UKD Universitätsklinikum Düsseldorf

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

UTZ Universitätstumorzentrum Düsseldorf
Comprehensive Cancer Center
Als Onkologisches Spitzenzentrum gefördert durch die Deutsche Krebshilfe e.V.

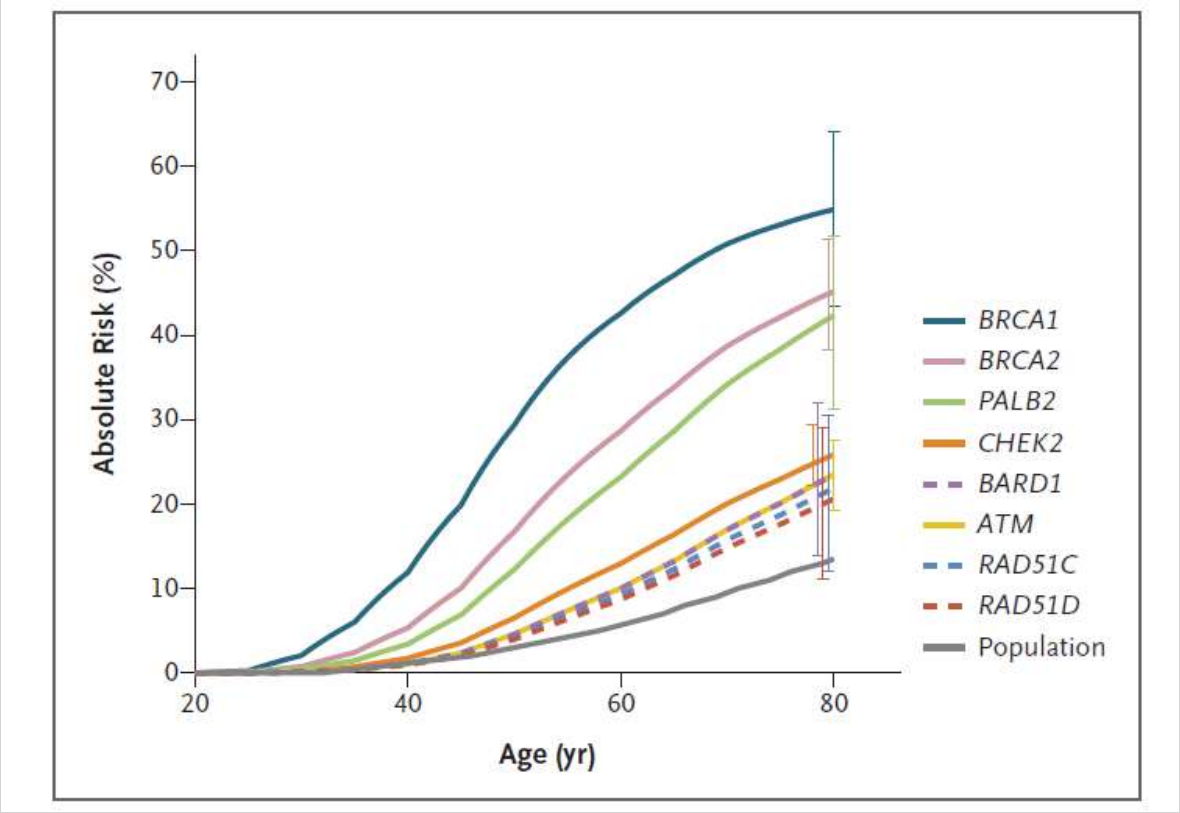
Mammakarzinom
Refresherkurs DEGRO 2023

Wilfried Budach / David Krug

Kliniken für Strahlentherapie und Radioonkologie
Universitätskliniken Düsseldorf / Kiel

Estimated Cumulative Risk of Breast Cancer with Protein-Truncating Variants in 8 Genes

Guidelines Breast
Version 2021.1D

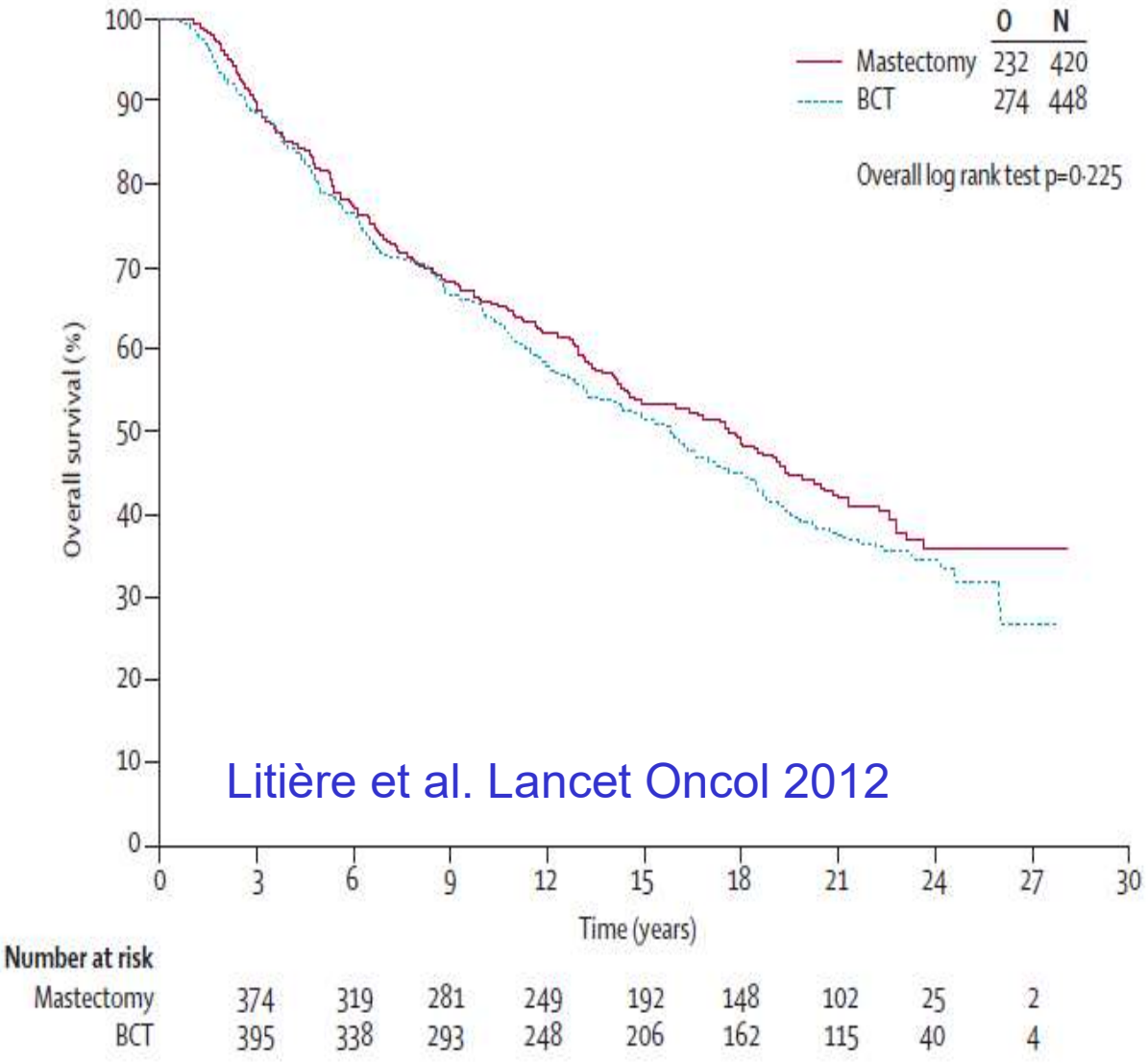


Shown are cumulative risks of breast cancer through 80 years of age for protein-truncating variants in 8 genes that had significant evidence of an association with breast cancer overall, on the basis of estimated odds ratios from population-based studies. Baseline absolute risks were derived from population incidences in the United Kingdom in 2016. The I bars indicate 95% confidence intervals.

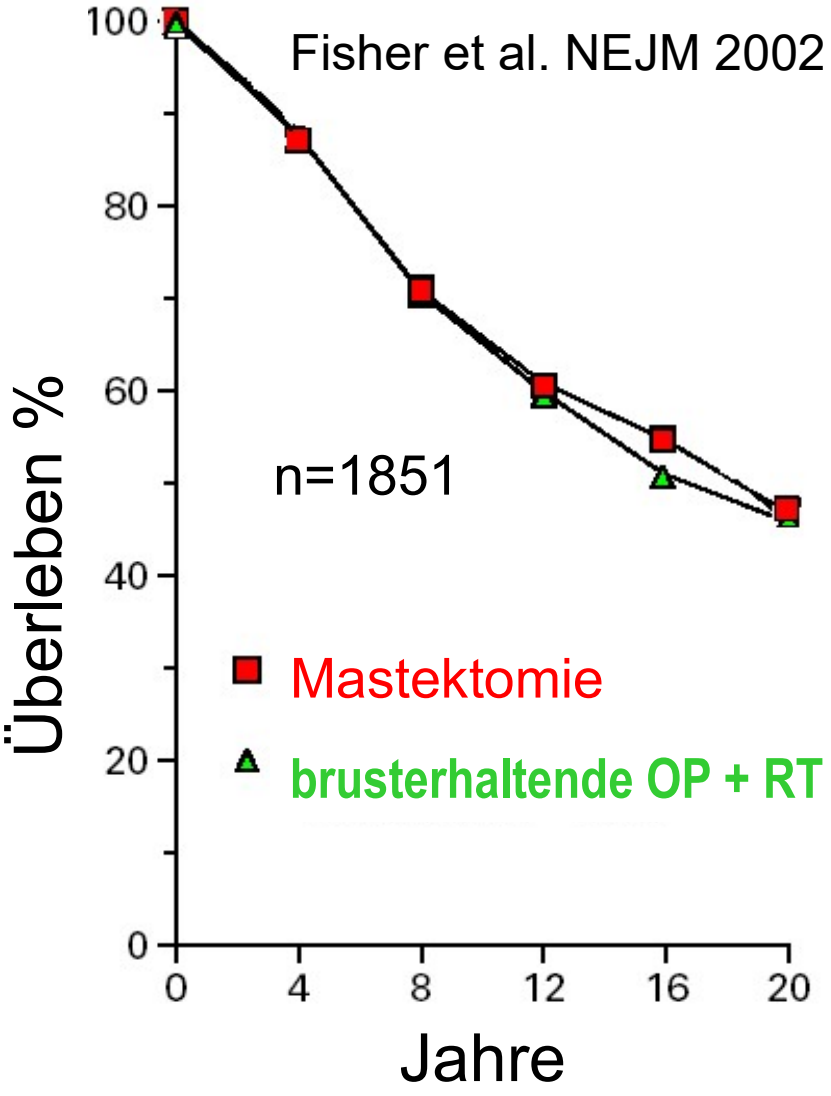
Dorling L, Carvalho S, Allen J et al. Breast-Cancer Risk Genes — Association Analysis in More than 113,000 Women. January 20, 2021 DOI: 10.1056/NEJMoa1913948

Brusterhaltende Operation vs. radikale Mastektomie beim Mamma-Ca.

Metaanalyse der EBCTCG, n=3100, NEJM 1995



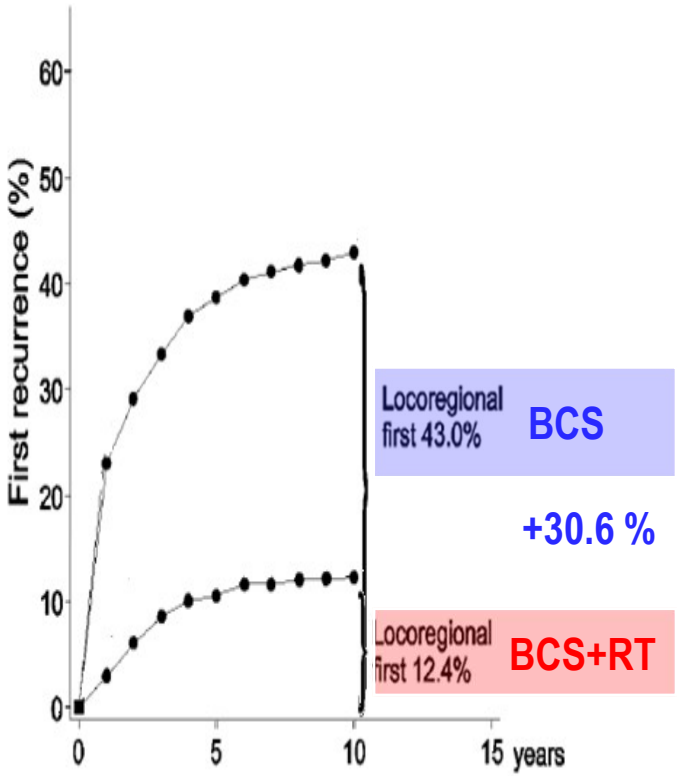
Litière et al. Lancet Oncol 2012



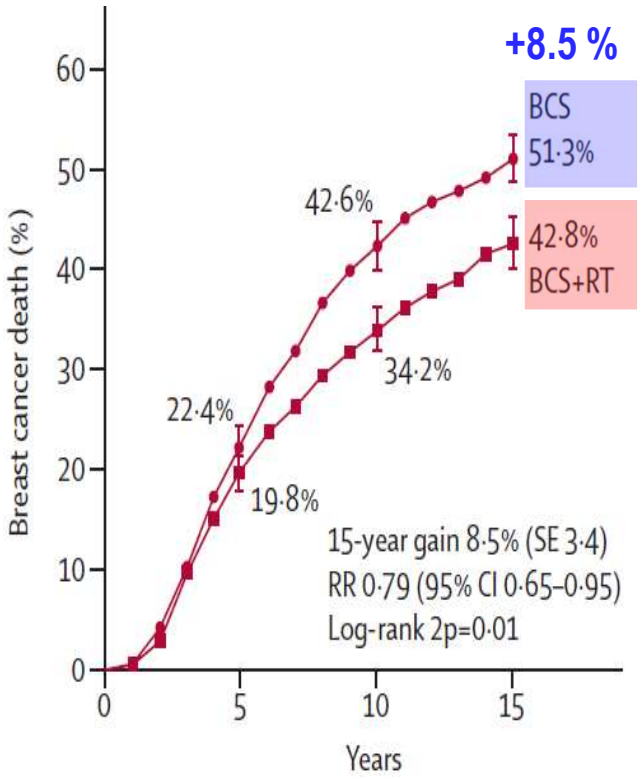
Radiotherapy after breast-conserving surgery

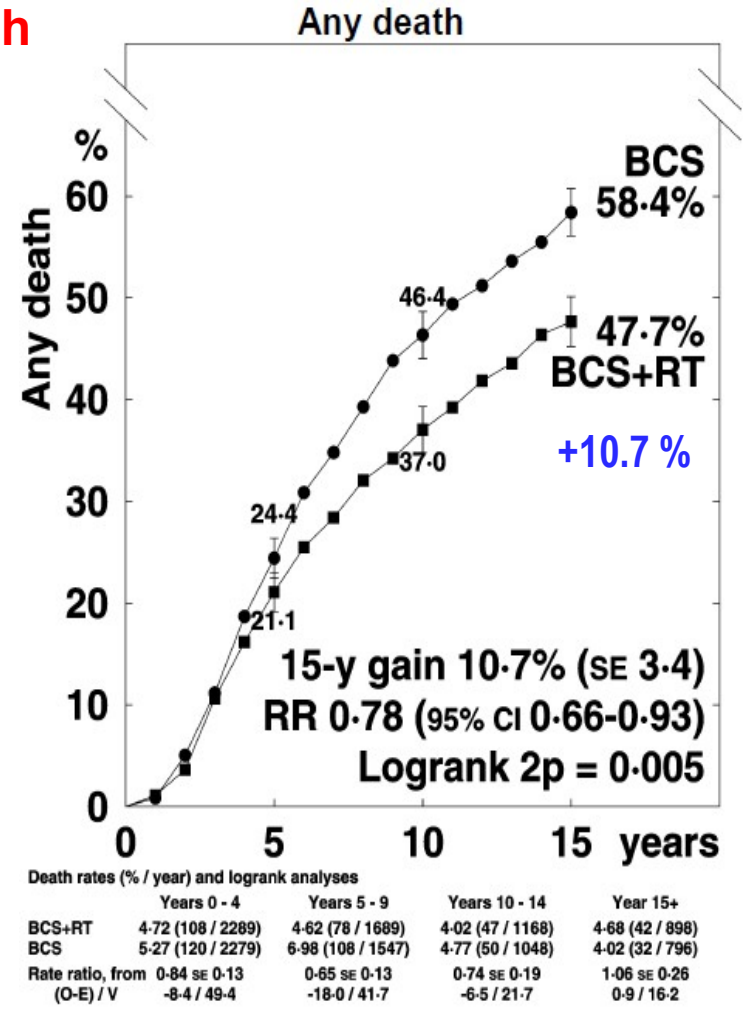
(1050 women, 10 years results) EBCTCG Lancet 2011

pN+: locoregional relapse



pN+: breast cancer death





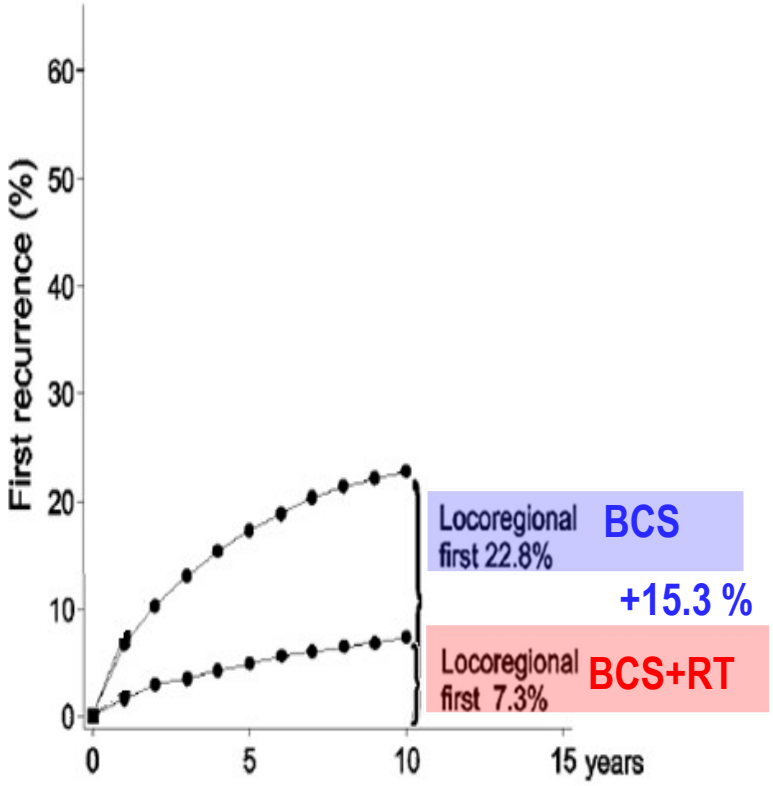
Death rates (% / year) and logrank analyses

	Years 0 - 4	Years 5 - 9	Years 10 - 14	Year 15+
BCS+RT	4·72 (108 / 2289)	4·62 (78 / 1689)	4·02 (47 / 1168)	4·68 (42 / 898)
BCS	5·27 (120 / 2279)	6·98 (108 / 1547)	4·77 (50 / 1048)	4·02 (32 / 796)
Rate ratio, from	0·84 SE 0·13	0·65 SE 0·13	0·74 SE 0·19	1·06 SE 0·26
(O-E) / V	-8·4 / 49·4	-18·0 / 41·7	-6·5 / 21·7	0·9 / 16·2

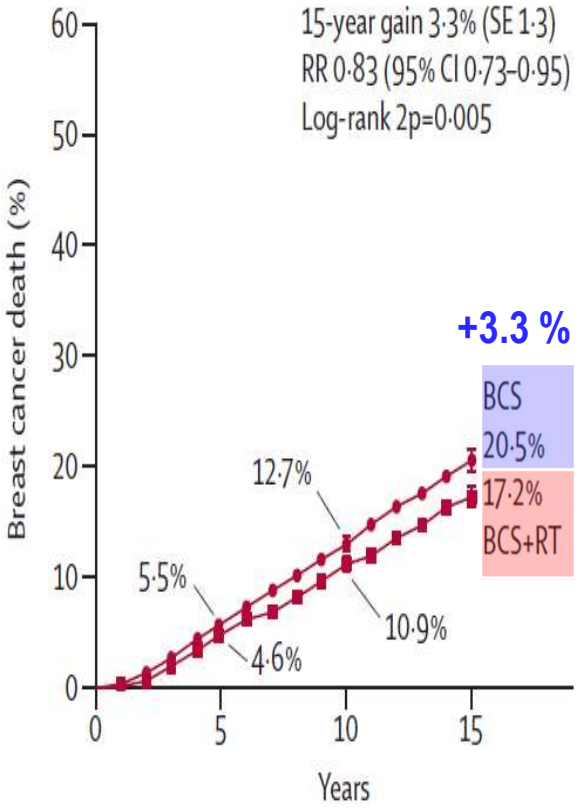
Radiotherapy after breast-conserving surgery

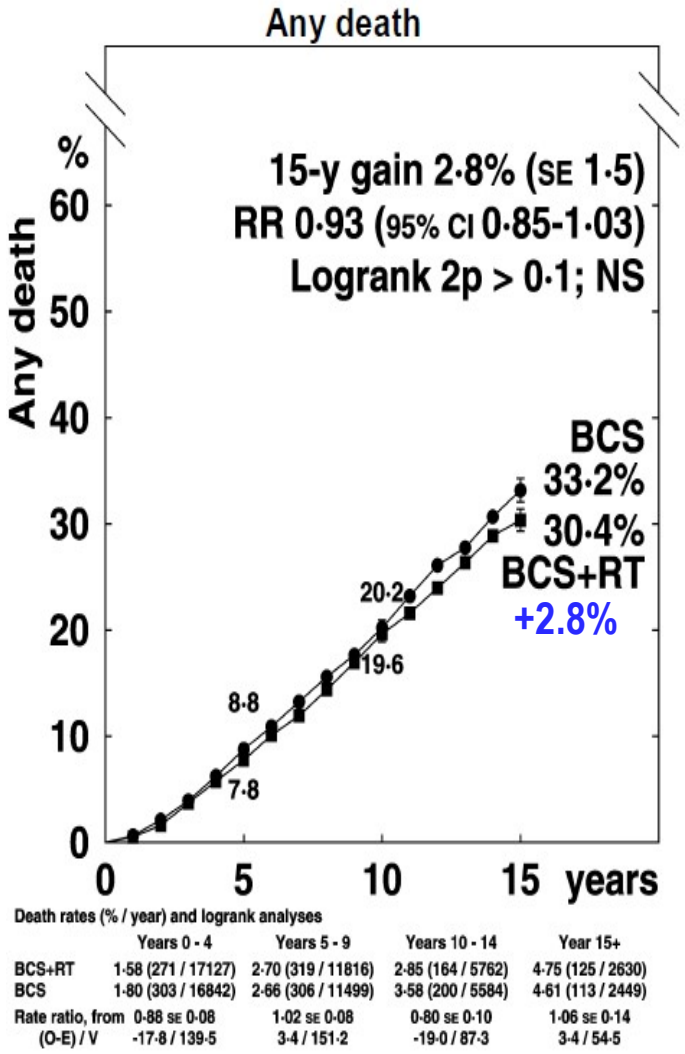
(7287 women, 10 years results) EBCTCG Lancet 2011

pN0: locoregional relapse



pN0: breast cancer death



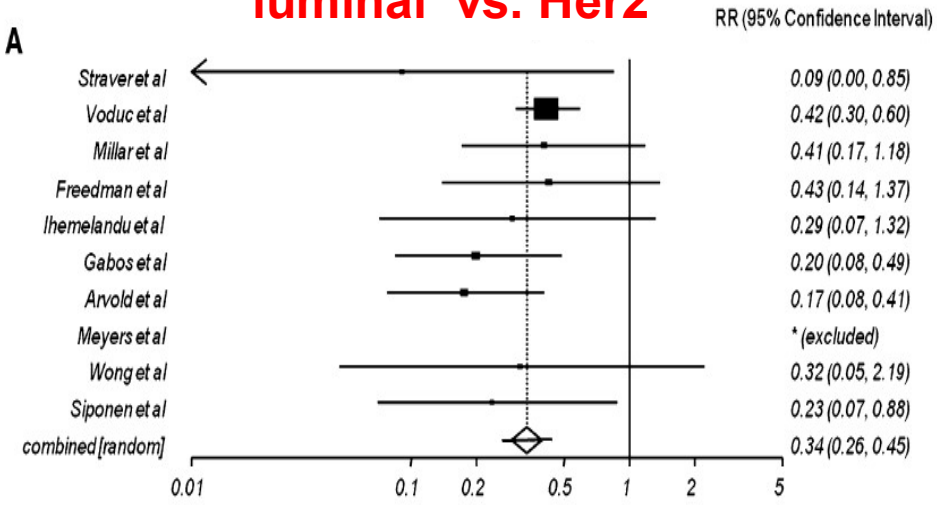


Death rates (% / year) and logrank analyses

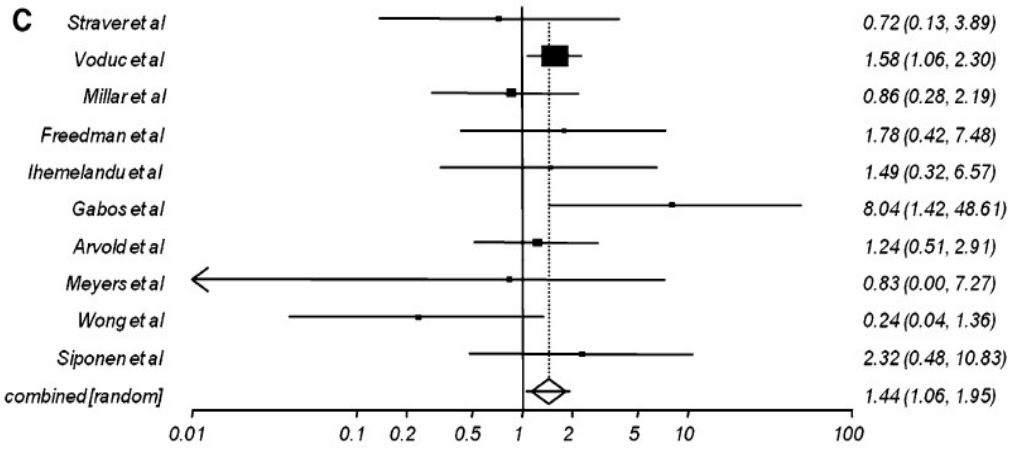
	Years 0 - 4	Years 5 - 9	Years 10 - 14	Year 15+
BCS+RT	1·58 (271 / 17127)	2·70 (319 / 11816)	2·85 (164 / 5762)	4·75 (125 / 2630)
BCS	1·80 (303 / 16842)	2·66 (306 / 11499)	3·58 (200 / 5584)	4·61 (113 / 2449)
Rate ratio, from	0·88 SE 0·08	1·02 SE 0·08	0·80 SE 0·10	1·06 SE 0·14
(O-E) / V	-17·8 / 139·5	3·4 / 151·2	-19·0 / 87·3	3·4 / 54·5

Breast cancer: Locoregional recurrence after BCT by molecular subtype

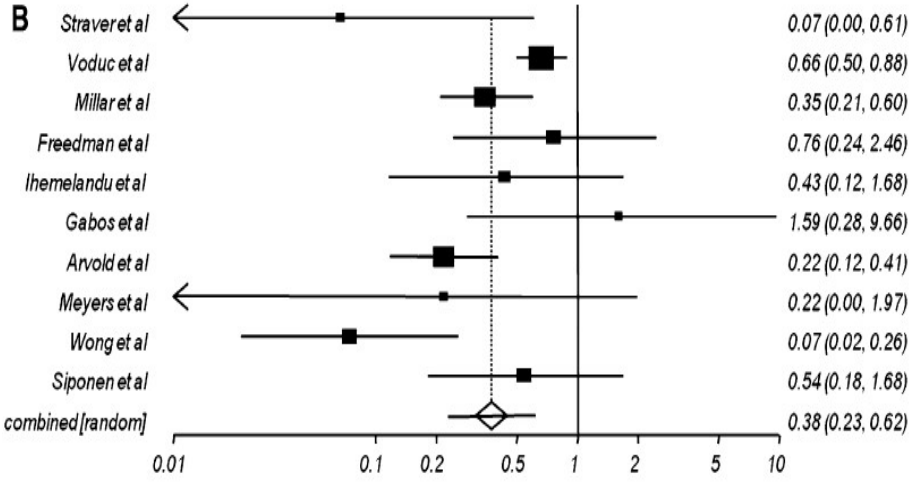
luminal vs. Her2



triple neg. vs. Her2



luminal vs. triple neg.



Lowery et al. Breast Cancer Res Treat 2012

Breast cancer: Radiation schedules trials on hypofractionated radiotherapy after breast conserving surgery

	Study name	Total dose	Fractionation	Week 1	Week 2	Week 3	Week 4	Week 5
	Conventional fraction	50 Gy	2 Gy × 25	●●●●●	●●●●●	●●●●●	●●●●●	●●●●●
Moderate HFX	UK RMH/GOC pilot	39 Gy 42.9 Gy	3 Gy × 13 3.3 Gy × 13	●●● ●●●	●● ●●	●●● ●●●	●● ●●	●●● ●●●
Moderate HFX	START A	39 Gy 41.6 Gy	3 Gy × 13 3.2 Gy × 13	●●● ●●●	●● ●●	●●● ●●●	●● ●●	●●● ●●●
Moderate HFX	START B	40 Gy	2.67 Gy × 15	●●●●●	●●●●●	●●●●●		
Moderate HFX	Canadian	42.5 Gy	2.66 Gy × 16	●●●●●	●●●●●	●●●●●	●	
Moderate HFX	DBCG HYPO 2020	40 Gy	2.67 Gy x 15	●●●●●	●●●●●	●●●●●		
Moderate HFX	China 2020	43.5 Gy	2.9 Gy x 15	●●●●●	●●●●●	●●●●●		
Moderate HFX	HypoG-01	40 Gy	2.67 Gy x 15	●●●●●	●●●●●	●●●●●		
Ultra HFX	UK FAST	28.5 Gy 30 Gy	5.7 Gy × 5 6 Gy × 5	● ●	● ●	● ●	● ●	● ●
Ultra HFX	UK FAST Forward	26 Gy 27 Gy	5.2 Gy x 5 5.4 Gy x 5	●●●●● ●●●●●				

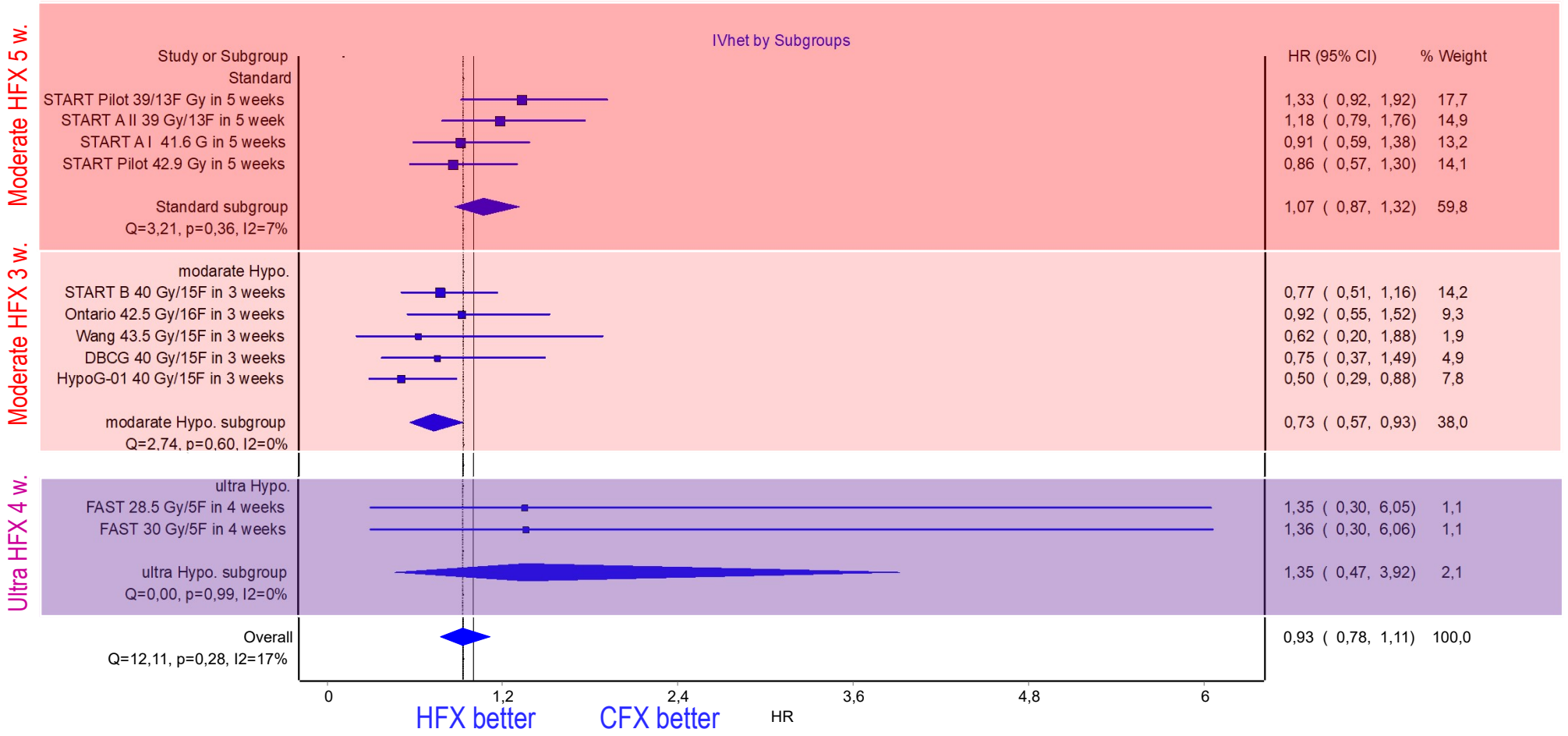
Patients characteristics in hypofractionaton trials

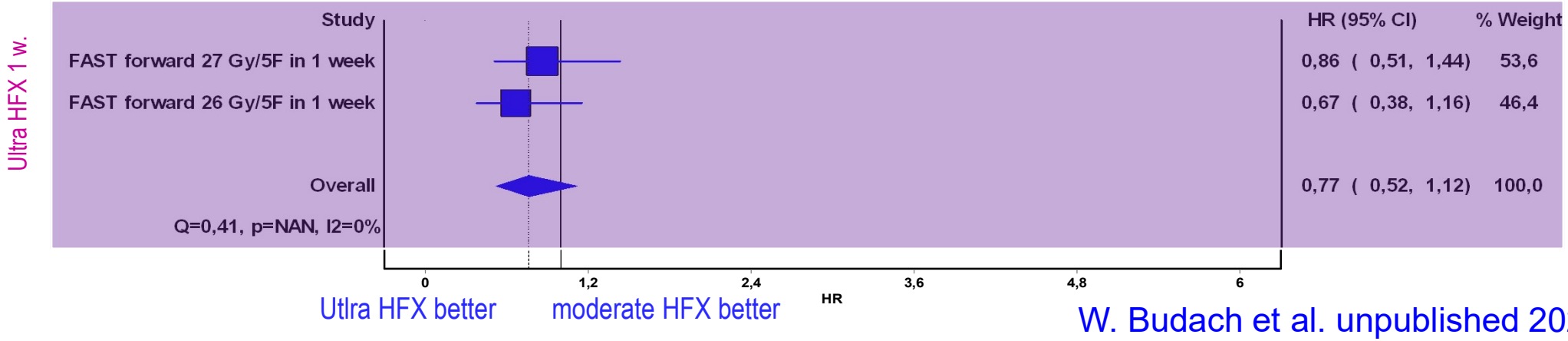
(adjuvant after breast conserving surgery)

	RMH/GOC	START A	START B	Canadian	DBCG	China	FAST	FAST FORWARD
Site	UK	UK	UK	Canada	Denmark	China	UK	UK
Years accrual	1986–98	1998–2002	1999–2001	1993–96	2009-2014	2010-2015	2004-2007	2011-2014
Standard arm	50 Gy/25F	50 Gy/25F	50 Gy/25F	50 Gy/25F	50 Gy /25 F	50 Gy /25 F	50 Gy/25F	40 Gy/15F
Experimental arm A	42.9 Gy/13F	41.6 Gy/13F	40 Gy/15F	42.5 Gy/16F	40 Gy / 15 F	43.5 Gy /15 F	30 Gy/5F	27 Gy/5F
Experimental arm B	39 Gy/13F	39 Gy/13F	N/A	N/A	N/A	N/A	28.5 Gy/5F	26 Gy/5F
Mean age (years)	54.5	57.2	57.4	Not reported	59.0	60.2	62.9	61
Node + (%)	32.7	28.8	22.8	0	8.1	20.3	0	18.5
Mastectomy (%)	0	15	8	0	0	0	0	6.4
Tumor size ≥ T2 (%)	42.5[a]	48.6	35.9	20	15.7	0	N/A(<3cm)	31.3
Boost (%)	74.5	60.6	42.6	0	23.2	100	0	24.7
Chemotherapy (%)	13.9	35.5	22.2	11	31.2	65.4	0	25.1
Regional RT (%)	20.6	14.2	7.3	0	0	3.9	0	0

Moderate HFX 5 w. Moderate HFX 3 w. Ultra HFX 4 w. Ultra HFX 1 w.

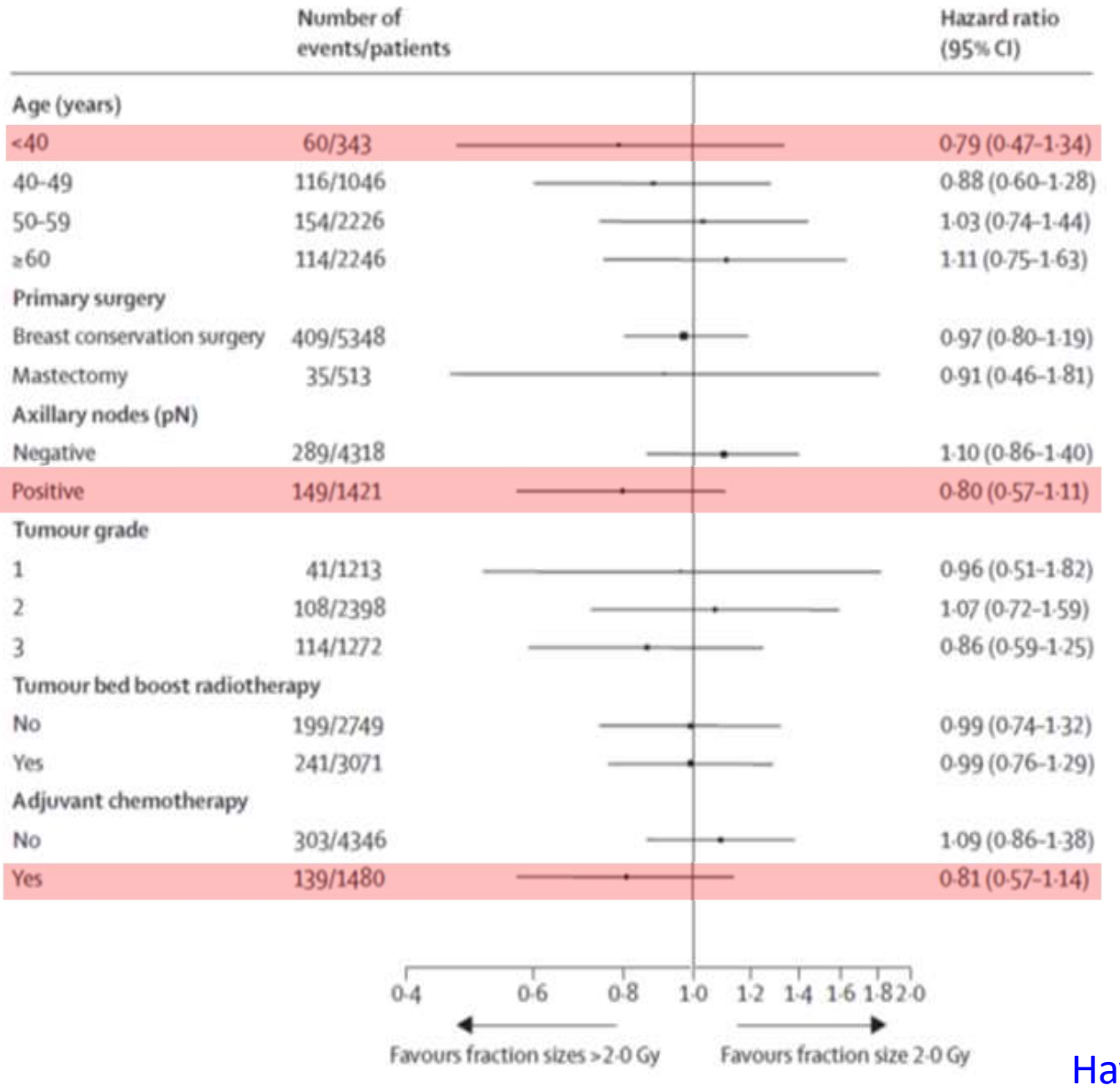
Metaanalyse Hypofraktionierte vs. konventionell fraktionierter RT:





W. Budach et al. unpublished 2023

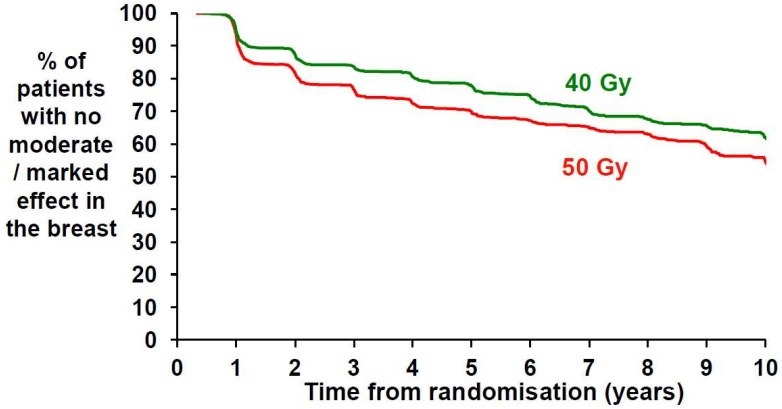
START A and B hypofractionation trials: Subgroup analysis on locoregional relapse



Haviland Lancet Oncol 2013

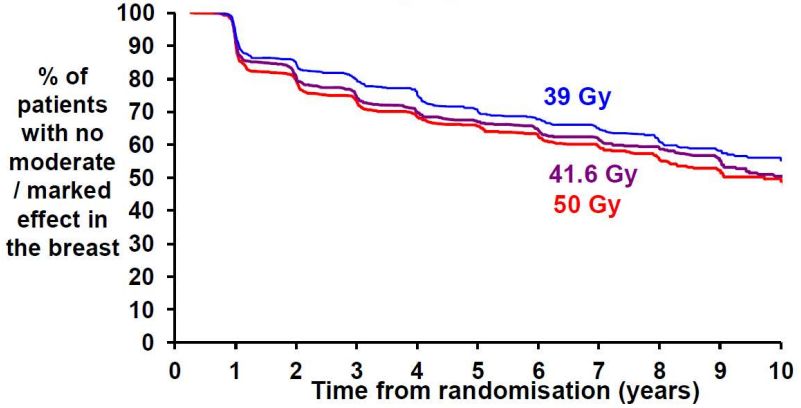
10 y. Update START-trials: Late effects

Trial B: Any moderate/marked effect in the conserved breast (physician assessments)



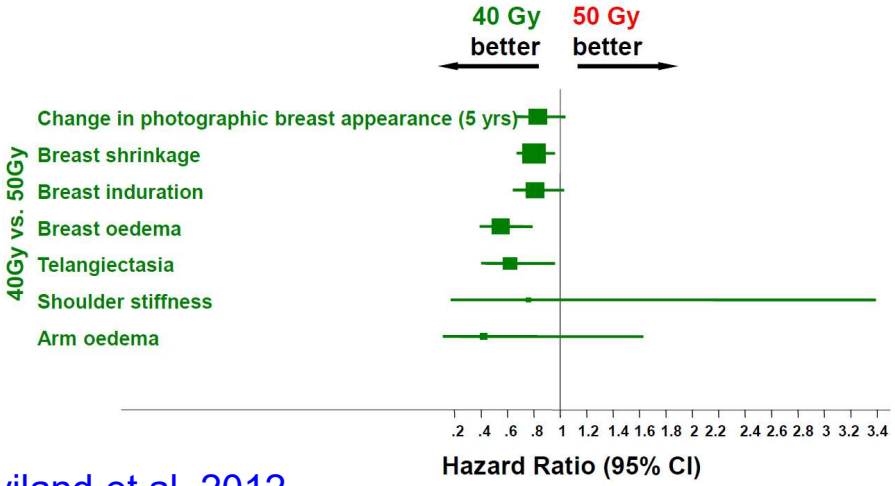
	Hazard Ratio (95%CI)	Absolute difference at 10 years (95%CI)
40Gy vs. 50Gy	0.77 (0.66-0.89)	-8.1% (-12.4 to -3.7%)

Trial A: Any moderate/marked adverse effect in conserved breast (physician assessments)

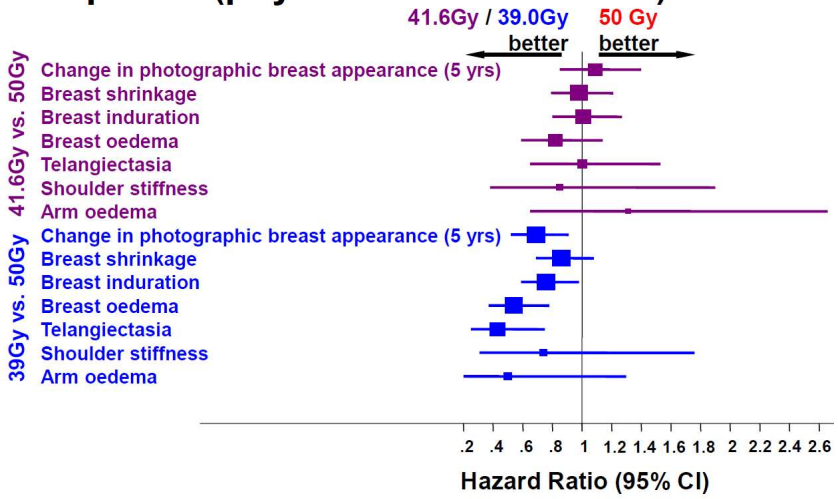


	Hazard Ratio (95%CI)	Absolute difference at 10 years (95%CI)
41.6Gy vs. 50Gy	0.94 (0.79-1.11)	-2.1% (-7.9 to 3.7%)
39Gy vs. 50Gy	0.80 (0.67-0.96)	-4.1% (-12.9 to -1.4%)

Trial B: Normal tissue effects – individual endpoints (physician assessments)



Trial A: Normal tissue effects – individual endpoints (physician assessments)



Haviland et al. 2012

Hypofractionated vs. Conventionally Fractionated RT in Breast Cancer

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with conventionally fractionated radiation therapy	Risk with hypofractionated radiation therapy				
Local recurrence-free survival (LR-FS) at 10 years	Study population 70 per 1,000[1]	66 per 1,000 (54 to 80)	HR 0.94 (0.77 to 1.15)	7095 (4 RCTs)	⊕⊕⊕⊕ HIGH	Local control
Cosmesis assessed with fair/poor on 4-point scale, follow-up: range 42 months-12 years	Study population 311 per 1,000	280 per 1,000 (252 to 314)	RR 0.90 (0.81 to 1.01)	2103 (4 RCTs)	⊕⊕⊕⊕ HIGH	Cosmesis
Mortality at 10 years	Study population 166 per 1,000[1]	153 per 1,000 (135 to 171)	HR 0.91 (0.80 to 1.03)	5685 (3 RCTs)	⊕⊕⊕⊕ HIGH	Mortality
Late subcutaneous toxicity assessed with ≥ Grade 2 on 4-point scale, follow-up: median 6 years	Study population		RR 0.93 (0.83 to 1.05)	5130 (4 RCTs)	⊕⊕⊕⊕ HIGH [2]	Late Tocicity
	4 per 1,000	4 per 1,000 (3 to 4)				
Breast cancer-specific survival (BC-SS) at 10 years	Study population 123 per 1,000[1]	113 per 1,000 (98 to 130)	HR 0.91 (0.78 to 1.06)	5685 (3 RCTs)	⊕⊕⊕⊕ HIGH	Breast cancer specific survival
Relapse-free survival (RFS) at 10 years	Study population 224 per 1,000[1]	210 per 1,000 (188 to 234)	HR 0.93 (0.82 to 1.05)	5685 (3 RCTs)	⊕⊕⊕◯ MODERATE [3]	RFS
Mastectomy rate - not measured	see comment	see comment	not estimable	(studies)	-	We found no data with respect to subsequent mastectomy

Hickey et al. Cochrane Review 2016

Radiotherapie (RT) nach brusterhaltenden Operationen (BEO; invasive Karzinome)

Guidelines Breast
Version 2021.1D

	Oxford		
	LoE	GR	AGO
▪ Bestrahlung der operierten Brust	1a	A	++
▪ Moderat hypofraktionierte RT (Gesamtdosis ca. 40 Gy in ca. 15-16 Fraktionen in ca. 3 bis 5 Wochen)	1a	A	++
▪ Ultra-hypofraktionierte RT (Gesamtdosis 26 Gy, d.h. 5 Fraktionen in einer Woche = 1 Fraktion/Tag bzw. 28,5 Gy, d.h. 5 Fraktionen in 5 Wochen = 1 Fraktion/Woche)	1b	B	+/-
▪ Konventionell fraktionierte RT (Gesamtdosis ca. 50 Gy in ca. 25-28 Fraktionen in ca. 5-6 Wochen)	1a	B	+
▪ Bei Lebenserwartung < 10 Jahre und pT1, pN0, R0, ER / PR positiv, HER2-negativ, endokriner adjuvanter Therapie (alle Faktoren) kann unter Inkaufnahme eines erhöhten Lokalrezidivrisikos nach individueller Beratung auf die RT verzichtet werden.	1a	B	+

Guidelines Breast
Version 2023.1D

FAST / FAST-Forward

	FAST	FAST Forward
Timeframe	2004-2007	2011-2014
Sample size	915	4096
Dose / Fractionation	50 Gy / 2 Gy / 5 weeks 30 Gy / 6 Gy / 5 weeks 28.5 Gy / 5.7 Gy / 5 weeks	40 Gy / 2.67 Gy / 3 weeks 27 Gy / 5.4 Gy / 1 weeks 26 Gy / 5.2 Gy / 1 weeks
Median follow-up	119.8 months	71.5 months
Primary endpoint	change in photographic breast appearance	Ipsilateral breast tumor recurrence (non-inferiority margin 1.6 %)
Inclusion criteria	pT1-2 (< 3 cm) pN0 Age ≥ 50 years Breast conserving surgery No chemotherapy	pT1-3 pN0-1 Age ≥ 18 years Breast-conserving surgery or mastectomy Approx. 25% adj. chemotherapy
Boost	No	Approx. 25%, 5-8 x 2 Gy

Brunt AM et al. J Clin Oncol. 2020 Oct 1;38(28):3261-3272. Brunt AM et al. Lancet. 2020 May 23;395(10237):1613-1626.

FAST / FAST-Forward

Guidelines Breast
Version 2023.1D

	FAST (10 year-data)			FAST Forward (5 year-data)		
	Dose	Frequency	Hazard ratio (95%-CI)	Dose	Frequency	Hazard ratio (95%-CI)
Ipsilateral in-breast recurrence	50 Gy	0.7%	-	40 Gy	2.1%	-
	30 Gy	1.4%	HR 1.36 (0.3-6.06)	27 Gy	1.7%	HR 0.86 (0.51-1.44)
	28.5 Gy	1.7%	HR 1.35 (0.3-6.05)	26 Gy	1.4%	HR 0.67 (0.38-1.16)
Moderate / marked normal tissue effects breast / chestwall	50 Gy	33.6%	-	40 Gy	26.8%	-
	30 Gy	50.4%	**HR 1.79 (1.37-2.34)**	27 Gy	35.1%	**HR 1.41 (1.23-1.61)**
	28.5 Gy	47.6%	**HR 1.45 (1.10-1.91)**	26 Gy	28.5%	HR 1.09 (0.95-1.27)

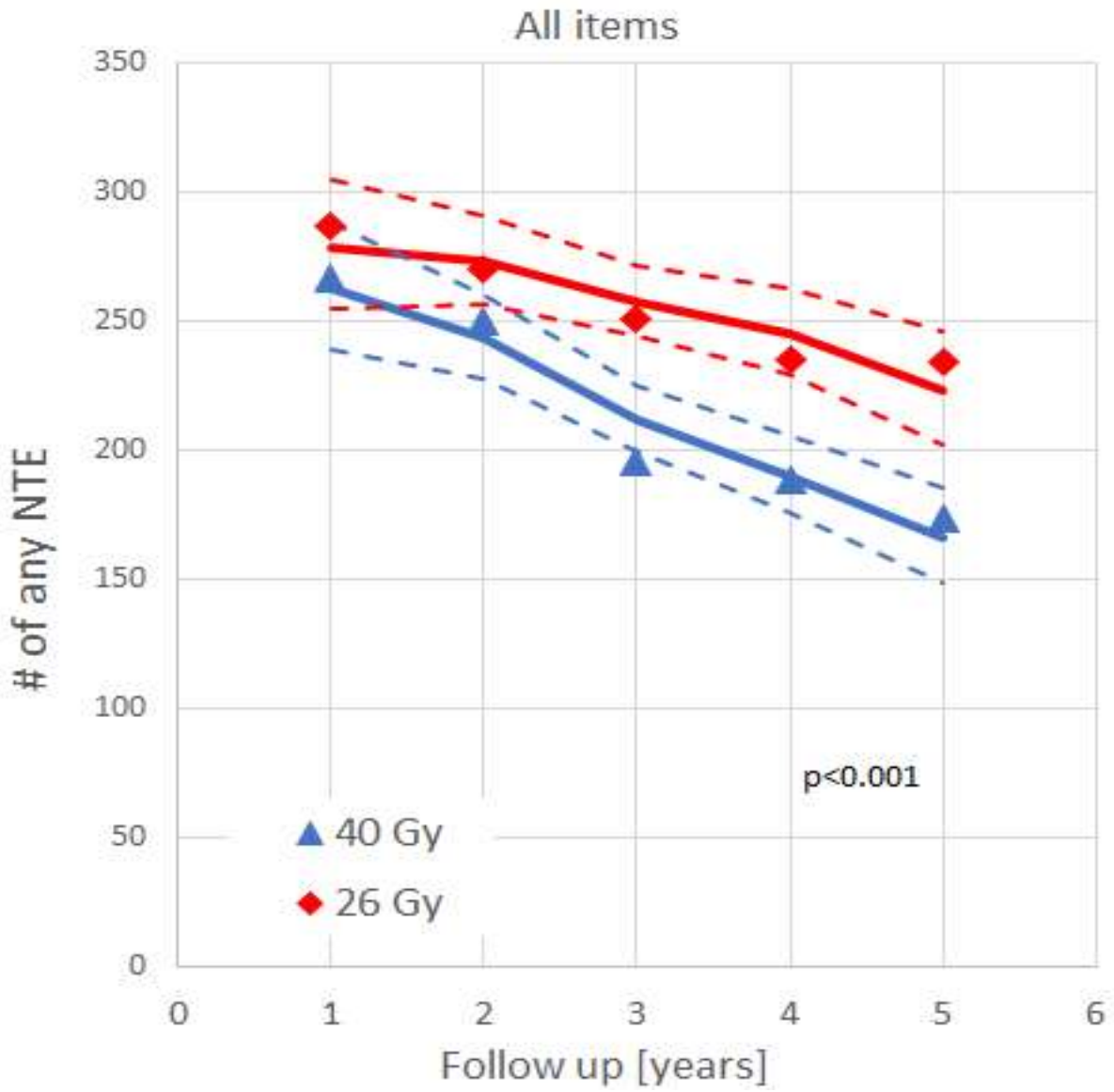
Brunt AM et al. J Clin Oncol. 2020 Oct 1;38(28):3261-3272. Brunt AM et al. Lancet. 2020 May 23;395(10237):1613-1626.

FASTFORWARD: 40 Gy in 15 fractions vs. 26 Gy in 5 fractions

Krug et al. Strahlenther Onk 2021

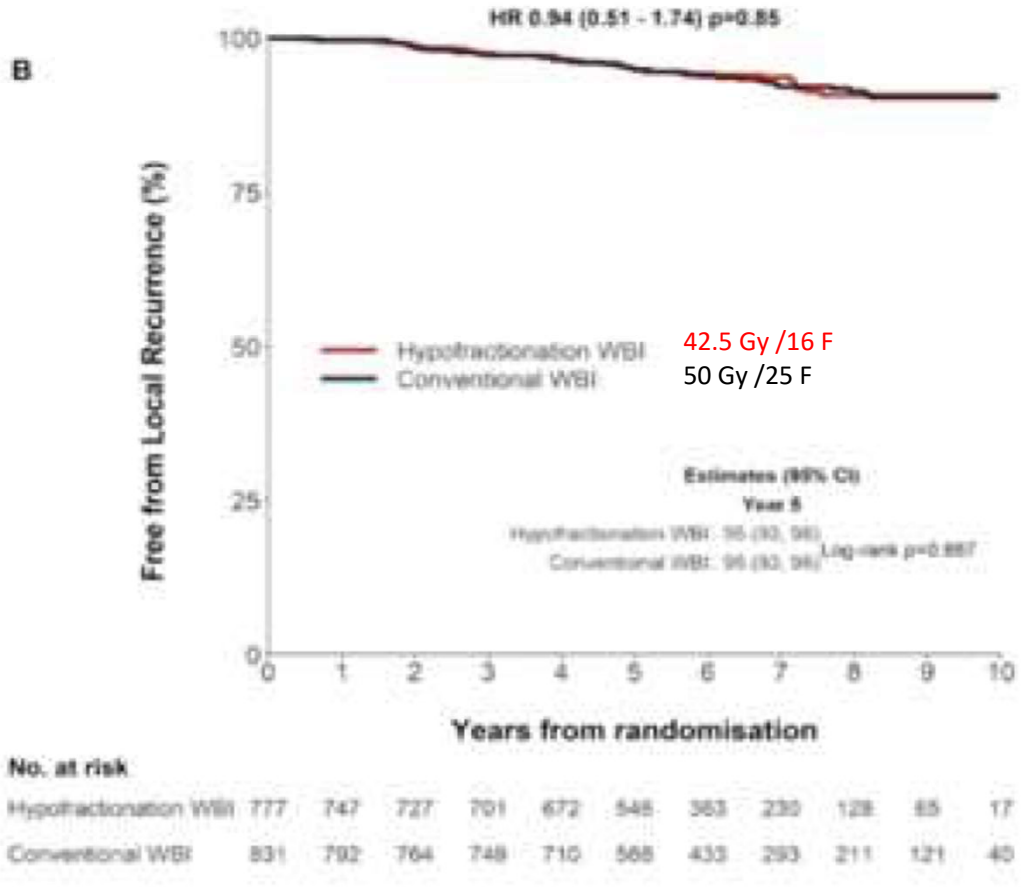
„total event burden“

“quite a bit or very much“



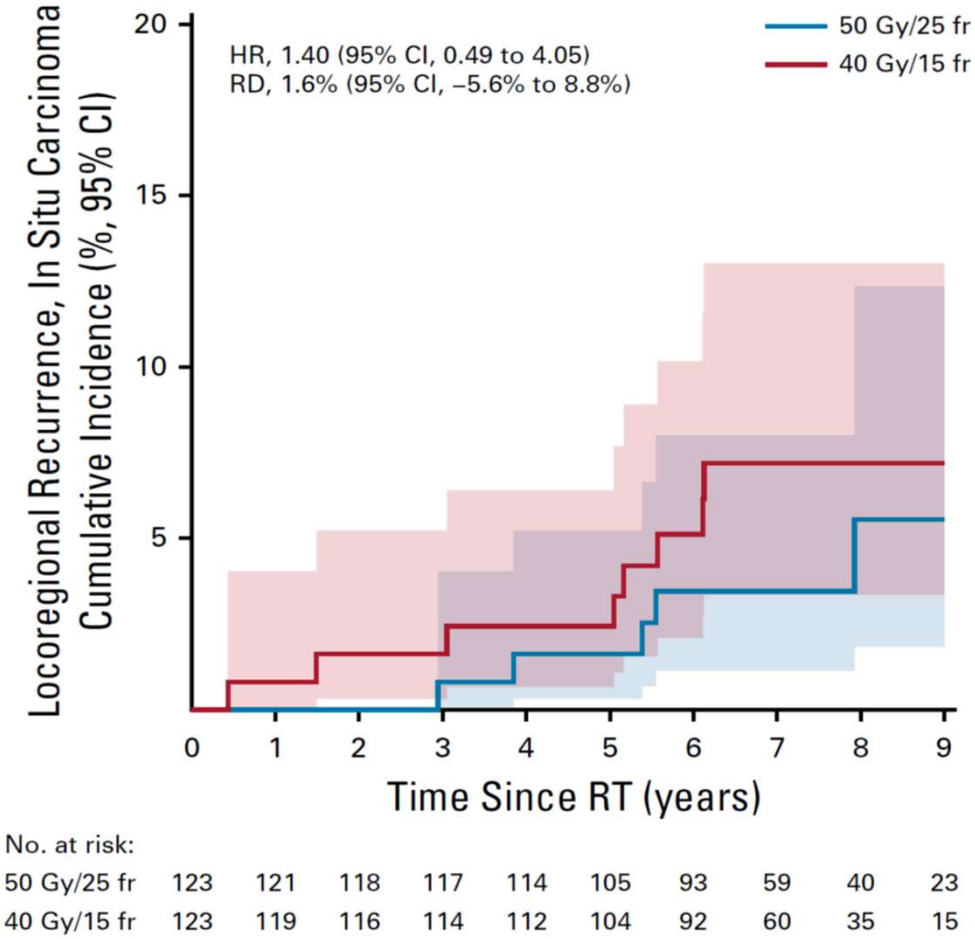
DCIS: conventional fractionation vs. moderately hypofractionated adjuvant RT

BIG 3-07/TROG 07.01



Chua et al. San Antonio Breast Cancer Meeting 2020

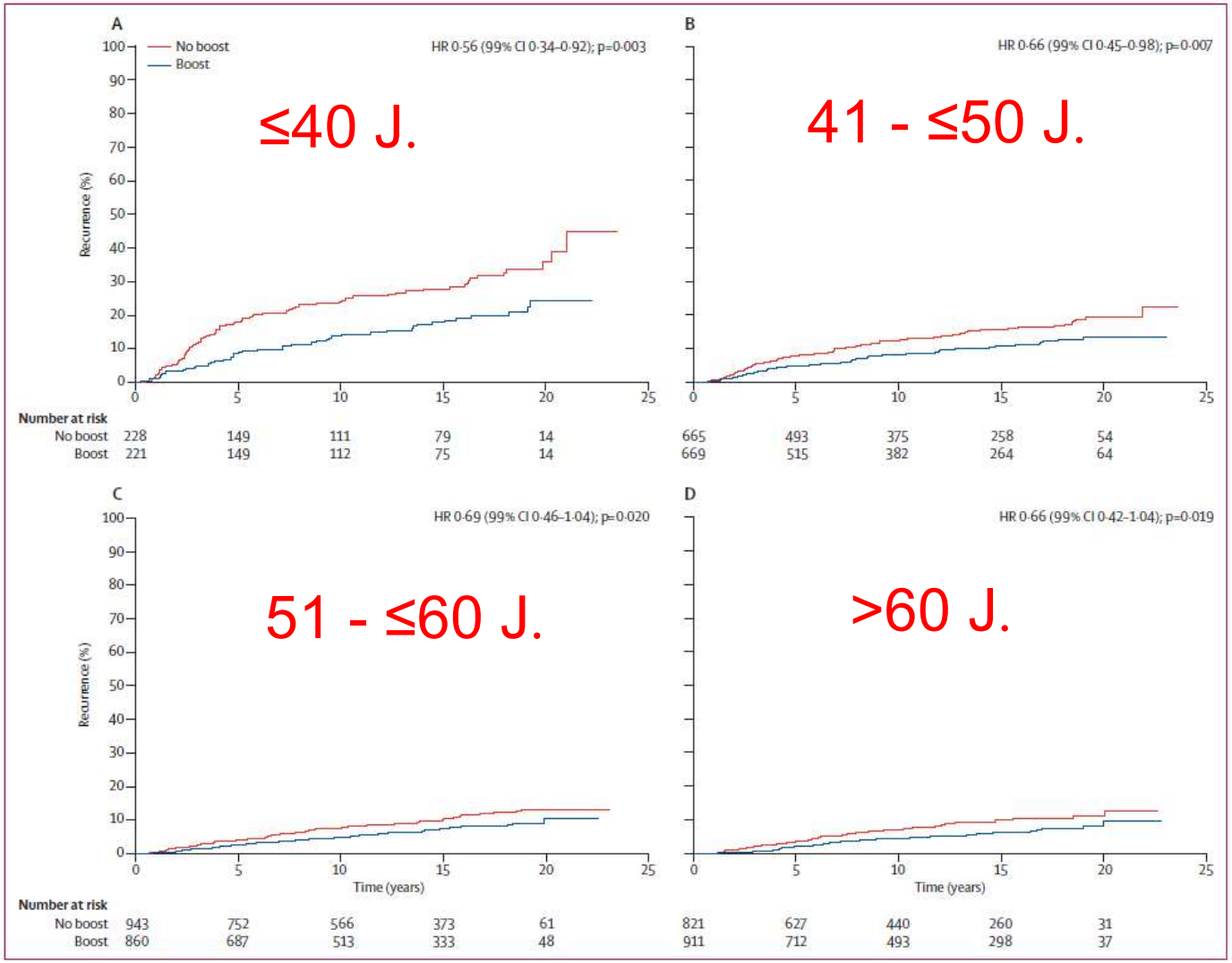
DBCG (subgroup)



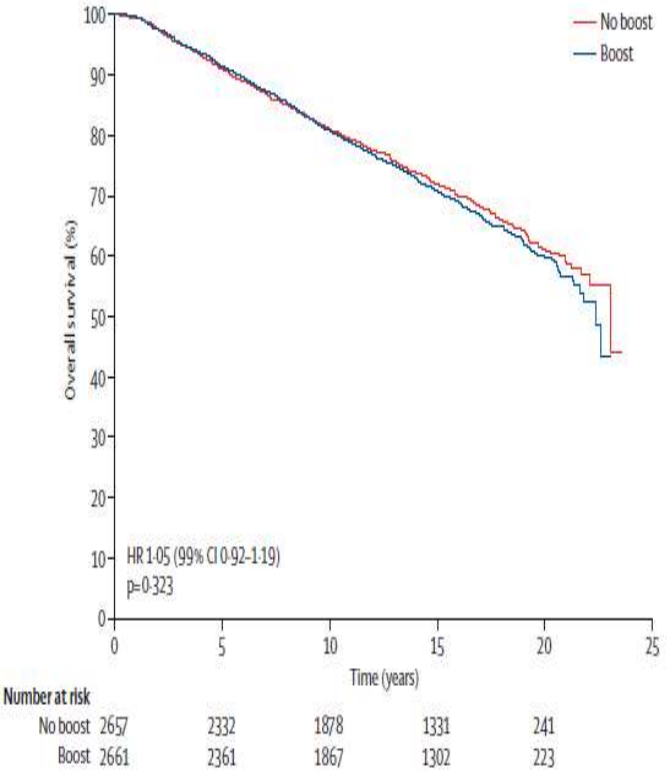
Offersen et al. JCO 2020

Effect of 16 Gy boost after whole breast RT

ipsilateral breast tumour recurrence



Overall survival



EORTC trial 22881-10882, (update) Bartelink et al. Lancet Oncol 2014

Multivariate Analyse: Lokale Rückfälle: Boost vs. kein Boost

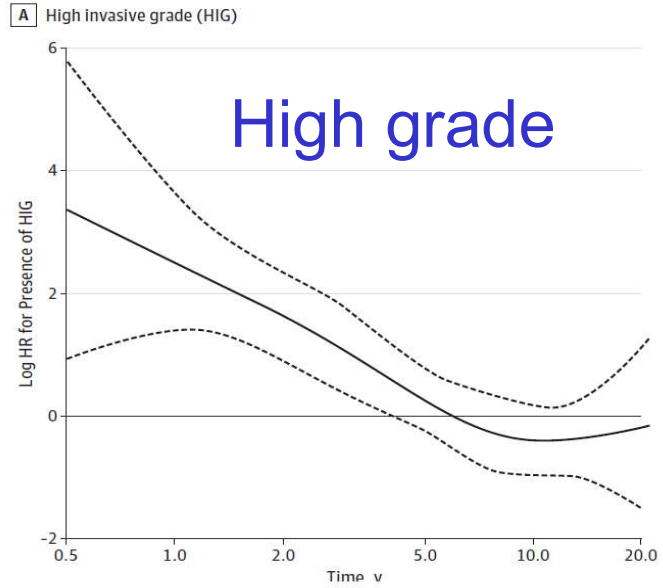
Multivariable model on time to local recurrence

	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		0.0003	
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

EORTC trial 22881-1088: Long term results



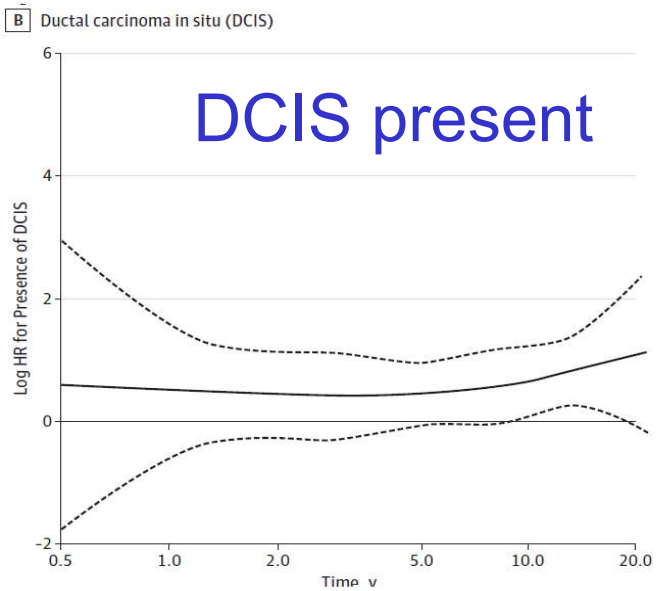


Table 2. Multivariable Analysis for Ipsilateral Breast Tumor Recurrence as First Event

Variable	HR (95% CIs)	*P* Value
Treatment		
No Boost vs 16 Gy Boost	0.62 (0.41-0.92)	.02
Age		
Per year[a]		<.001
Positive nodes		
No vs yes	0.82 (0.43-1.56)	.55
Systemic therapy[b]		
No vs yes	0.76 (0.44-1.29)	.31
Diameter		
Per mm	1.03 (1.00-1.06)	.05
Grade invasive tumor		
Intermediate/low vs high	0.87 (0.52-1.46)	.60
DCIS		
No vs yes	2.15 (1.36-3.38)	.001
Estrogen		
Negative vs positive	1.11 (0.67-1.85)	.67
Progesterone		
Negative vs positive	0.79 (0.48-1.29)	.34

Abbreviations: DCIS, ductal carcinoma in situ; mm, millimeter.

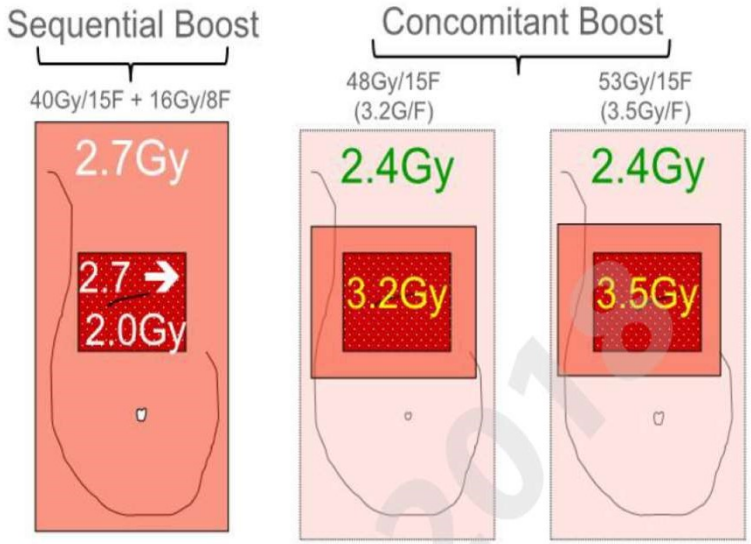
[a] See eFigure 5 in Supplement 2.

[b] Systemic therapy indicates tamoxifen or chemotherapy.

Vrieling et al JAMA Oncol 2017

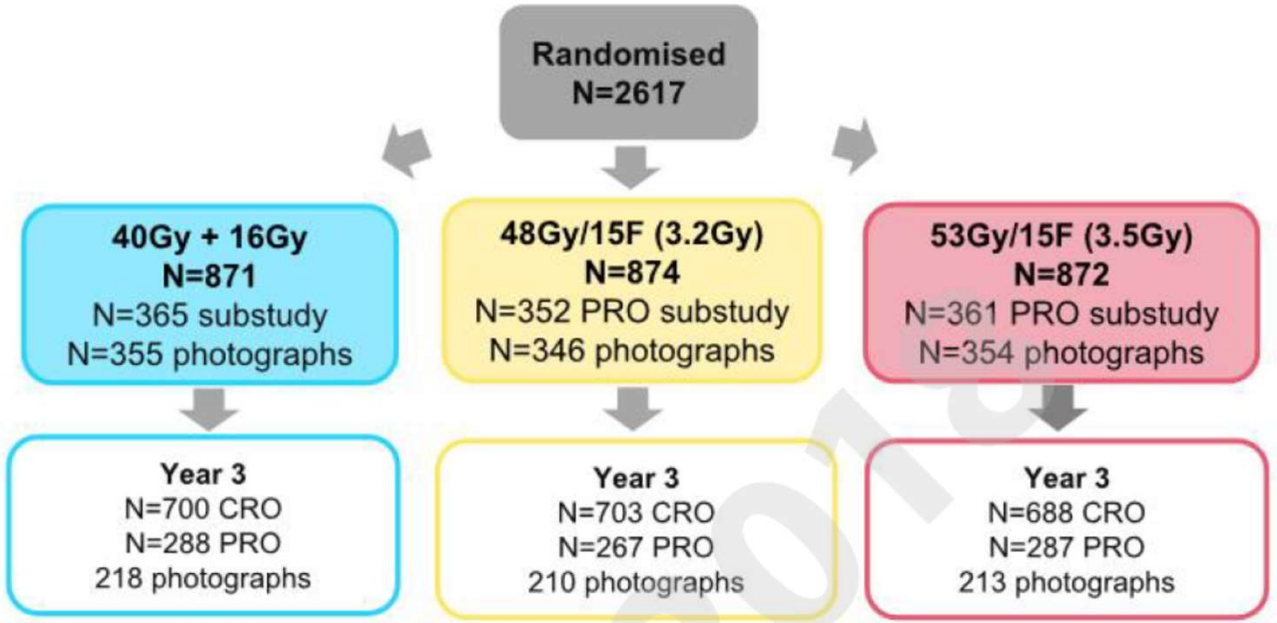
Moderate hypofractionation with simultaneous-integrated boost Important-High (ESTRO 2021)

TRIAL DESIGN: Dose Escalated Intensity Modulated RT



San Antonio Breast Cancer Symposium, December 4-8, 2018

TRIAL DESIGN: Patient flow & endpoint data availability



- Median follow-up 58.9 (IQR 42.5-72.0) months

Coles C, Haviland JS, Kirby AM, et al OC-0291 IMPORT HIGH trial: Dose escalated simultaneous integrated boost radiotherapy in early breast cancer. Radiother Oncol 2021. 161:S197–S199

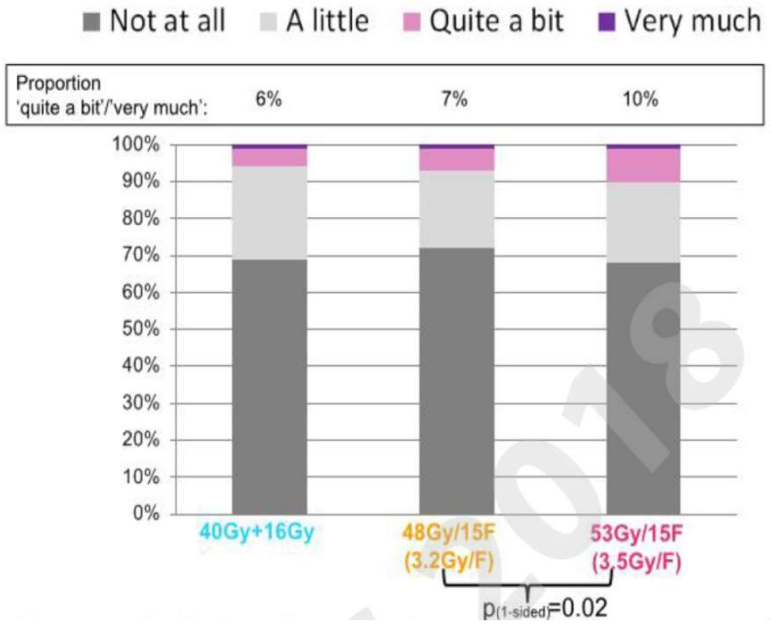
Moderate hypofractionation with simultaneous-integrated boost Important-High (ESTRO 2021)

Endpunkte	40 + 16 Gy	48 Gy SIB	53 Gy SIB	p-Wert 40+16 Gy vs. 48 Gy SIB
Lokalrezidiv 5 J.	1,9%	2,0%	3,2%	Nicht-Unterlegenheit für 48 Gy SIB
Any Breast AE	17%	13%	18%	0,041
Change in breast appearance (Foto)	37%	24%	28%	0,014

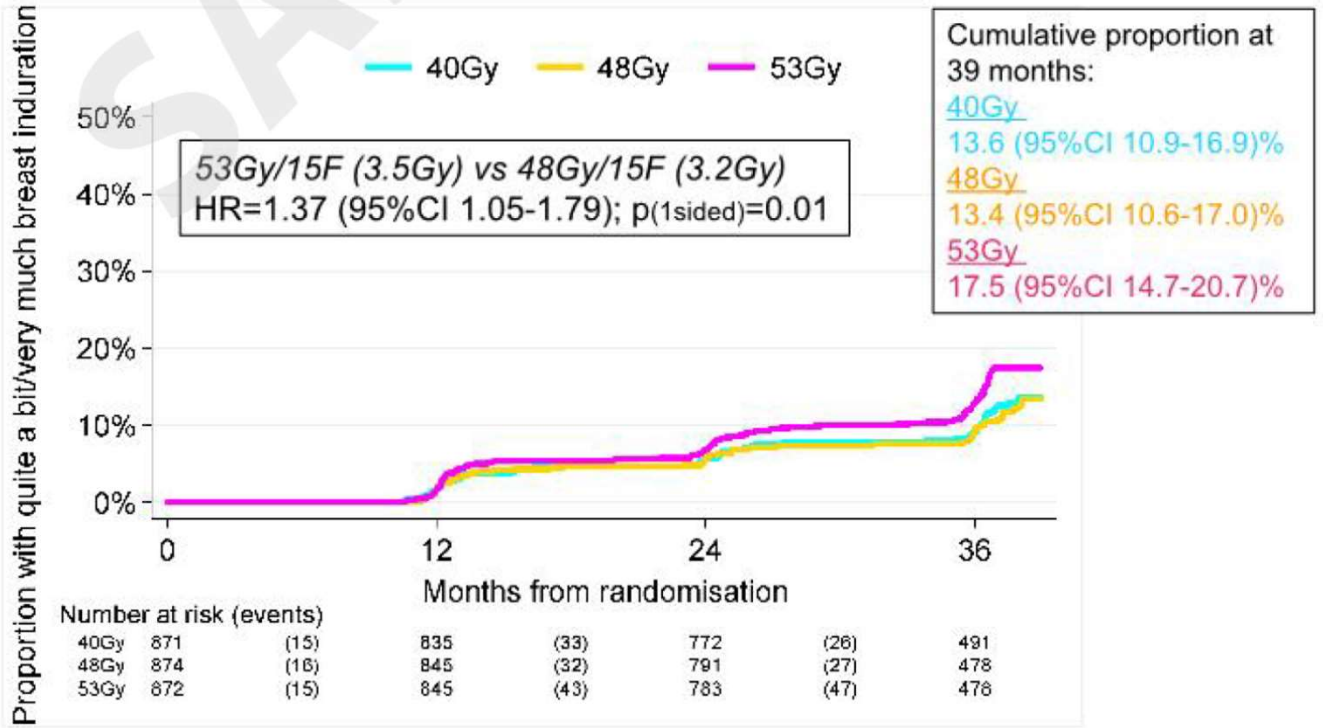
Coles C, Haviland JS, Kirby AM, et al OC-0291 IMPORT HIGH trial: Dose escalated simultaneous integrated boost radiotherapy in early breast cancer. Radiother Oncol 2021. 161:S197–S199

Moderate hypofractionation with simultaneous-integrated boost Important-High (ESTRO 2021)

ENDPOINTS: CRO: *breast induration* at 3 years



ENDPOINTS: CRO - Time to first *breast induration* event graded as 'quite a bit/very much'



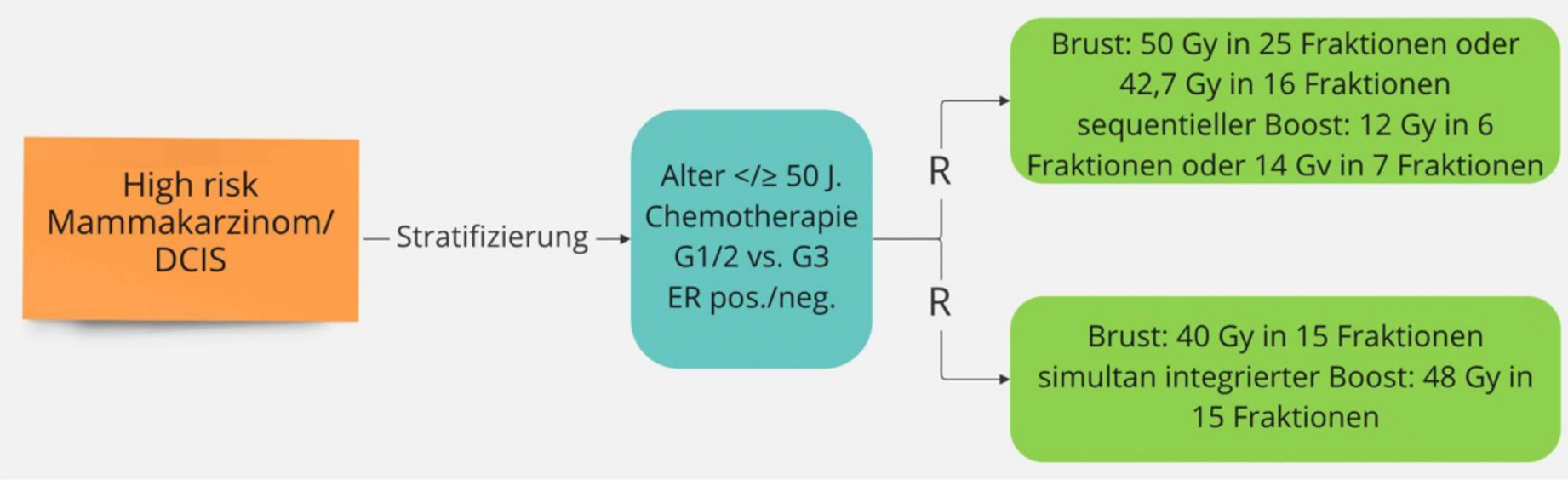
Coles C, Haviland JS, Kirby AM, et al OC-0291 IMPORT HIGH trial: Dose escalated simultaneous integrated boost radiotherapy in early breast cancer. Radiother Oncol 2021. 161:S197–S199

Moderate hypofractionation with simultaneous-integrated boost

RTOG 1005-Studie

Studiendesign

- Randomisierte Phase III-Studie bei Patientinnen mit high risk-Mammakarzinom/DCIS:
- T1-3 N0-1 mit mindestens 1 Risikofaktor: Alter < 50 J., N+, L1, knappe Resektionsrander (2 x >0-2mm oder 1x wenn EIC), fokal R1, ER und PR-neg., G3, Oncotype DX >25, neoadjuvante Therapie
- DCIS G3 UND Alter < 50 J.
- Primare Endpunkt: Lokalrezidivrate und kosmetisches Ergebnis



Vicini FA et al. NRG RTOG 1005. Int J Radiat Oncol Biology Phys 2022. 114:S1

Moderate hypofractionation with simultaneous-integrated boost

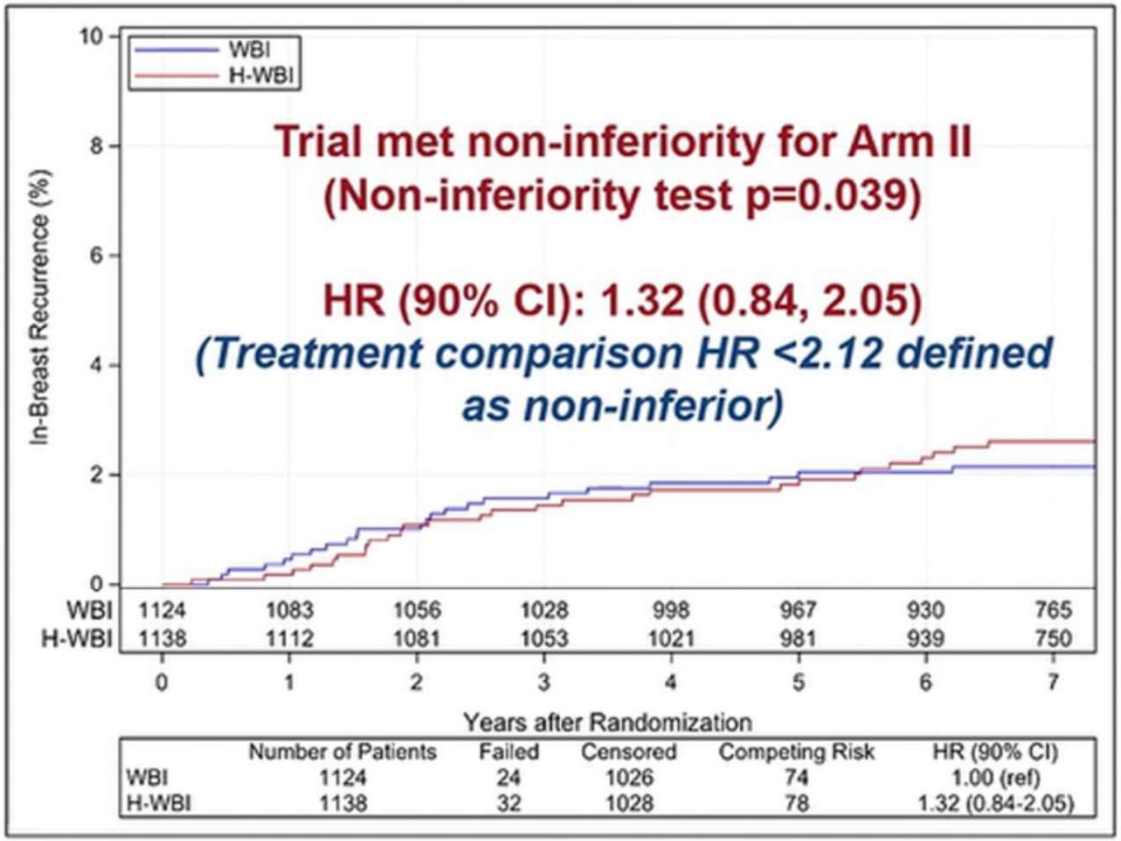
RTOG 1005-Studie

Results: Primary Endpoint - IBR

Median follow-up: 7.4 years

IBR events: 56

	WBI Sequential Boost (n=1124)	H-WBI Concurrent Boost (n=1138)
5-year estimate (90% CI)	2.0% (1.4%, 2.9%)	1.9% (1.3%, 2.7%)
7-year estimate (90% CI)	2.2% (1.5%, 3.0%)	2.6% (1.9%, 3.5%)



NRG ONCOLOGY™

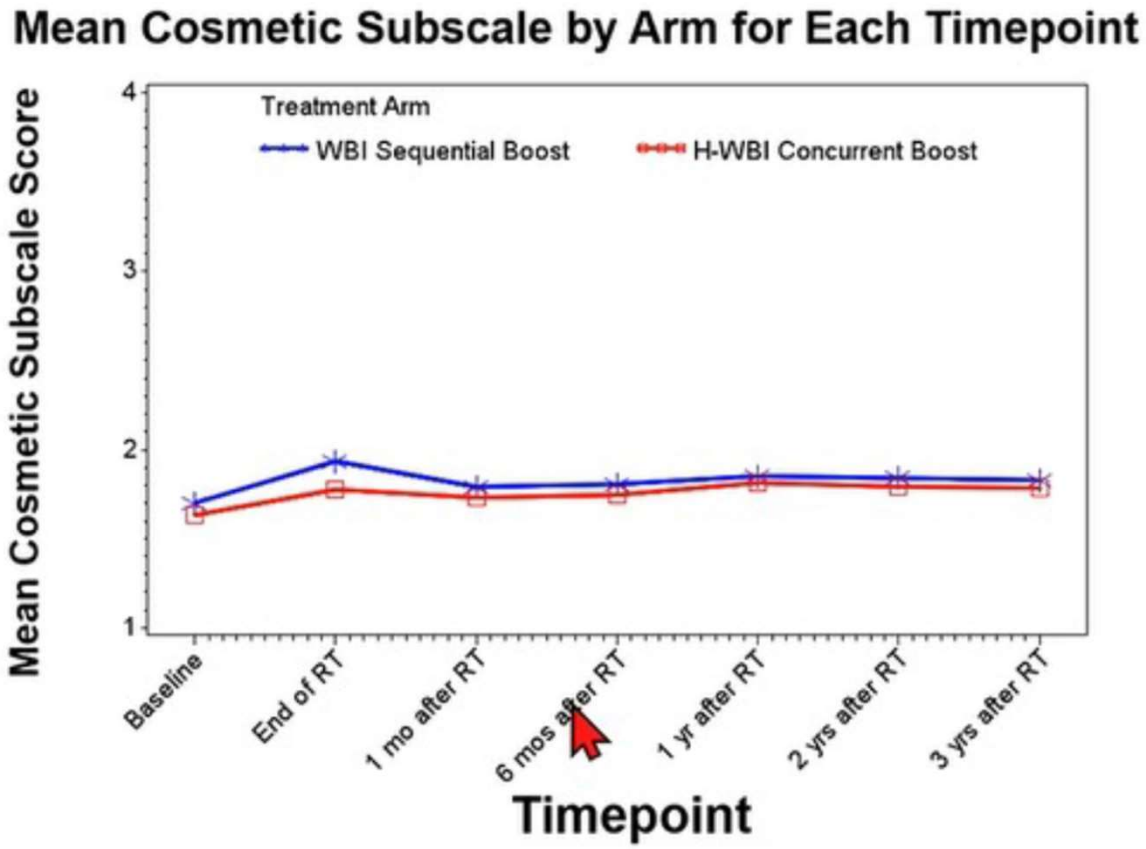
NRG/RTOG 1005

Vicini FA et al. NRG RTOG 1005. Int J Radiat Oncol Biology Phys 2022. 114:S1

Moderate hypofractionation with simultaneous-integrated boost
RTOG 1005-Studie

Results: BCTOS Mean Cosmetic SubScale Score by Timepoint

- *BCTOS*: Patient assessed difference between treated and untreated breast and area (22 items)
- *Cosmetic Subscale*: 8 items
- 4-point scale:
  - 1 = None
  - 2 = Slight
  - 3 = Moderate
  - 4 = Large



NRG ONCOLOGY™

NRG/RTOG 1005

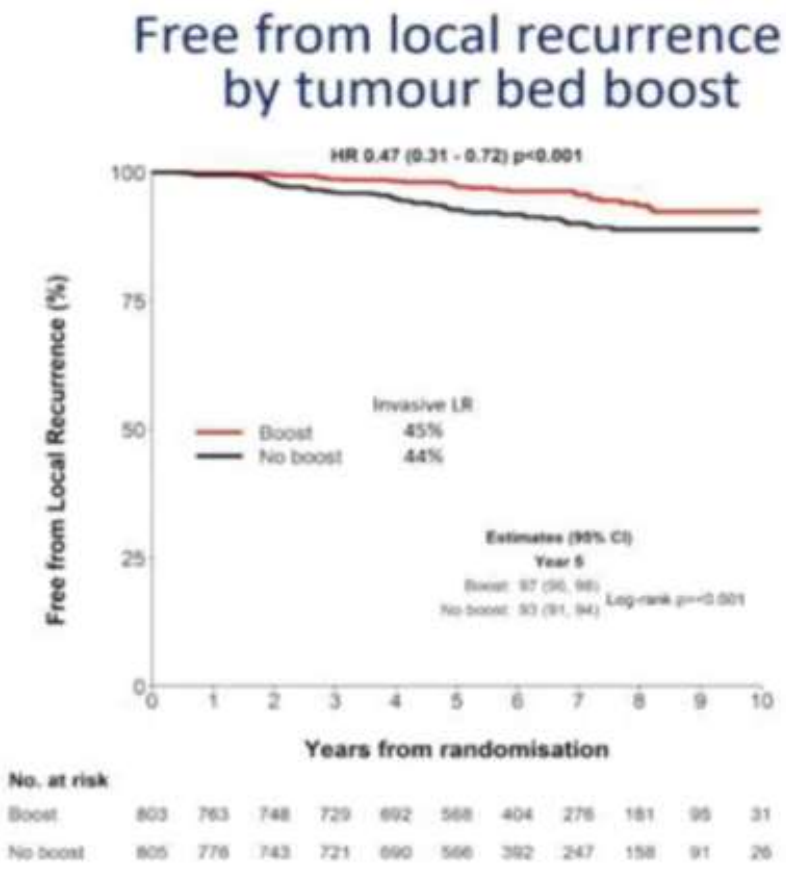
Vicini FA et al. NRG RTOG 1005. Int J Radiat Oncol Biology Phys 2022. 114:S1

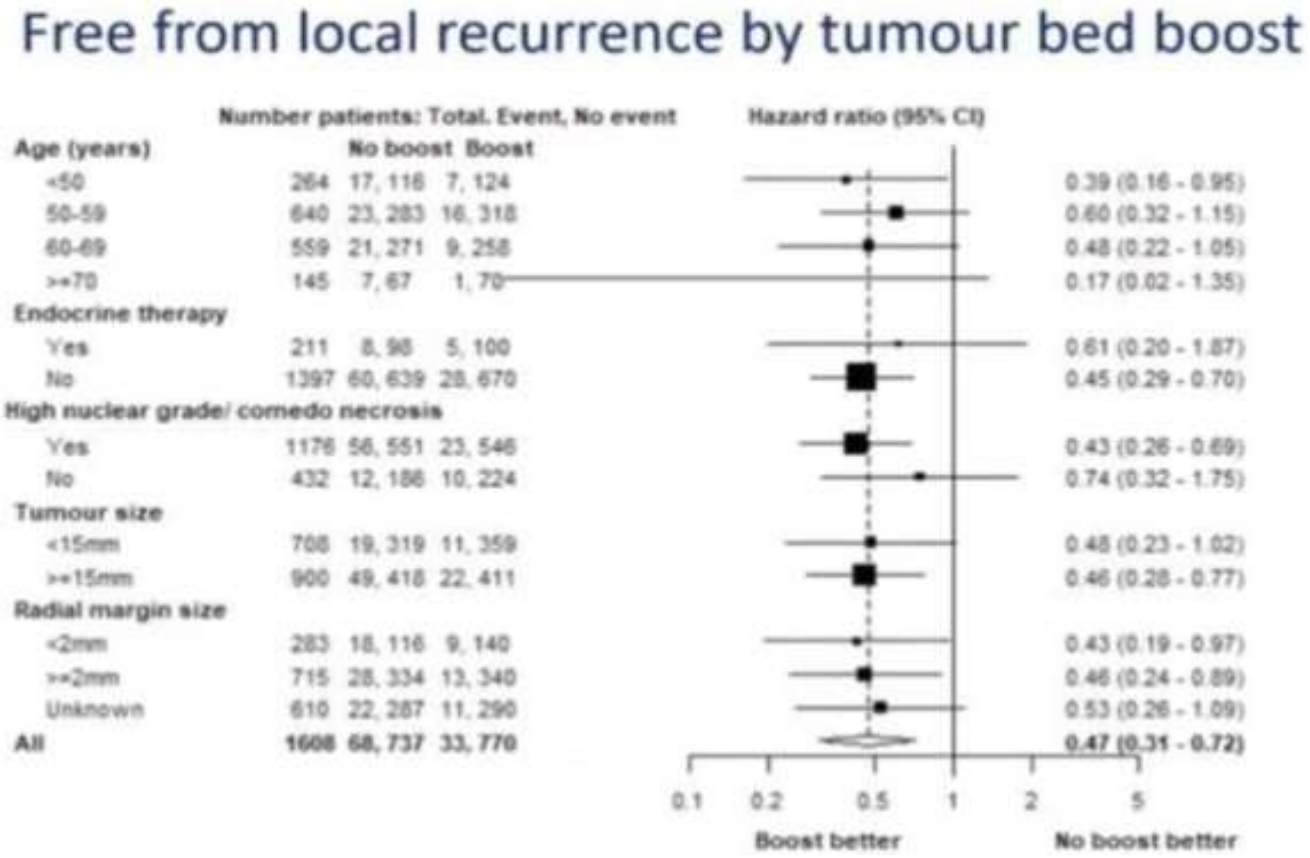
Boostbestrahlung nach BEO beim invasiven Karzinom

	Oxford LoE	GR	AGO
Boost-RT des Tumorbettes (verbesserte lokale Kontrolle, kein Überlebensvorteil)			
Prämenopausal	1b	B	++
Postmenopausal, sofern > T1*, G3, HER2-positiv, tripel-negativ, EIC (mindestens 1 Faktor)	2b	B	+
Techniken			
Perkutan (Photonen, Elektronen) als sequentieller Boost	1a	A	++
Multikatheter-Brachytherapie	1a	A	++
Perkutan als simultan integrierter Boost (bei konventionell fraktionierter RT)	1b	B	+
Perkutan als simultan integrierter Boost (bei hypofraktionierter RT)	1b[a]	B	+
Intraoperative Radiotherapie (als vorgezogener Boost)	2b	B	+
Intraoperative Clipmarkierung des Tumorbetts bei Indikation für Boost-bestrahlung	2b	B	+

*kontinuierliche Variable bzgl. Rezidiv

Non-low-risk DCIS: Boost (8x 2 Gy) vs. no Boost [BIG 3-07/TROG 07.01]





Definition of non-low-risk

- Age <50 years or
- age ≥50 years plus at least one of the risk factors:
- palpable tumor, multifocal disease,
- tumor size ≥ 1.5cm
- intermediate or high nuclear grade
- central necrosis
- comedo histology
- surgical margin <10 mm

Chua et al. San Antonio Breast Cancer Meeting 202

Guidelines Breast
Version 2021.1D

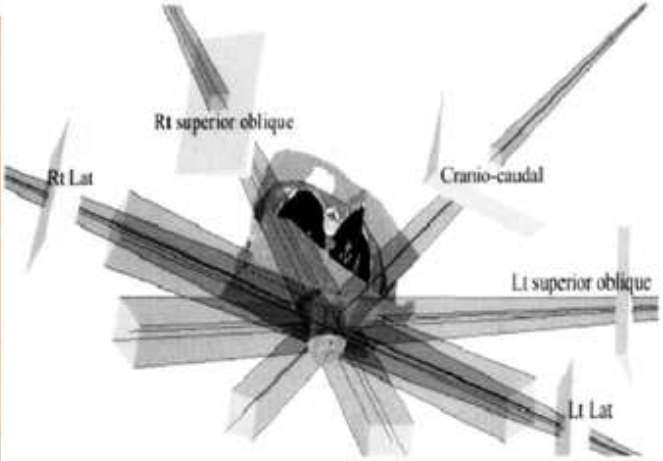
DCIS
adjuvante Strahlentherapie

	Oxford LoE	Oxford GR	AGO
Radiotherapie nach:			
▪ Brusterhaltender Operation (BEO) ; (gesamte Brust, WBI)	1a	A	++
▪ Mastektomie	2b	B	--
Durchführung der Radiotherapie:			
▪ Konventionell fraktionierte Radiotherapie (50 Gy in 25 Frakt.)	1a	A	+
▪ Hypofraktionierte Radiotherapie (40-42,5 Gy in 15-16 Frakt.)	1a	A	+
▪ Boost-RT des Tumorbettes	1b	B	+/-
▪ Bei Risikofaktoren* (absoluter Vorteil 5-J-RFS 4%, Fibroserate signifikant erhöht)	1b[a]	B	+/-
▪ Ohne Risikofaktoren	2b	B	-
▪ Teilbrustbestrahlung [Alter ≥50 Jahre, DCIS ≤ 3 cm, G1-2, R0 (≥ 5 mm), unifokal/ unizentrisch]	1b	B	+

NW und Nachteile der Radiotherapie müssen gegenüber der erreichbaren Risikoreduktion abgewogen werden. Ein Verzicht auf eine Strahlentherapie nach BEO bedeutet ein erhöhtes lokales Rezidivrisiko ohne Einfluss auf das Überleben. Dieses gilt auch für Patientinnen mit günstigen prognostischen Faktoren (low-risk-Subgruppe; Level I-Evidenz): < 2,5 cm, low and intermediate nuclear grade, mammographisch entdeckt

***< 50 J. oder ≥ 50 J. und Diagnose durch Symptomatik, ≥ 15 mm, Multifokalität, tastbarer Tumor, Resektionsränder < 10 mm, G2/3, zentrale Nekrose, Komedo-Typ**

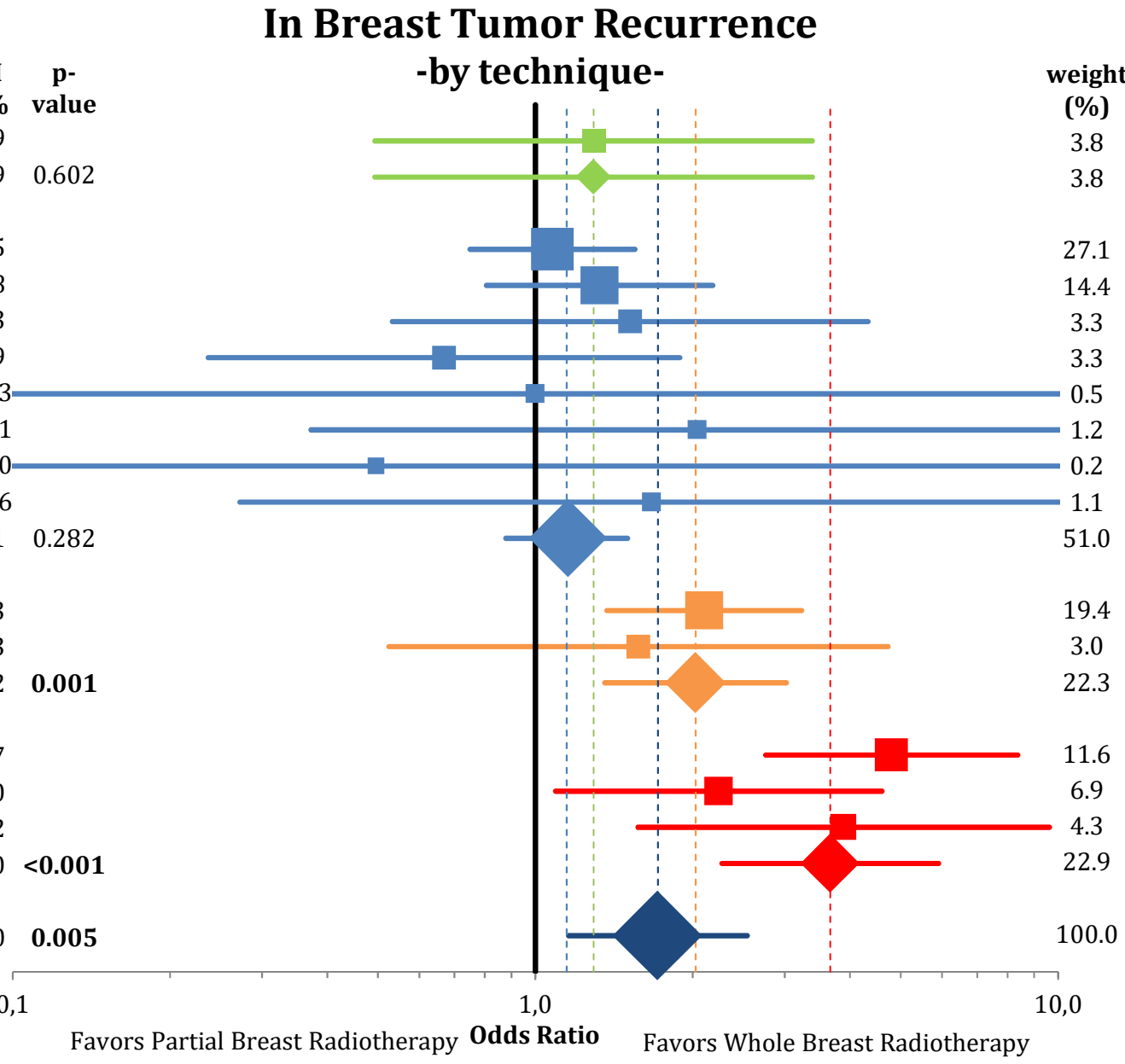
Teilbrustbestrahlung



3D / IMRT

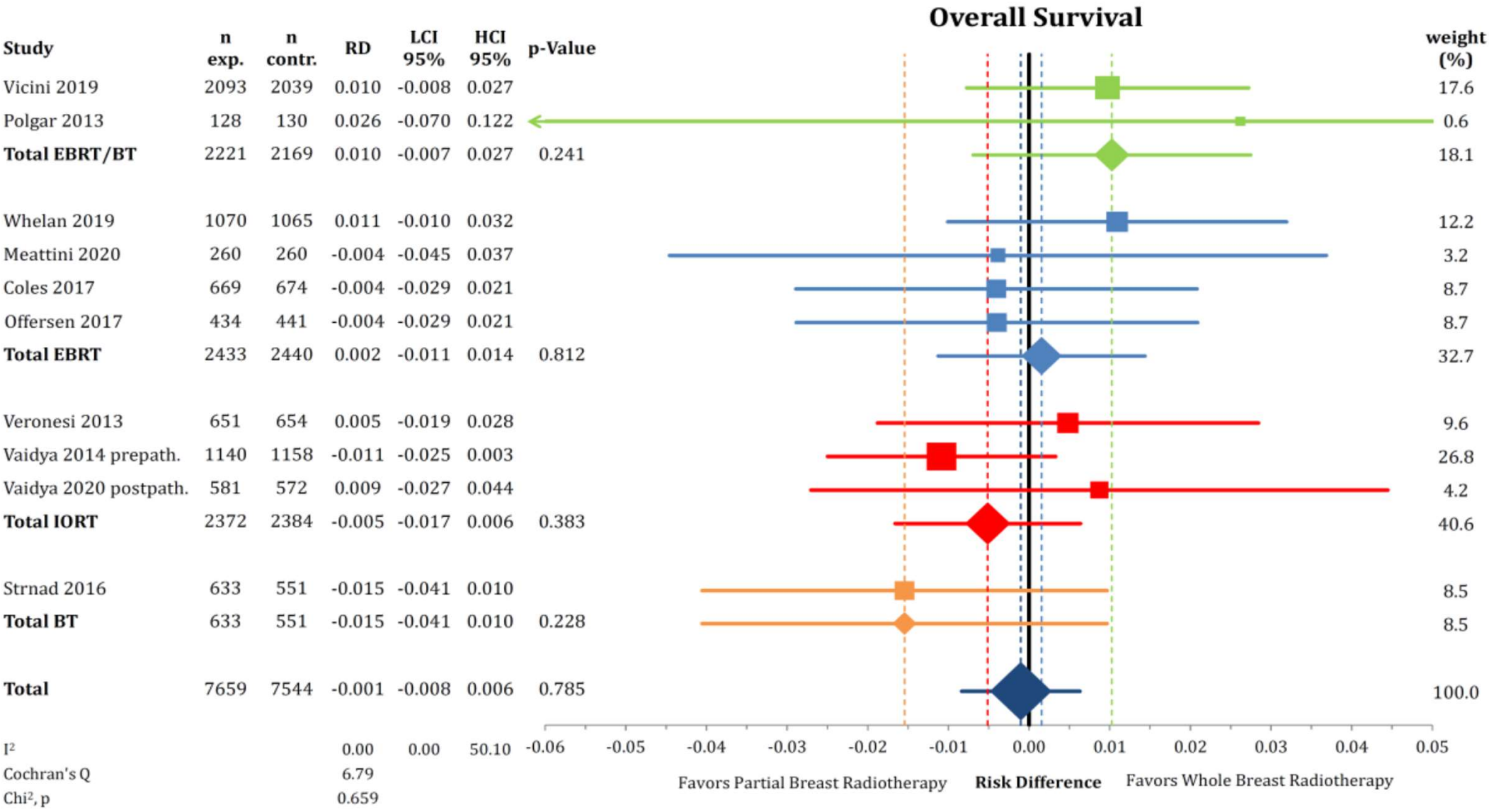
Meta-analysis: whole breast vs. partial breast radiotherapy in breast cancer

Study	n PBI	Rate [%]	n WBI	Rate [%]	OR	LCI 95%	HCI 95%	p-value	weight (%)
Polgar 2020	128	7.81	130	6.16	1.29	0.49	3.39		3.8
Total EBRT/BT	128	7.81	130	6.16	1.29	0.49	3.39	0.602	3.8
Vicini 2019 EBRT	1535	3.58	2011	3.33	1.08	0.75	1.55		27.1
Whelan 2019	1070	3.46	1065	2.63	1.33	0.81	2.18		14.4
Meattini 2020	260	3.46	260	2.31	1.52	0.53	4.33		3.3
Coles 2017	669	0.90	674	1.34	0.67	0.24	1.89		3.3
Li 2021	51	2.80	51	2.80	1.00	0.06	16.43		0.5
Offersen 2017	434	0.92	441	0.45	2.04	0.37	11.21		1.2
Boutrus 2018	61	0.40	30	0.81	0.50	0.01	25.60		0.2
Franceschini 2020	82	3.66	90	2.22	1.67	0.27	10.26		1.1
Total EBRT	4162	2.64	4622	2.43	1.16	0.89	1.51	0.282	51.0
Vicini 2019 BT	488	6.76	2011	3.33	2.10	1.37	3.23		19.4
Strnad 2016	633	1.42	551	0.91	1.58	0.52	4.73		3.0
Total BT	1121	3.33	2562	2.71	2.03	1.36	3.02	**0.001**	22.3
Orecchia 2021	651	10.75	654	2.45	4.80	2.76	8.37		11.6
Vaidya 2020 prepath	1140	2.11	1158	0.95	2.24	1.09	4.60		6.9
Vaidya 2020 postpath	581	3.96	572	1.05	3.89	1.57	9.62		4.3
Total IORT	2372	4.42	2384	1.36	3.67	2.28	5.90	**<0.001**	22.9
Total	7783	3.33	9698	2.26	1.71	1.17	2.50	**0.005**	100.0
I^2	58.84		24.05		77.69				
Cochran's Q	29.15								
Chi^2, p	0.004								



Haussmann et al. Cancers 2021 in press

Meta-analysis: whole breast vs. partial breast radiotherapy in breast cancer



Haussmann et al. Cancers 2020

Teilbrustbestrahlung nach BEO beim invasiven Karzinom

Guidelines Breast
Version 2021.1D

	Oxford		
	LoE	GR	AGO
Intraoperative Radiotherapie (niedriges Risiko)*			
Als alleinige Radiotherapie-Maßnahme während der ersten Brust-OP (IORT 50 kV, IOERT)			
>50 Jahre	1b	A	+/-
>70 Jahre	1b	A	+
Postoperative Teilbrustbestrahlung (niedriges Risiko)*			
Interstitielle Multikatheter-Brachytherapie	1b	A	+
Intrakavitäre Ballontechnik	2b	B	-
Intensitätsmodulierte Radiotherapie (IMRT) (5x6 Gy über 2 Wochen)	1b	A	+
3D-konformale Radiotherapie (15x2,67 Gy über 3 Wochen)	1b	A	+
3D-konformale Radiotherapie (10x3,8 Gy über 2 Wochen)	2b	B	+/-
3D-konformale Radiotherapie (10x3,85 Gy über 1 Woche)	1b	A	+/-

Definition des Zielvolumens und praktische Durchführung siehe DEGRO practical guidelines

* **nur bei pT1 pN0 R0 G1-2, HR+, nicht-lobulär, >50 J., kein extensives DCIS**

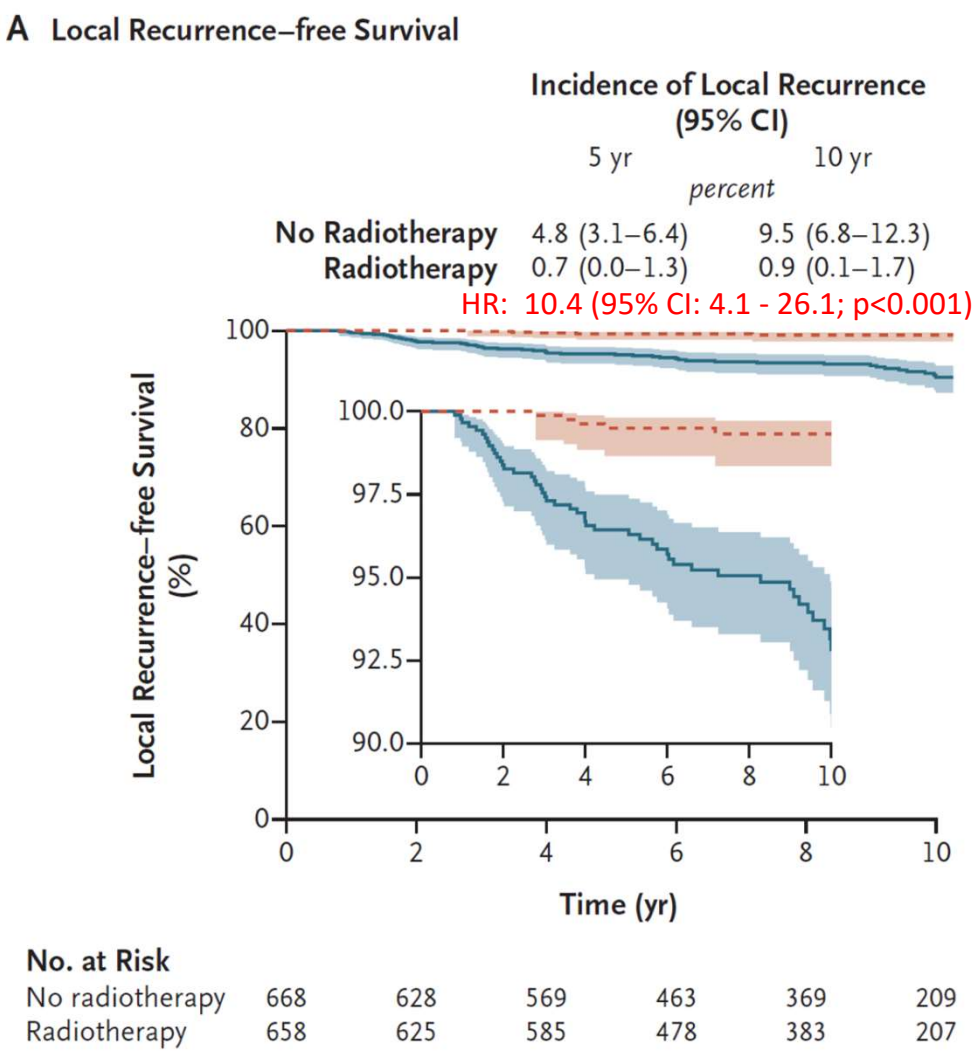
Die ältere Mammakarzinompatientin

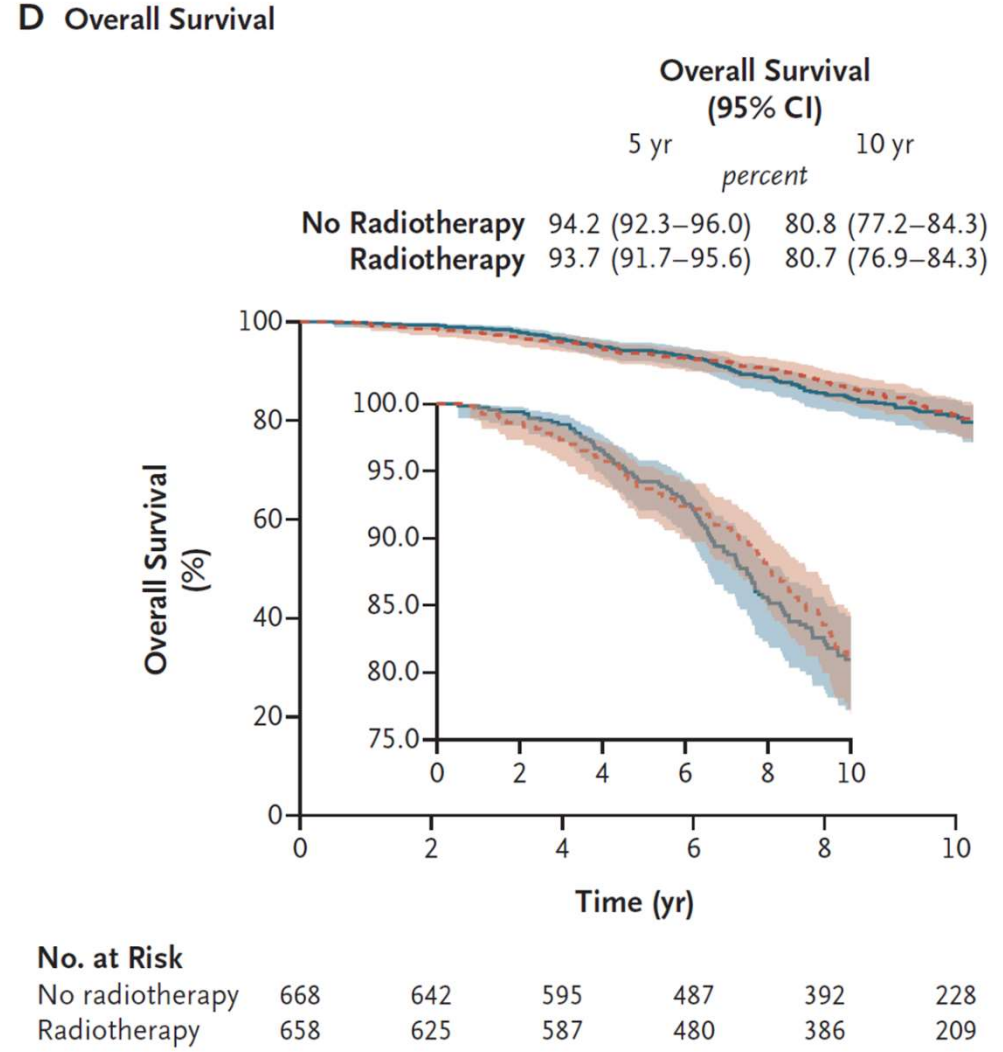
Benötigt die ältere Patienten eine

adjuvante Strahlentherapien

nach brusterhaltender Operation?

Breast-Conserving Surgery with or without Irradiation in Early Breast Cancer (T1-2 <3cm, N0, HR+, >65 years)

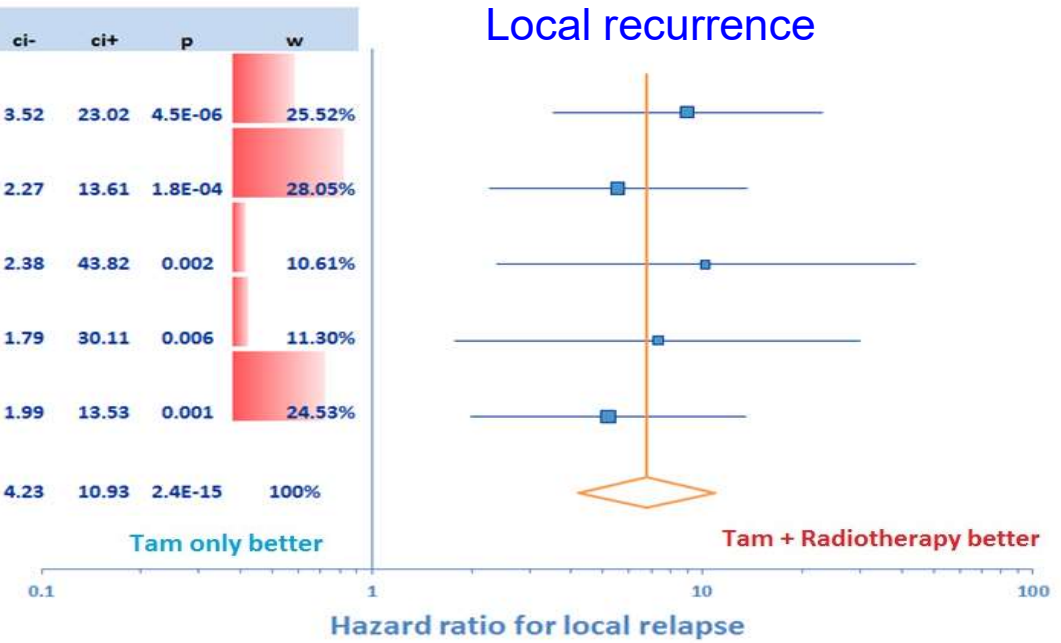




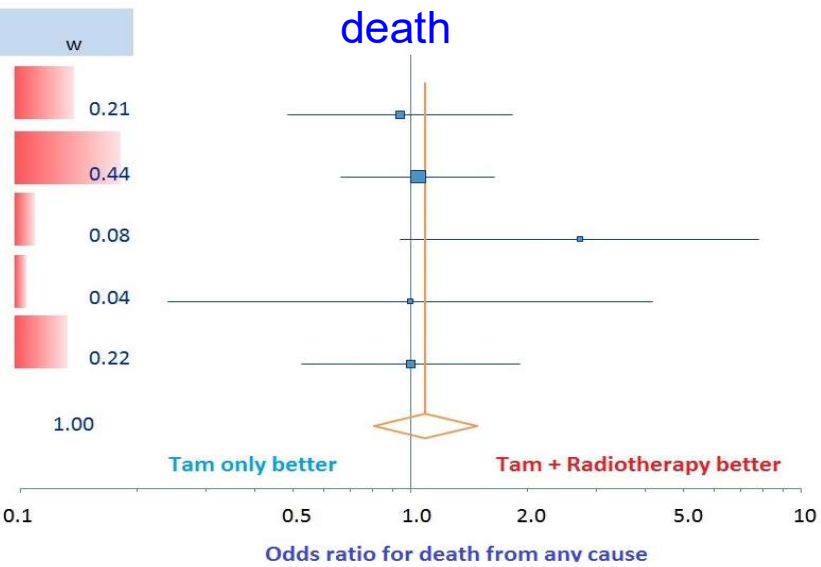
Kunkler et al. N Engl J Med 2023;388:585-94

Meta-analysis: no RT vs. RT in low risk breast cancer (T1-2 [<3 cm] N0, HR+)

id	N	hr	ci-	ci+	p	w
Fyles et al 2004	769	9.00	3.52	23.02	4.5E-06	25.52%
Hughes et al. 2013	636	5.56	2.27	13.61	1.8E-04	28.05%
Pötter et al 2007	831	10.21	2.38	43.82	0.002	10.61%
Blamey et al. 2013	204	7.34	1.79	30.11	0.006	11.30%
Kunkler et al. Lancet Oncol 2015	1326	5.19	1.99	13.53	0.001	24.53%
Total	3766	6.80	4.23	10.93	2.4E-15	100%



authors	N	years	OR	ci-	ci+	p	w
Fyles et al. 2004	769	5	0.94	0.48	1.82	0.86	0.21
Hughes et al. 2013	636	10	1.05	0.66	1.65	0.85	0.44
Pötter et al. 2007	831	5	2.71	0.94	7.82	0.06	0.08
Blamey et al. 2013	204	10	1.00	0.24	4.18	1.00	0.04
Kunkler et al. 2015	1326	5	1.00	0.53	1.90	1.00	0.22
Total	3766		1.09	0.81	1.48	0.57	1.00



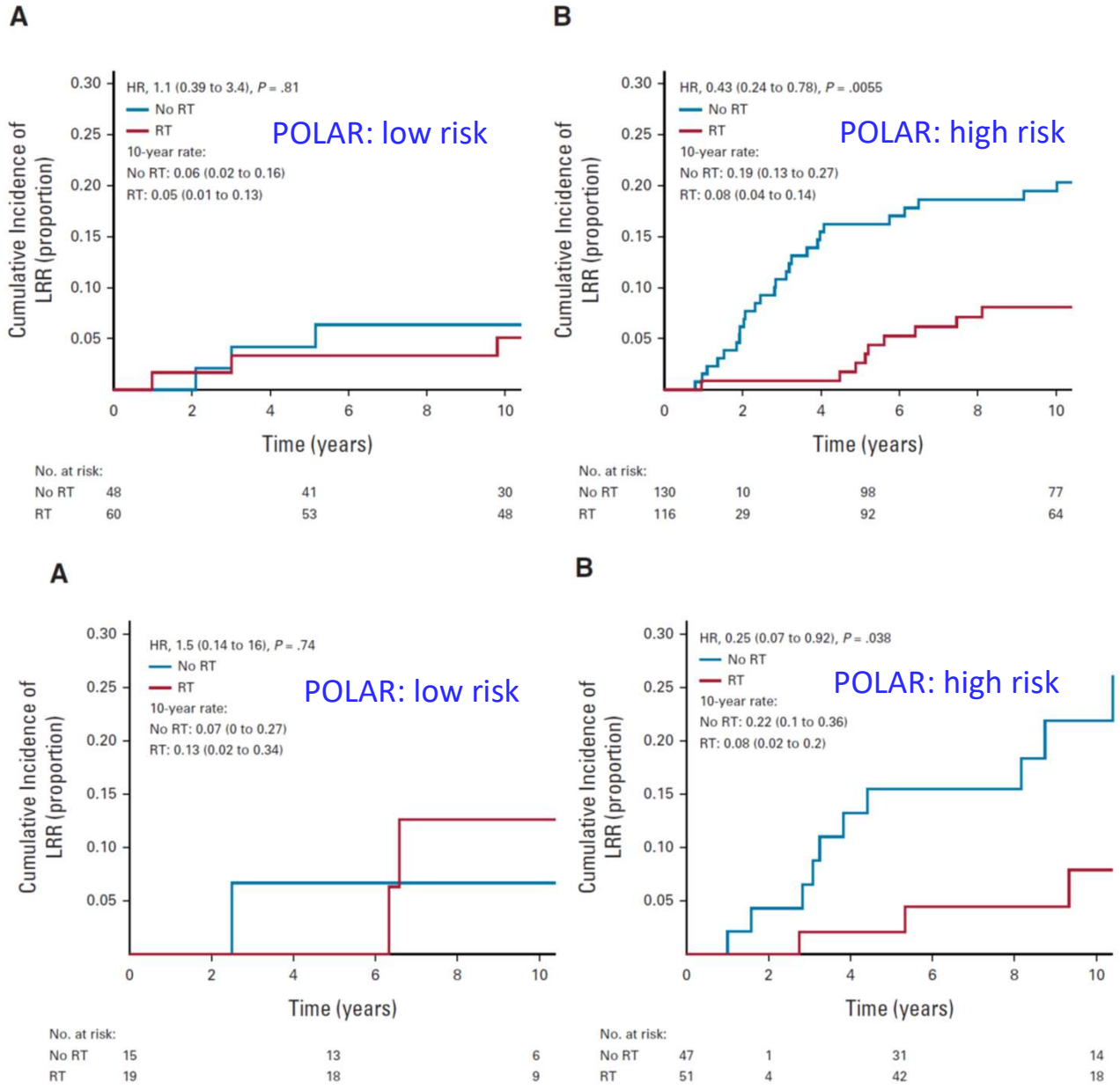
Matuschek, .W. Budach Radiat Oncol 2017

Development and Validation of a Genomic Profile for the Omission of Adjuvant RT in Breast Cancer

(T1-2, N0, ER+, >50y)

TABLE 1. Final 16 Genes Included in POLAR

Gene Symbol	Gene Name
AGR2	Anterior Gradient 2, Protein Disulfide Isomerase
B4GALT1	Beta-1,4-Galactosyltransferase 1
CLDN7	Claudin 7
EZR	Ezrin
GNG11	G Protein Subunit Gamma 11
JUN	Jun Proto-Oncogene, AP-1 Transcription Factor Subunit
MMP11	Matrix Metallopeptidase 11
PKIB	cAMP-Dependent Protein Kinase Inhibitor Beta
PRPS1	Phosphoribosyl Pyrophosphate Synthetase 1
PSMD10	Proteasome 26S Subunit, Non-ATPase 10
SH3BP5	SH3 Domain Binding Protein 5
SLC16A3	Solute Carrier Family 16 Member 3
SLC7A11	Solute Carrier Family 7 Member 11
SPP1	Secreted Phosphoprotein 1
TNNT1	Troponin T1, Slow Skeletal Type
UBE2E1	Ubiquitin Conjugating Enzyme E2 E1



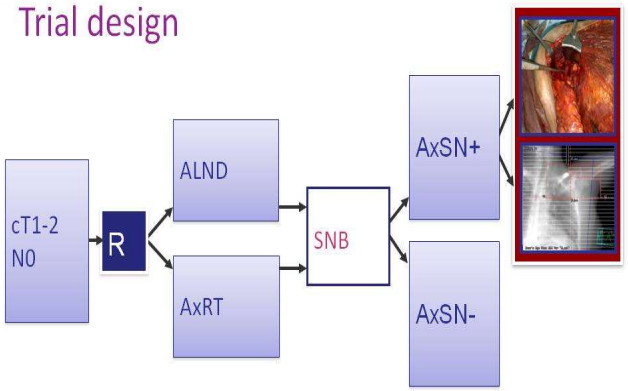
Sjöström et al- JCO 2023

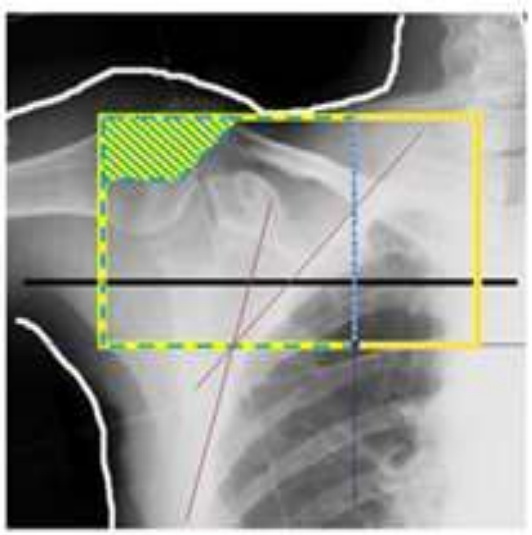
Radiotherapie (RT) nach brusterhaltenden Operationen (BEO; invasive Karzinome)

Guidelines Breast
Version 2021.1D

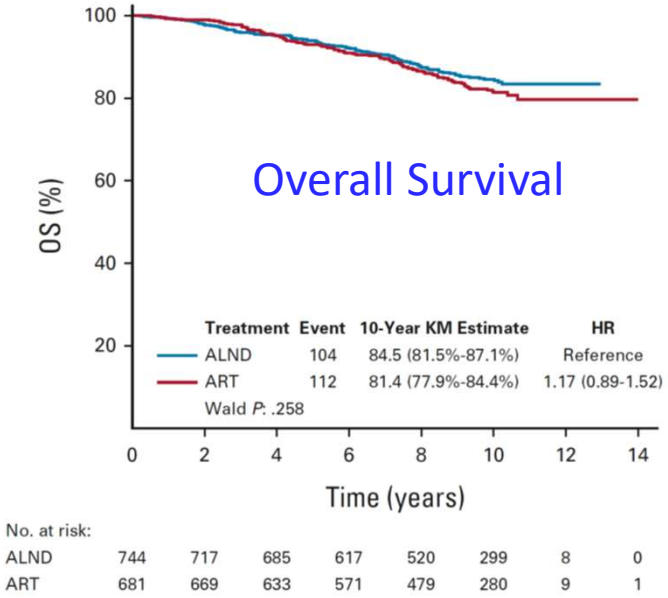
	Oxford		
	LoE	GR	AGO
▪ Bestrahlung der operierten Brust	1a	A	++
▪ Moderat hypofraktionierte RT (Gesamtdosis ca. 40 Gy in ca. 15-16 Fraktionen in ca. 3 bis 5 Wochen)	1a	A	++
▪ Ultra-hypofraktionierte RT (Gesamtdosis 26 Gy, d.h. 5 Fraktionen in einer Woche = 1 Fraktion/Tag bzw. 28,5 Gy, d.h. 5 Fraktionen in 5 Wochen = 1 Fraktion/Woche)	1b	B	+/-
▪ Konventionell fraktionierte RT (Gesamtdosis ca. 50 Gy in ca. 25-28 Fraktionen in ca. 5-6 Wochen)	1a	B	+
▪ Bei Lebenserwartung < 10 Jahre und pT1, pN0, R0, ER / PR positiv, HER2-negativ, endokriner adjuvanter Therapie (alle Faktoren) kann unter Inkaufnahme eines erhöhten Lokalrezidivrisikos nach individueller Beratung auf die RT verzichtet werden.	1a	B	+

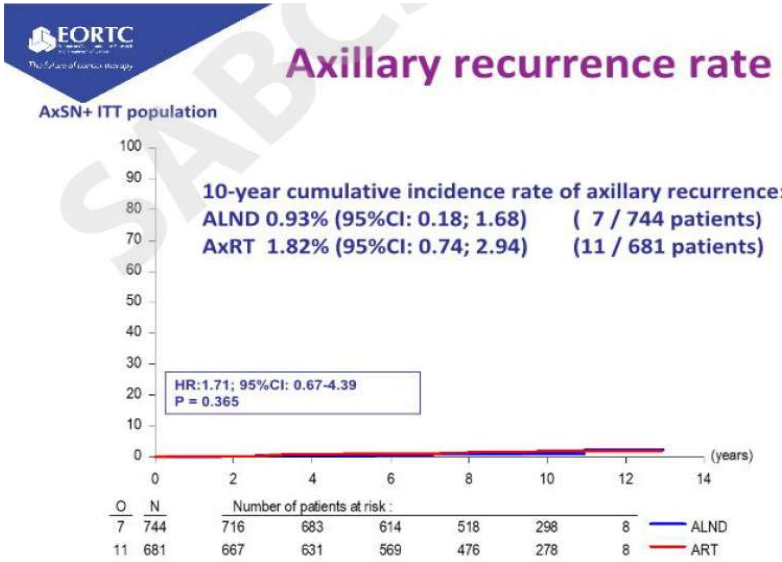
EORTC 10981-22023 AMAROS

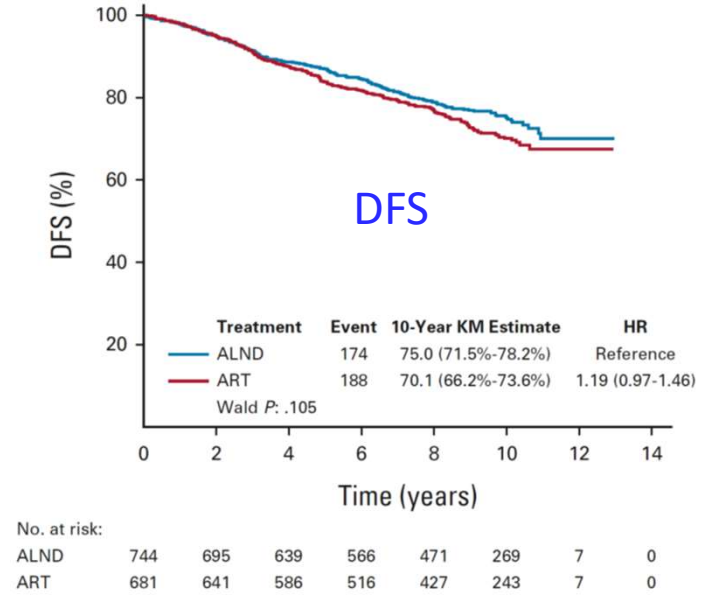




AxRT



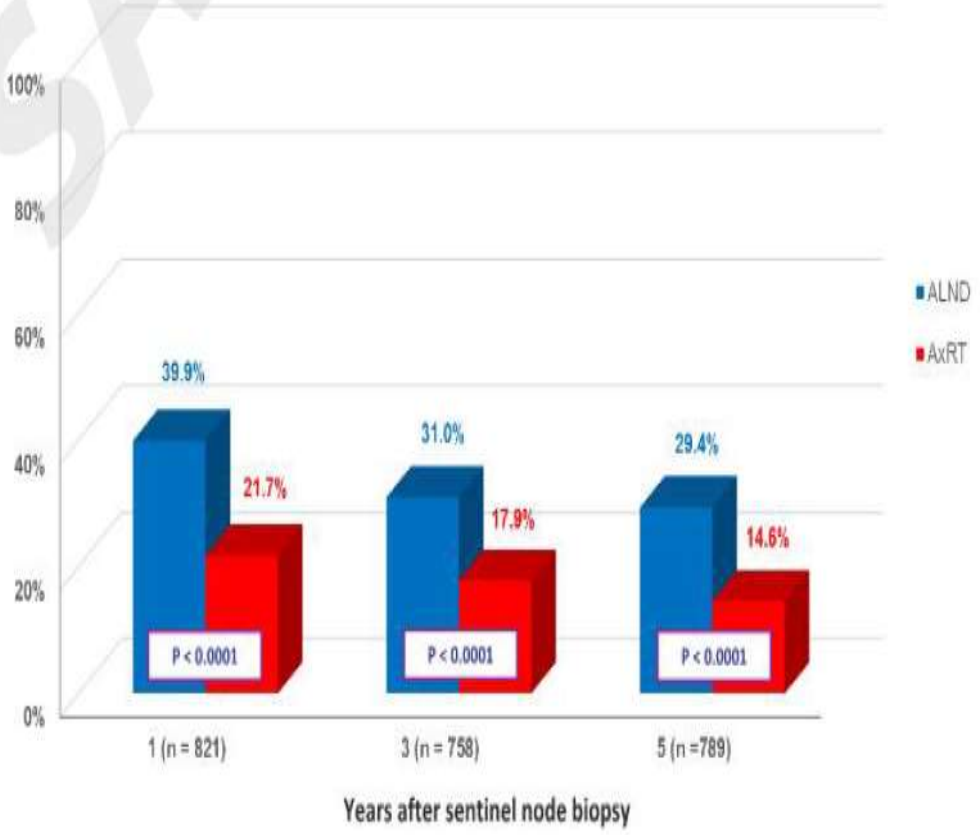




Donker et al. Lancet Oncol 2014

Bartels et al. JCO 2022

Lymphedema: clinical observation and/or treatment

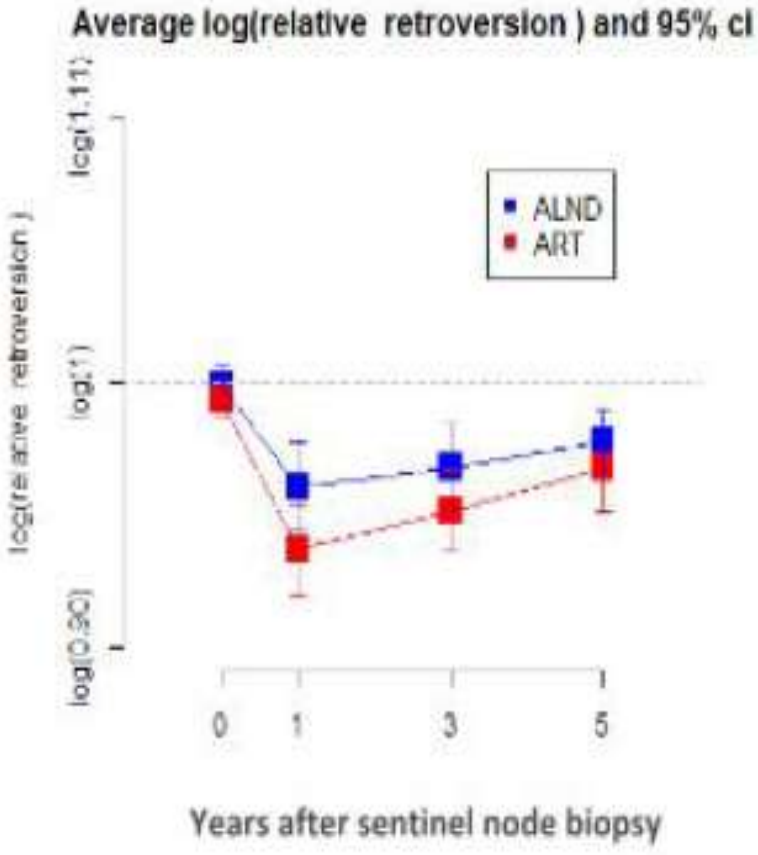


Shoulder function

Results:

No significant differences in all 4 excursions

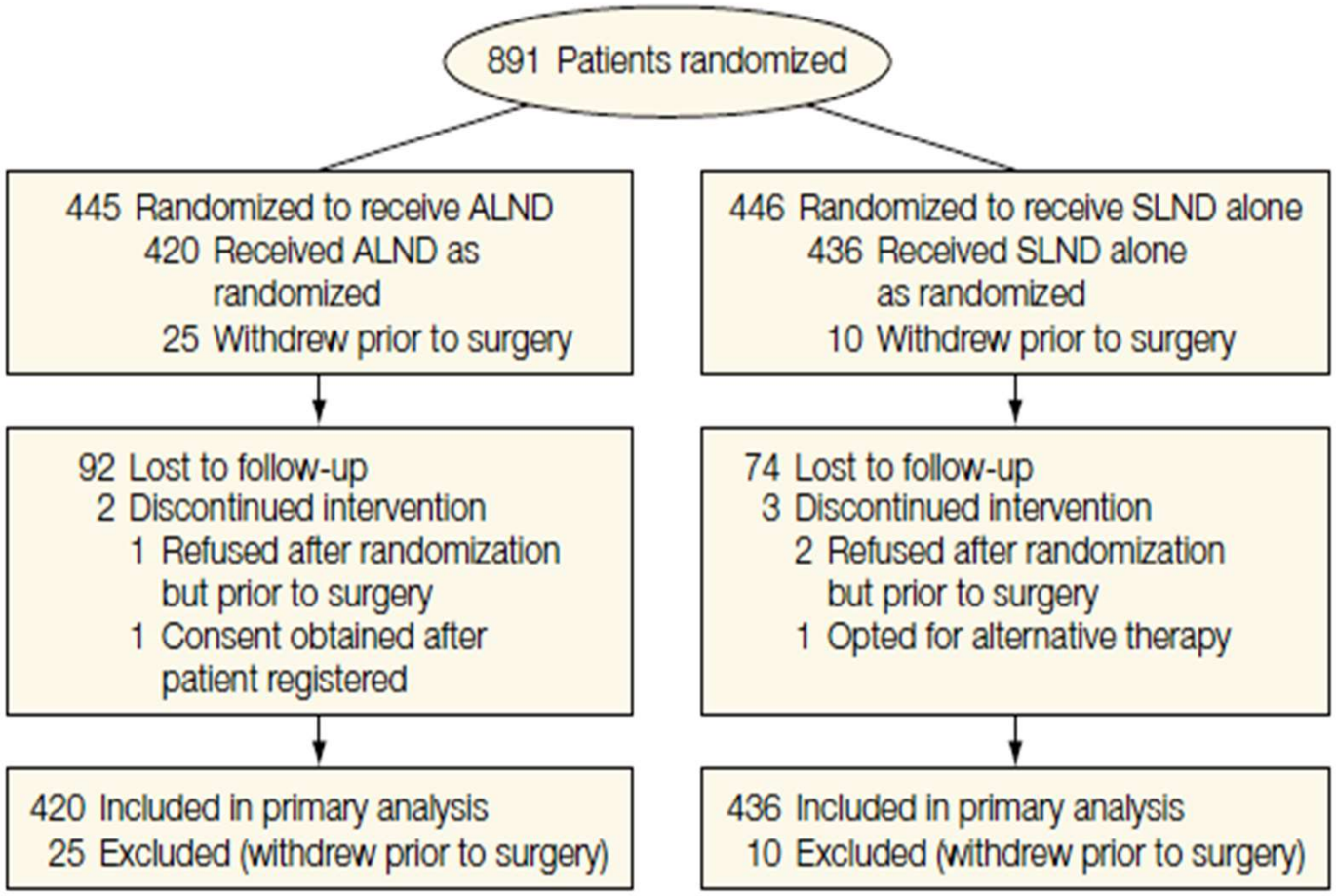
Trend towards impaired movement after AxRT in first year only



Rutgers et al. Update, San Antonio 2018

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)	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

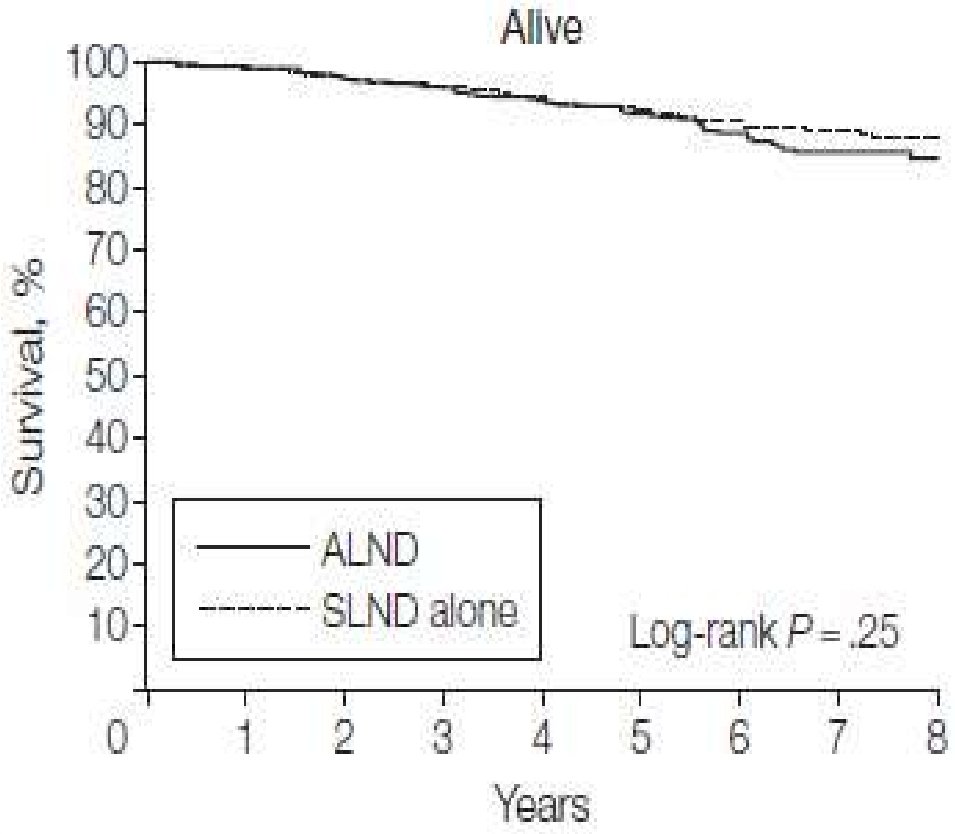
micrometastases
ALND: 137 of 365 (37.5%)
SLND: 164 of 366 (44.8%) (p=0.05)

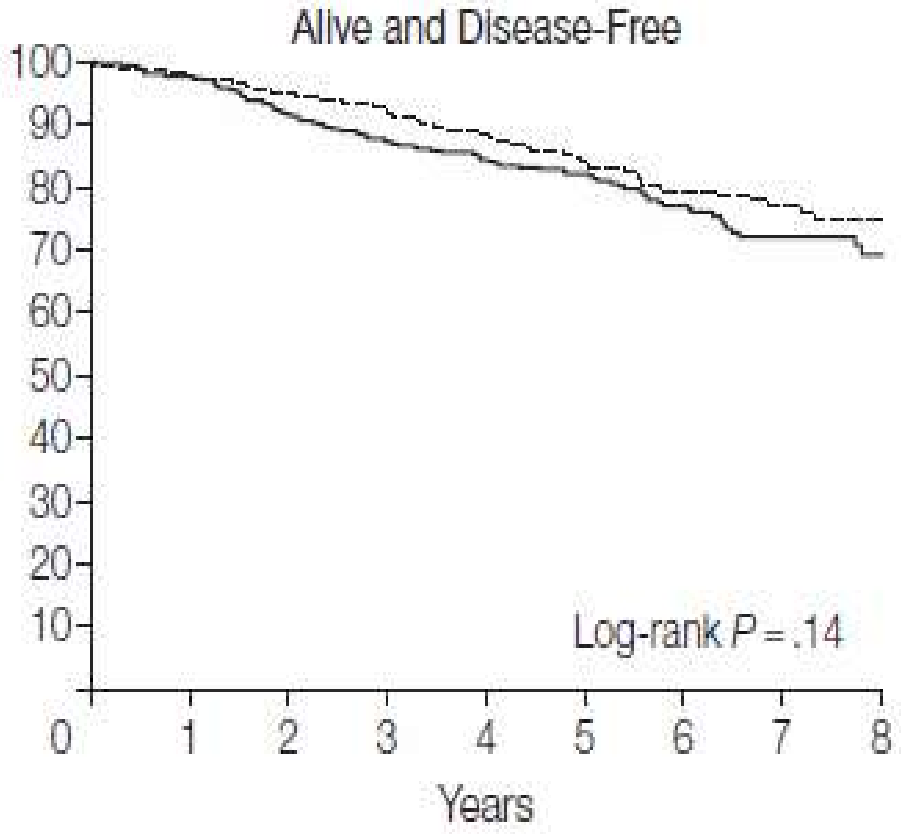
Giuliano et al. JAMA 2011

Z0011 trial

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

All patients were planned to receive tangential radiotherapy to the breast





No. at risk

ALND	420	408	398	391	378	313	223	141	74
SLND alone	436	421	411	403	387	326	226	142	74

420	369	335	310	286	226	152	83	37
436	395	363	337	307	231	147	81	36

Giuliano et al. JAMA 2011

Z0011 trial

Dose in the Axillary LN-levels I + II using different RT-Techniques

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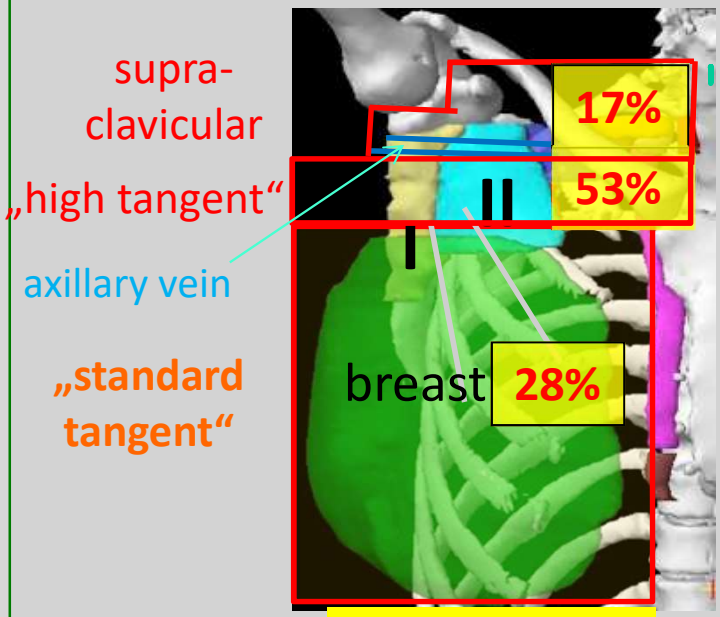
ACOSOG Z0011 Trial
45% micrometast. in the exp. arm

RT-volume
% of patients



Data from 228/856 pat.

	mean dose*	encompassed volume**
LN level 1		
AMAROS	> 95%	> 95%
high tangent	86%	79%
standard tangent	66%	51%
IMRT+	29%	1%
LN-level 2		
AMAROS	> 95%	> 95%
high tangent	71%	51%
standard tangent	44%	26%
IMRT+	7%	0%

* in relation to the prescribed dose in the breast
** % volume receiving the prescribed dose
\+ Lee et al. Medicine 2016 (3)

Jagsi (2): “The results of Z0011 should not be extrapolated to patients who receive RT using partial-breast or prone techniques, in which substantially less of the axilla is included”

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Radiotherapie der Axilla bei Patientinnen mit positiven Sentinel-Lymphknoten** ohne axilläre Dissektion

	Oxford		
	LoE	GR	AGO
BET und ACOSOG Z0011-Kriterien⁺ erfüllt	2b	B	+*
▪ Radiotherapie der Brust unter Einschluss von Level 1 + 2 bis 5 mm unterhalb der Vena axillaris (PTV)			
BET und ACOSOG Z0011-Kriterien⁺ nicht erfüllt	1b	B	++*
▪ Radiotherapie der Axilla (analog AMAROS)			
Nach ME, RT der Thoraxwand indiziert und ACOSOG Z011-Kriterien⁺ nicht erfüllt oder ME und RT der Thoraxwand nicht geplant			
▪ Radiotherapie der Axilla (analog AMAROS)	1b	B	++
≥ 3 pos. SLN			
▪ Radiotherapie der Axilla (analog AMAROS)	1b	B	+

* Studienteilnahme empfohlen
** Makrometastasen
⁺ < T3, keine palpablen LK, R0, 1-2 befallene SN, keine NACT