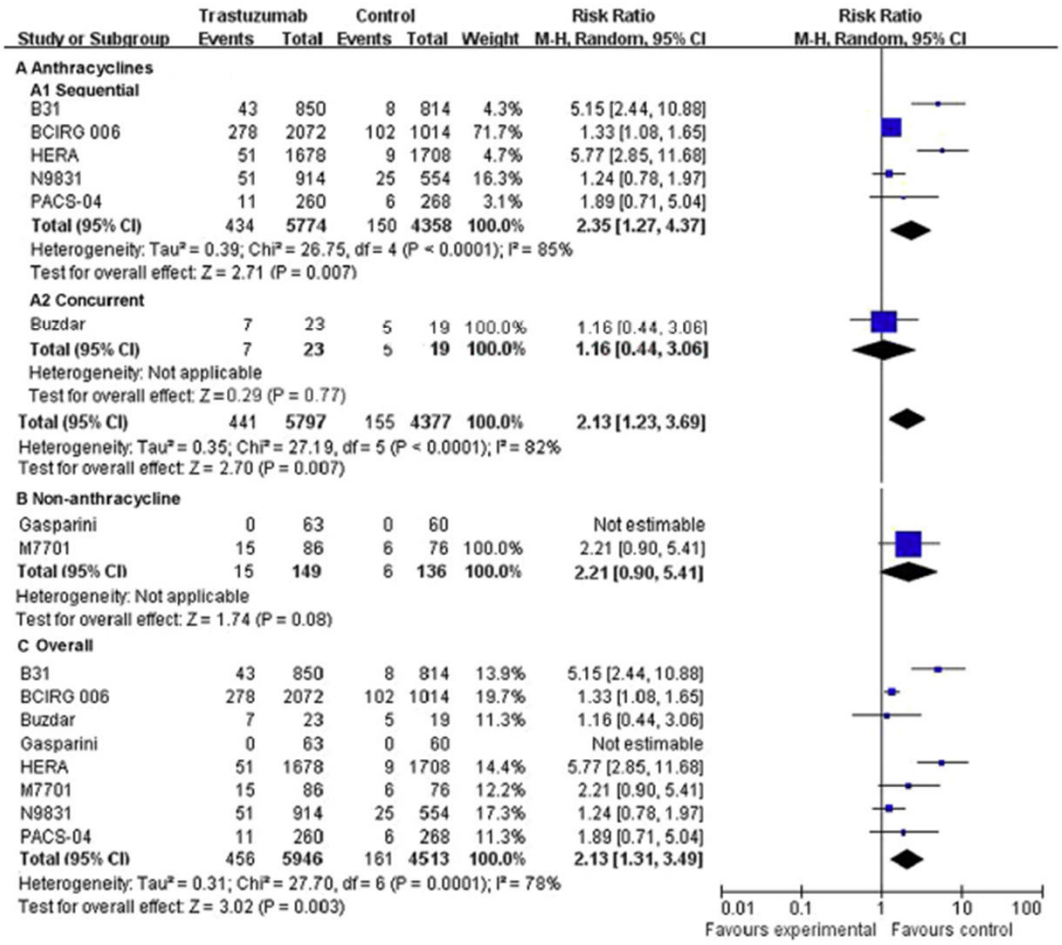


Viani et al. BMC Cancer 2007

Meta-analysis: Adjuvant Trastuzumab in breast cancer

Cardial toxicity

Relative Risk of asymptomatic LVEF decrease



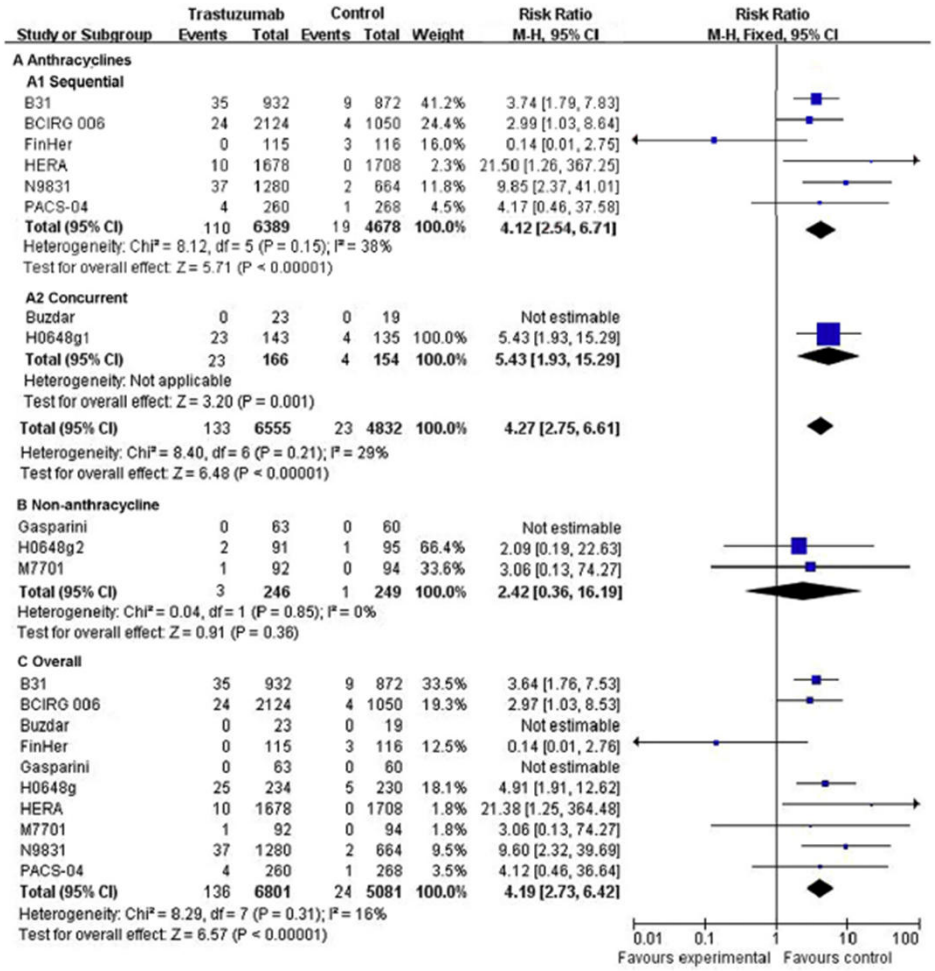
Study or Subgroup	Trastuzumab Events	Trastuzumab Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
A Anthracyclines						
A1 Sequential						
B31	43	850	8	814	4.3%	5.15 [2.44, 10.88]
BCIRG 006	278	2072	102	1014	71.7%	1.33 [1.08, 1.65]
HERA	51	1678	9	1708	4.7%	5.77 [2.85, 11.68]
N9831	51	914	25	554	16.3%	1.24 [0.78, 1.97]
PACS-04	11	260	6	268	3.1%	1.89 [0.71, 5.04]
Total (95% CI)	434	**5774**	150	**4358**	**100.0%**	**2.35 [1.27, 4.37]**
Heterogeneity: Tau² = 0.39; Chi² = 26.75, df = 4 (P < 0.0001); I² = 85%						
Test for overall effect: Z = 2.71 (P = 0.007)						
A2 Concurrent						
Buzdar	7	23	5	19	100.0%	1.16 [0.44, 3.06]
Total (95% CI)	7	**23**	5	**19**	**100.0%**	**1.16 [0.44, 3.06]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.29 (P = 0.77)						
Total (95% CI)	441	**5797**	155	**4377**	**100.0%**	**2.13 [1.23, 3.69]**
Heterogeneity: Tau² = 0.35; Chi² = 27.19, df = 5 (P < 0.0001); I² = 82%						
Test for overall effect: Z = 2.70 (P = 0.007)						
B Non-anthracycline						
Gasparini	0	63	0	60		Not estimable
M7701	15	86	6	76	100.0%	2.21 [0.90, 5.41]
Total (95% CI)	15	**149**	6	**136**	**100.0%**	**2.21 [0.90, 5.41]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.74 (P = 0.08)						
C Overall						
B31	43	850	8	814	13.9%	5.15 [2.44, 10.88]
BCIRG 006	278	2072	102	1014	19.7%	1.33 [1.08, 1.65]
Buzdar	7	23	5	19	11.3%	1.16 [0.44, 3.06]
Gasparini	0	63	0	60		Not estimable
HERA	51	1678	9	1708	14.4%	5.77 [2.85, 11.68]
M7701	15	86	6	76	12.2%	2.21 [0.90, 5.41]
N9831	51	914	25	554	17.3%	1.24 [0.78, 1.97]
PACS-04	11	260	6	268	11.3%	1.89 [0.71, 5.04]
Total (95% CI)	456	**5946**	161	**4513**	**100.0%**	**2.13 [1.31, 3.49]**
Heterogeneity: Tau² = 0.31; Chi² = 27.70, df = 6 (P = 0.0001); I² = 78%						
Test for overall effect: Z = 3.02 (P = 0.003)						

Risk Ratio M-H, Random, 95% CI

0.01 0.1 1 10 100

Favours experimental Favours control

Relative Risk of congestive heart failure



Study or Subgroup	Trastuzumab Events	Trastuzumab Total	Control Events	Control Total	Weight	Risk Ratio M-H, 95% CI
A Anthracyclines						
A1 Sequential						
B31	35	932	9	872	41.2%	3.74 [1.79, 7.83]
BCIRG 006	24	2124	4	1050	24.4%	2.99 [1.03, 8.64]
FinHer	0	115	3	116	16.0%	0.14 [0.01, 2.75]
HERA	10	1678	0	1708	2.3%	21.50 [1.26, 367.25]
N9831	37	1280	2	664	11.8%	9.85 [2.37, 41.01]
PACS-04	4	260	1	268	4.5%	4.17 [0.46, 37.58]
Total (95% CI)	110	**6389**	19	**4678**	**100.0%**	**4.12 [2.54, 6.71]**
Heterogeneity: Chi² = 8.12, df = 5 (P = 0.15); I² = 38%						
Test for overall effect: Z = 5.71 (P < 0.00001)						
A2 Concurrent						
Buzdar	0	23	0	19		Not estimable
H0648g1	23	143	4	135	100.0%	5.43 [1.93, 15.29]
Total (95% CI)	23	**166**	4	**154**	**100.0%**	**5.43 [1.93, 15.29]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.20 (P = 0.001)						
Total (95% CI)	133	**6555**	23	**4832**	**100.0%**	**4.27 [2.75, 6.61]**
Heterogeneity: Chi² = 8.40, df = 6 (P = 0.21); I² = 29%						
Test for overall effect: Z = 6.48 (P < 0.00001)						
B Non-anthracycline						
Gasparini	0	63	0	60		Not estimable
H0648g2	2	91	1	95	66.4%	2.09 [0.19, 22.63]
M7701	1	92	0	94	33.6%	3.06 [0.13, 74.27]
Total (95% CI)	3	**246**	1	**249**	**100.0%**	**2.42 [0.36, 16.19]**
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.91 (P = 0.36)						
C Overall						
B31	35	932	9	872	33.5%	3.64 [1.76, 7.53]
BCIRG 006	24	2124	4	1050	19.3%	2.97 [1.03, 8.53]
Buzdar	0	23	0	19		Not estimable
FinHer	0	115	3	116	12.5%	0.14 [0.01, 2.76]
Gasparini	0	63	0	60		Not estimable
H0648g	25	234	5	230	18.1%	4.91 [1.91, 12.62]
HERA	10	1678	0	1708	1.8%	21.38 [1.25, 364.48]
M7701	1	92	0	94	1.8%	3.06 [0.13, 74.27]
N9831	37	1280	2	664	9.5%	9.60 [2.32, 39.69]
PACS-04	4	260	1	268	3.5%	4.12 [0.46, 36.64]
Total (95% CI)	136	**6801**	24	**5081**	**100.0%**	**4.19 [2.73, 6.42]**
Heterogeneity: Chi² = 8.29, df = 7 (P = 0.31); I² = 16%						
Test for overall effect: Z = 6.57 (P < 0.00001)						

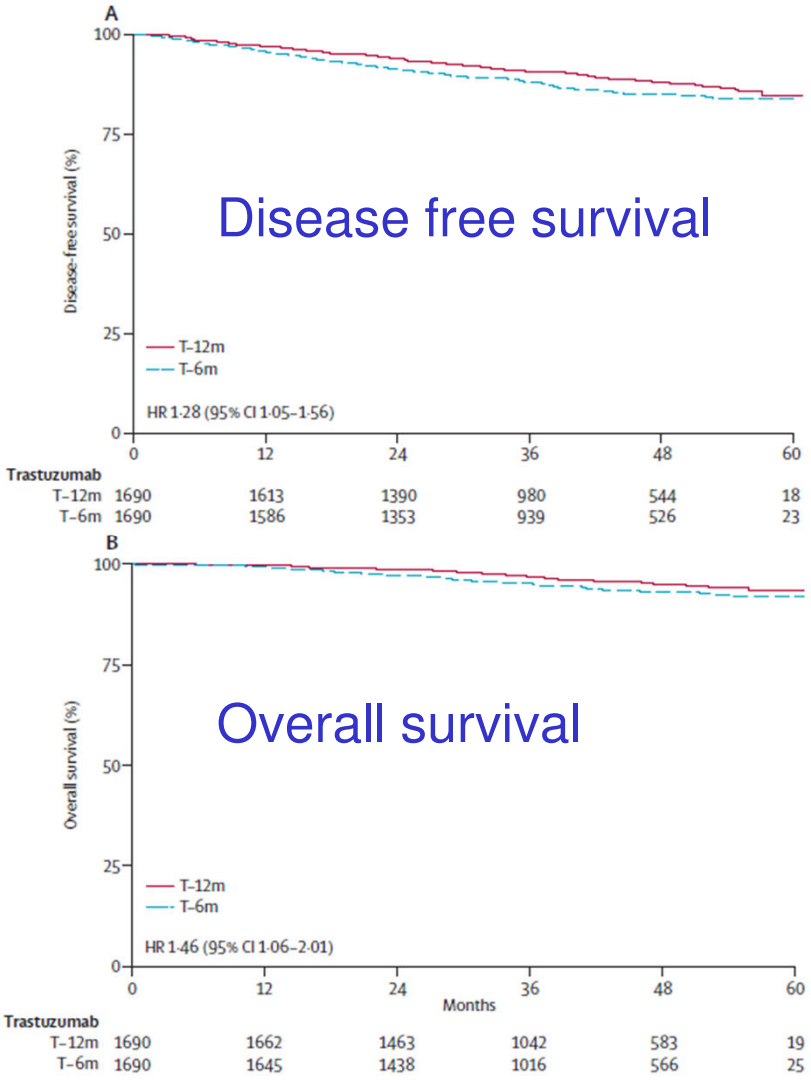
Risk Ratio M-H, Fixed, 95% CI

0.01 0.1 1 10 100

Favours experimental Favours control

Chen et al. Cancer Treatment Reviews 2011

6 months vs. 12 months adjuvant Trastuzumab in breast cancer



Disease free survival

Overall survival

Disease free survival

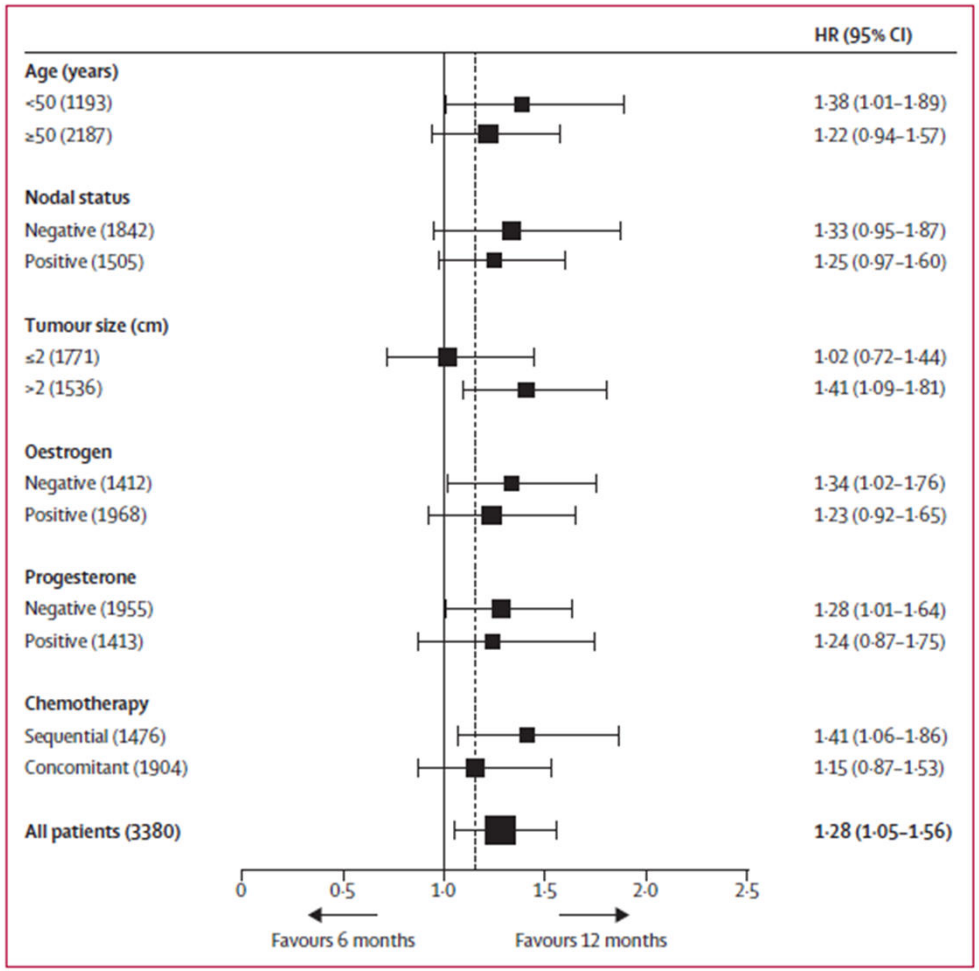


Figure 3: **Univariate forest plot for disease-free survival**

Pivot et al. Lancet Oncol 2013

S3 Leitlinie Mamma-Ca. 2012

Sequenz RT und Antikörpertherapie

RT-8	Therapiesequenz von Antikörper- und Radiotherapie
	Die simultane Applikation von Trastuzumab zur Strahlentherapie kann verantwortet werden, sofern keine Bestrahlung des Mammaria interna-Lymphabflusses vorgesehen ist.
GCP	(Azria, D et al. 2010b; Balduzzi, A et al. 2010; Belkacemi, Y et al. 2008; Belkacemi, Y et al. 2010; Chargari, C et al. 2011a; Chargari, C et al. 2011b; Halyard, MY et al. 2009; Kirova, YM et al. 2009; Romond, EH et al. 2005; Shaffer, R et al. 2009)

Adjuvant bisphosphonates in breast Cancer

Analysis 3.11. Comparison 3 Early Breast Cancer (EBC), Outcome 11 Survival in EBC: bisphosphonate vs control.

Review: Bisphosphonates and other bone agents for breast cancer

Comparison: 3 Early Breast Cancer (EBC)

Outcome: 11 Survival in EBC: bisphosphonate vs control

Survival

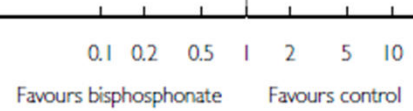
Study or subgroup	bisphosphonate n/N	control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Coleman 2010 (1)	108/1681	122/1678		0.88 [0.69, 1.13]
Diel 1998 (2)	32/157	59/145		0.50 [0.35, 0.72]
Gnant 2009 (3)	26/899	39/904		0.67 [0.41, 1.09]
Hershman 2008 (4)	0/53	0/50		0.0 [0.0, 0.0]
Kristensen 2008 (5)	253/460	266/493		1.02 [0.91, 1.14]
Powles 2002 (6)	98/530	129/539		0.77 [0.61, 0.98]
Saarto 2001 (7)	64/139	55/143		1.20 [0.91, 1.58]
Total (95% CI)	**3919**	**3952**		**0.84 [0.68, 1.04]**

Total events: 581 (bisphosphonate), 670 (control)

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 21.77$, df = 5 (P = 0.00058); $I^2 = 77\%$

Test for overall effect: Z = 1.59 (P = 0.11)

Test for subgroup differences: Not applicable



Wong et al. Cochrane Review 2012

Guidelines Breast
Version 2014.1D

Bisphosphonate beim Mammakarzinom

	Oxford / AGO LoE	GR	
➢ Hyperkalzämie	1a	A	++
➢ Reduktion skelettaler Komplikationen	1a	A	++
➢ Reduktion von Knochenschmerzen	1a	A	++
➢ Therapie nach ossärer Progression	5	D	++
➢ In Kombination mit neoadjuvanter Chemotherapie	2b	C	+/-
➢ Prävention von Knochenmetastasen / Überlebensvorteil			
➢ Adjuvant bei postmenopausalen Patientinnen	1a	A	+
➢ Bei fortgeschrittener Erkrankung	2b	C	+/-
➢ Prävention von MammaCa durch orale BPs (bei Frauen unter BP-Therapie mit niedriger Knochendichte)	3b	C	+/-