RadioOnkologie

Behandeln
Forschen
Lehren

UniversitätsKlinikum Heidelberg

Standards And Innovation In Adiuvant Radiotherapy After Breast-conserving Surgery (BCS)

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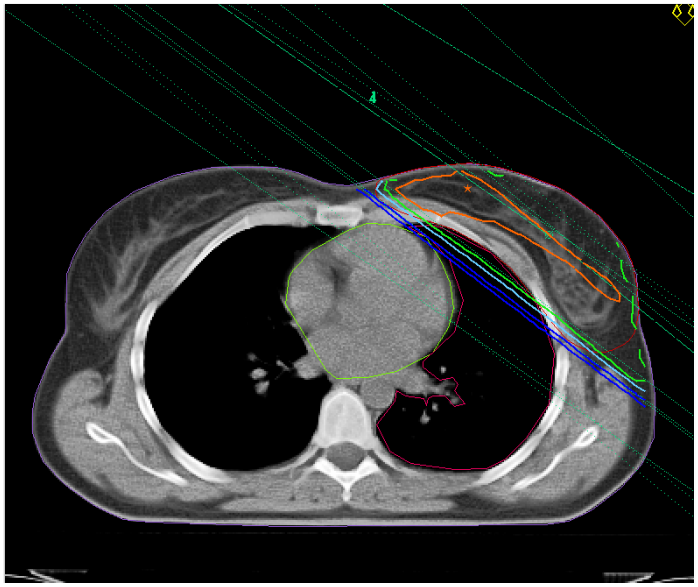
Radiotherapy Breast Cancer

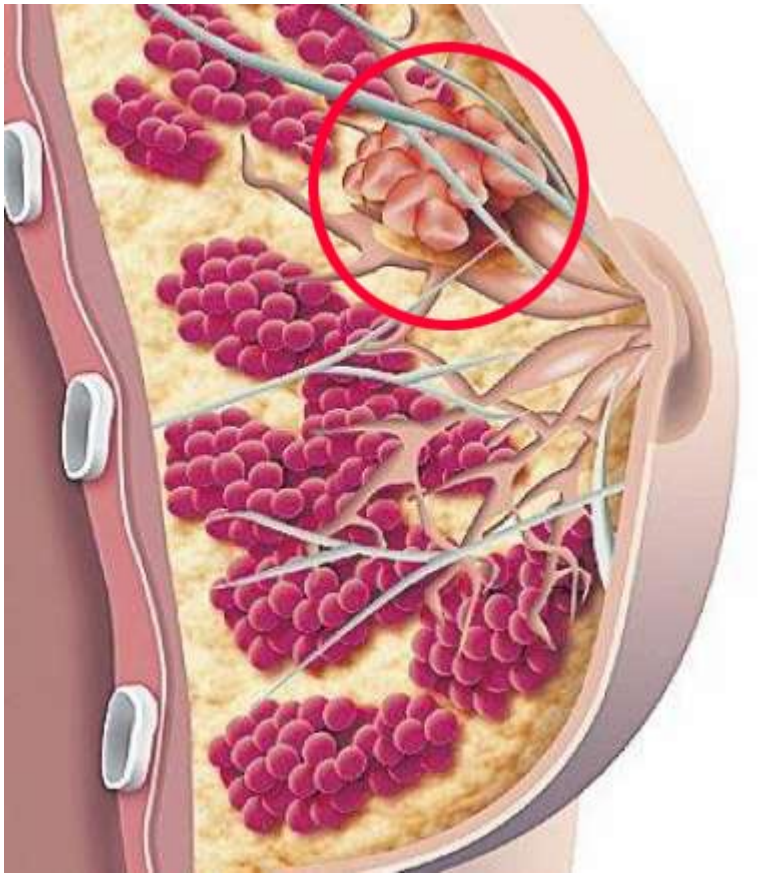
CT-based 3D treatment planning



Target volume: whole breast, chest wall
Organs at risk: lung, heart, contralateral breast

Fractionation: dose application in > 30 sessions
Aim: to take advantage of DNA-repair in normal cells

Adjuvant Radiotherapy Invasive Carcinoma



Holland et al., Cancer, 1985:

no residual tumor:	37%
Residual tumor 0-2 cm from PT:	20%
Residual tumor > 2 cm from PT:	43%
Residual tumor > 4 cm from PT:	10%

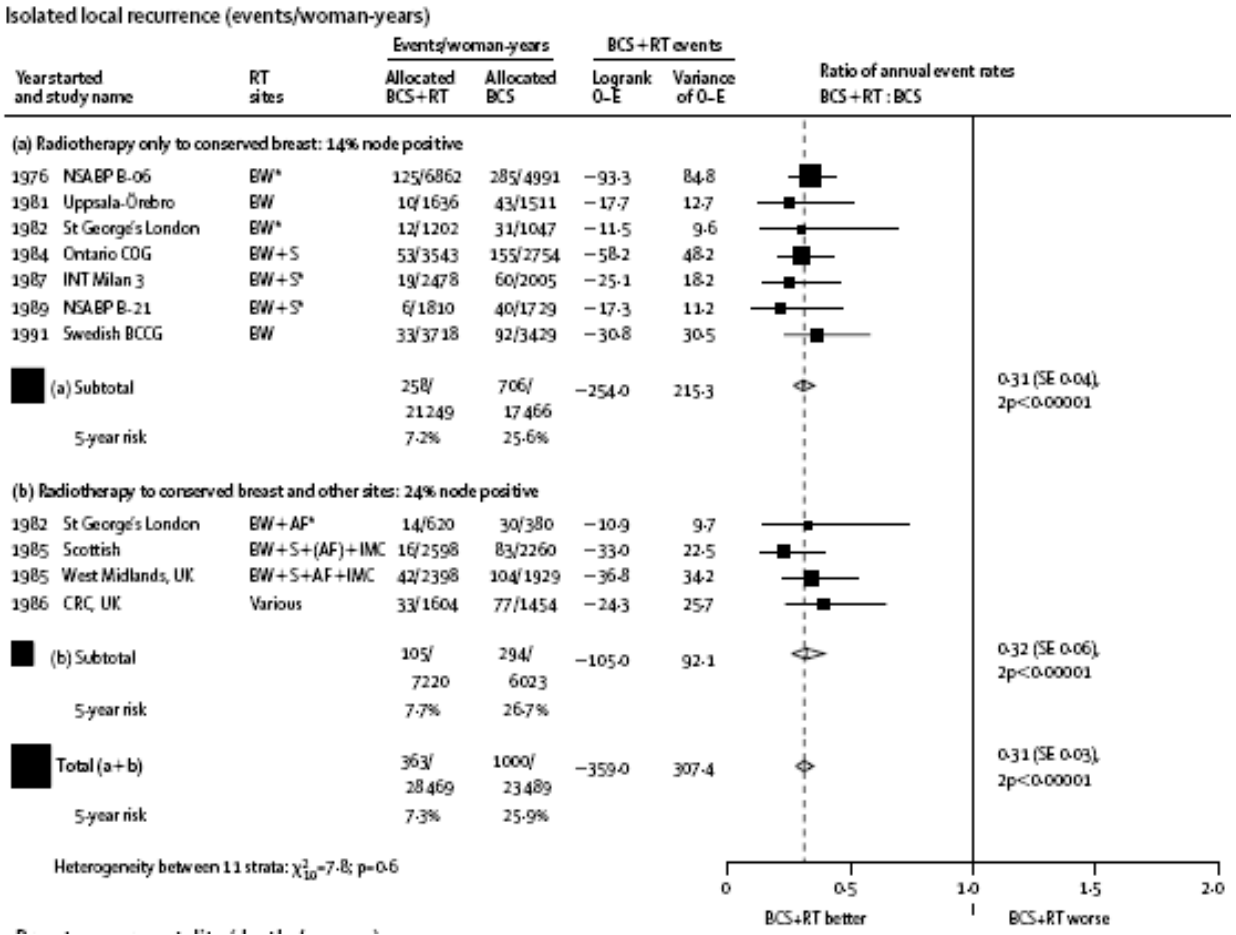
Sole breast-conserving surgery associated with significantly higher recurrence rates than primary ablation

Veronesi et al., NEJM 2002

Adjuvant Radiotherapy Invasive Cancer

Influence of radiation on local tumor control

Metaanalysis Early Breast Cancer Trialists Collaborative Group (EBCTCG) Lancet 2005; 366: 2087–2106



Adjuvant Radiotherapy Invasive Carcinoma

Influence of radiation on local tumor control

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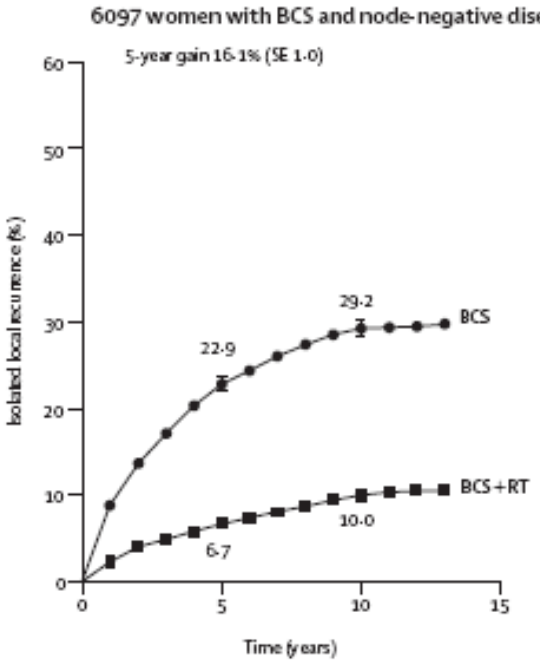
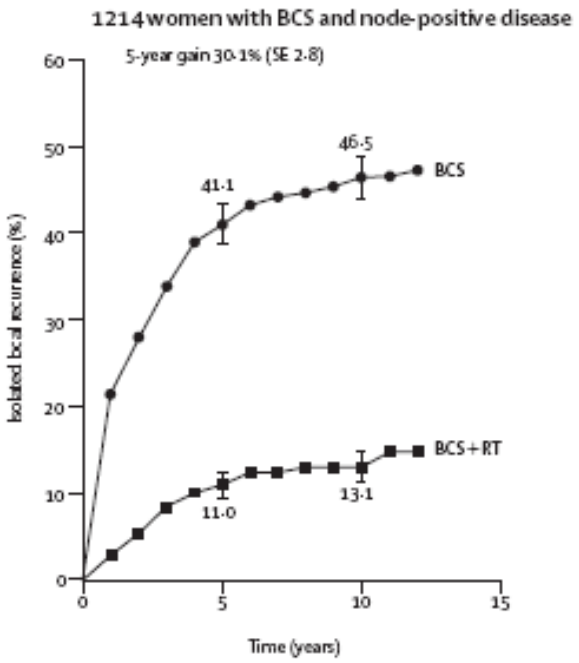


node negative



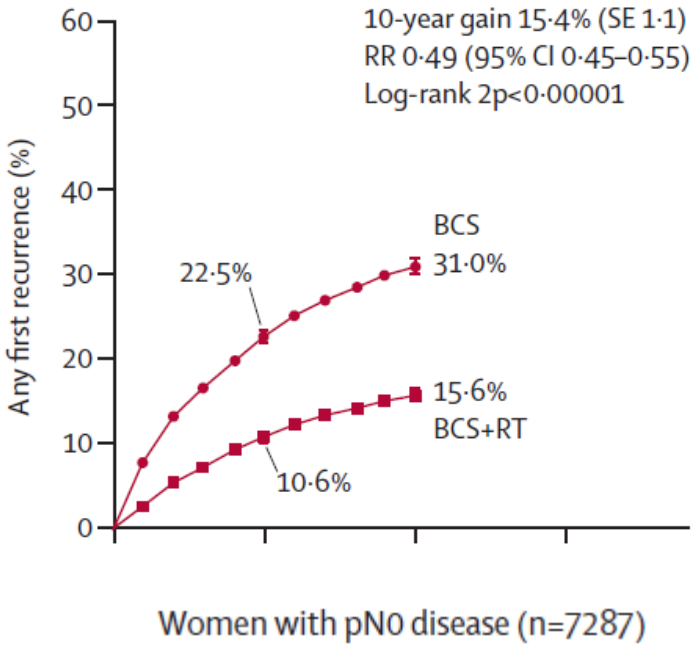
node positive

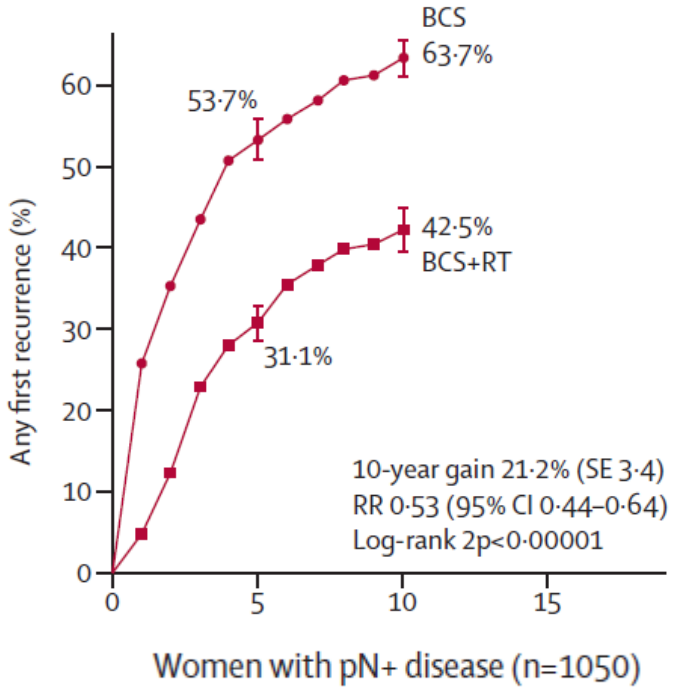
Relative reduction of local recurrence rates of approx. 70%

Adjuvant Radiotherapy Invasive Carcinoma

Influence of radiation on total recurrence rate

Metaanalysis Early Breast Cancer Trialists Collaborative Group (EBCTCG) *Lancet* 2011; 378: 1707–16



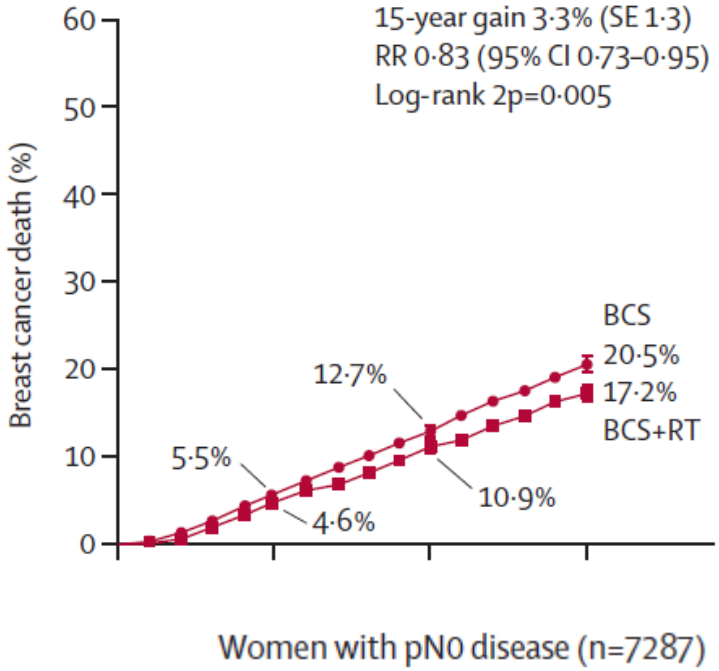


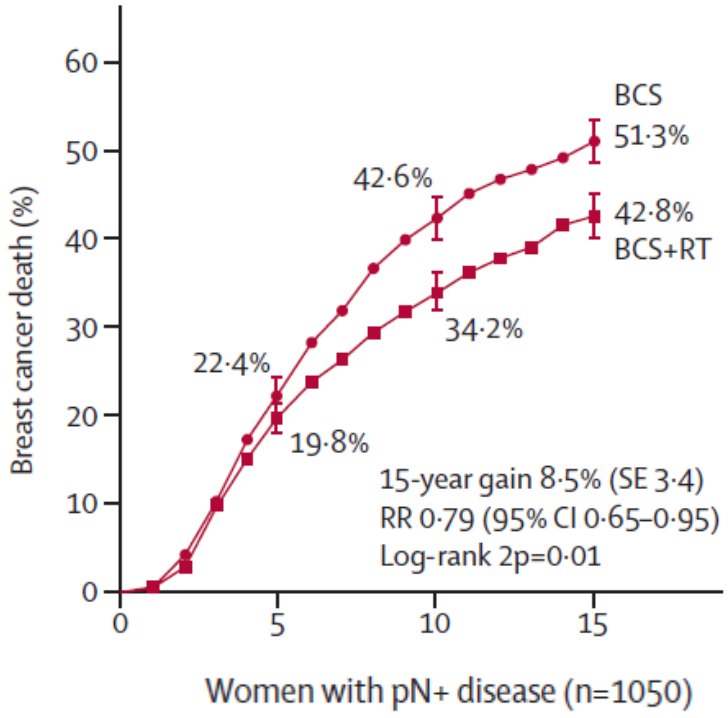
Relative reduction of any recurrence rates of approx. 50%

Adjuvant Radiotherapy Invasive Carcinoma

Influence of radiation on mortality

Metaanalysis Early Breast Cancer Trialists Collaborative Group (EBCTCG) *Lancet* 2011; 378: 1707–16





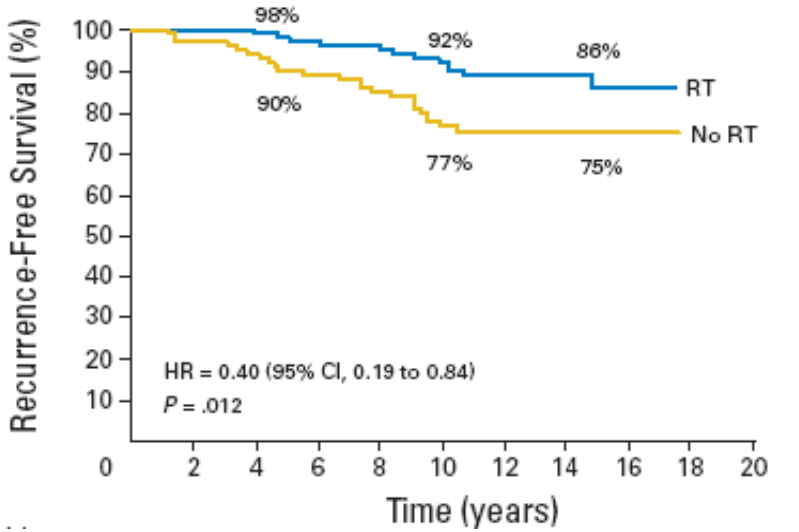
Radiotherapy in BCS improves survival

Adjuvant Radiotherapy Invasive Carcinoma

Are there certain subgroups where adjuvant radiotherapy can be omitted?

Holli et al. JCO, 2009

>50J, T1, N0, HR:+, G1-2, RR >1cm



Adiuvant RT is standard after BCS
even in patients with favorable prognosis!

Adjuvant Radiotherapy Invasive Carcinoma

Can outcome be optimized any further by an additional boost-irradiation of the tumor bed?

Reason: 90% of local recurrences occur in proximity of the primary

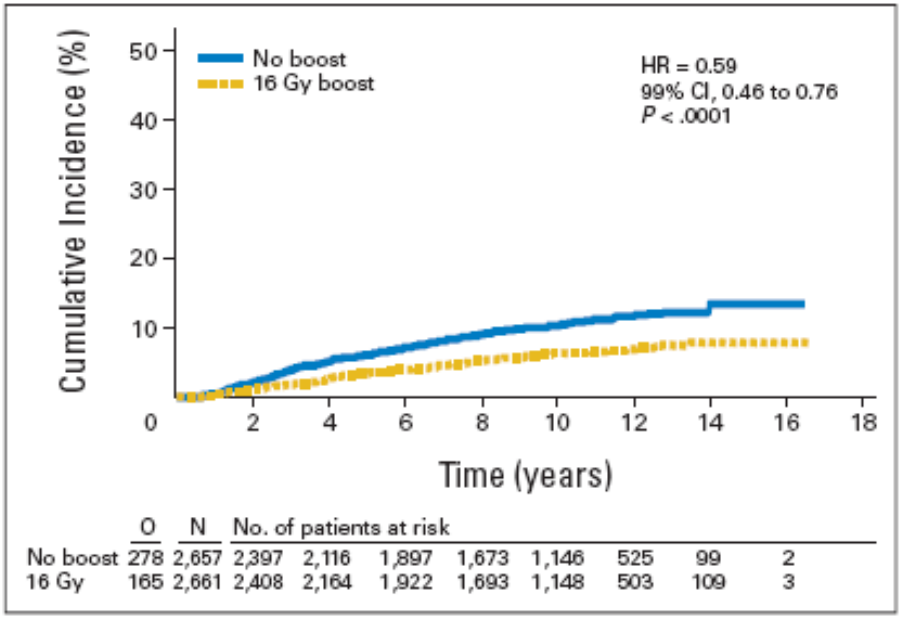
EORTC Trial, Bartelink et al., 2007:

5318 patients, prospectively randomised

Whole-breast RT (50 Gy)

vs.

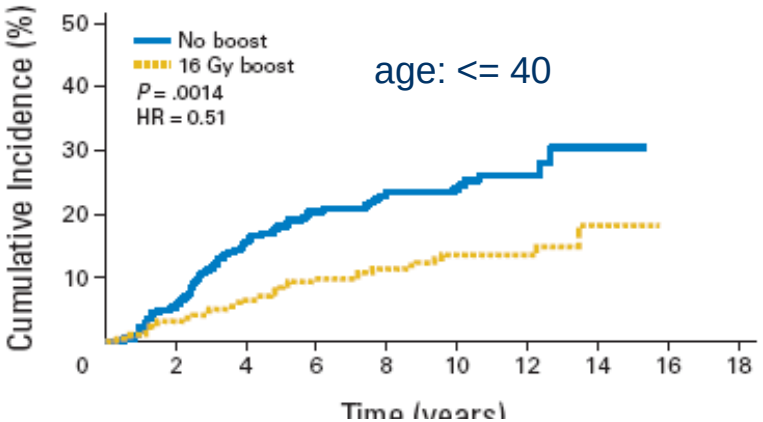
Whole-breast RT + 16 Gy Boost

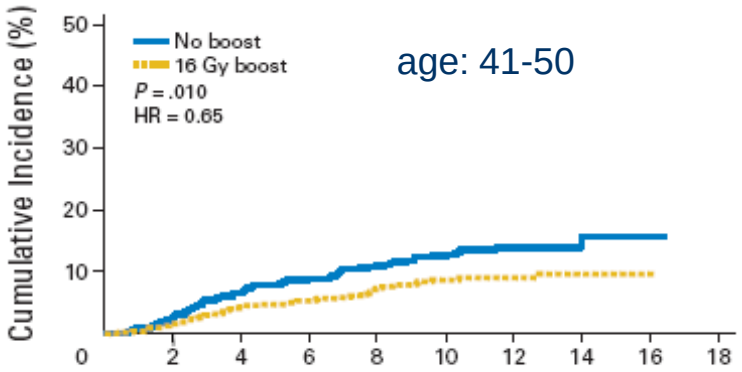


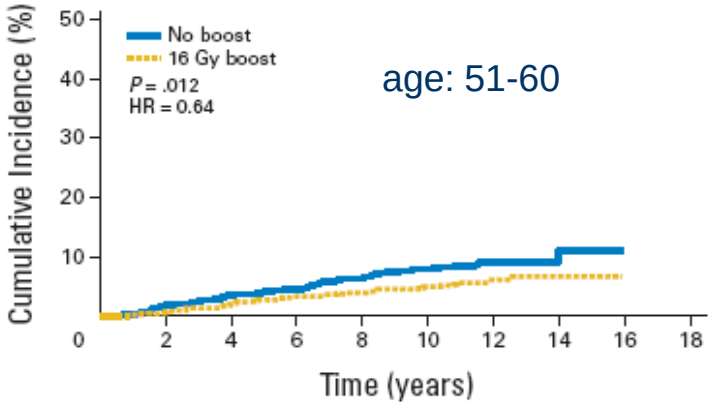
Adjuvant Radiotherapy Invasive Carcinoma

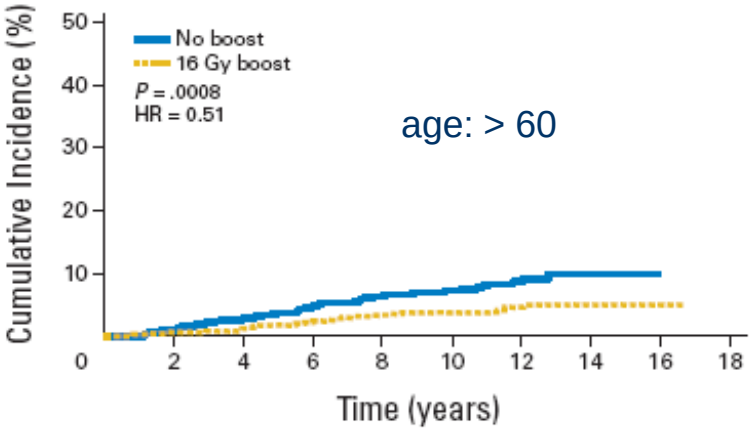
Boost-irradiation of the tumor bed

EORTC Trial, Bartelink et al., 2007:









Adjuvant Radiotherapy Invasive Carcinoma

Boost-irradiation of the tumor bed

Further risk factors for In-Breast-Recurrences:

- Tumor size >2 cm (T2)
- Close margin (< 3 mm)
- Extensive intraductal component (EIC)
- Lymphangiosis (L1)
- High grade (G3)
- ER/PR-Negativity
- Multifocality

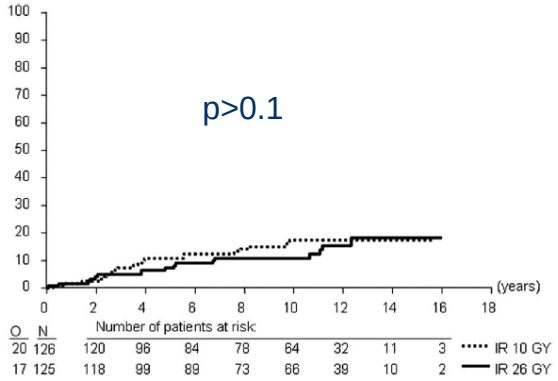
Adjuvant Radiotherapy Invasive Carcinoma

Boost-irradiation of the tumor bed

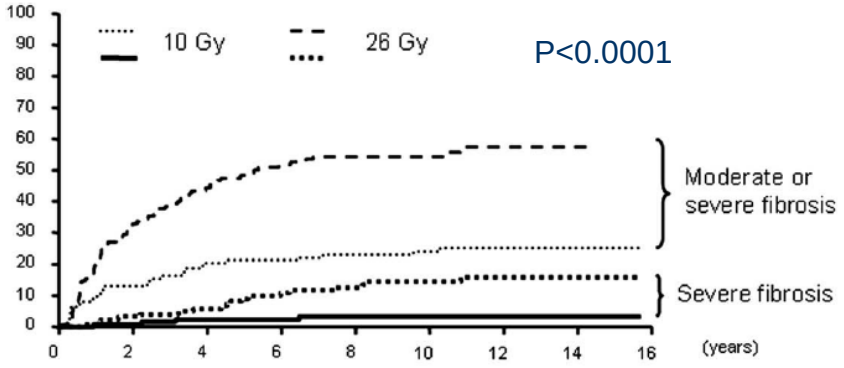
Can dose escalation of the boost dose compensate for incomplete resections?

Poortmanns et al., Radiother Oncol 2009:

251 patients, T1-2 N0-1, R1-Resection, randomised 10 Gy vs. 26 Gy Boost



Local control

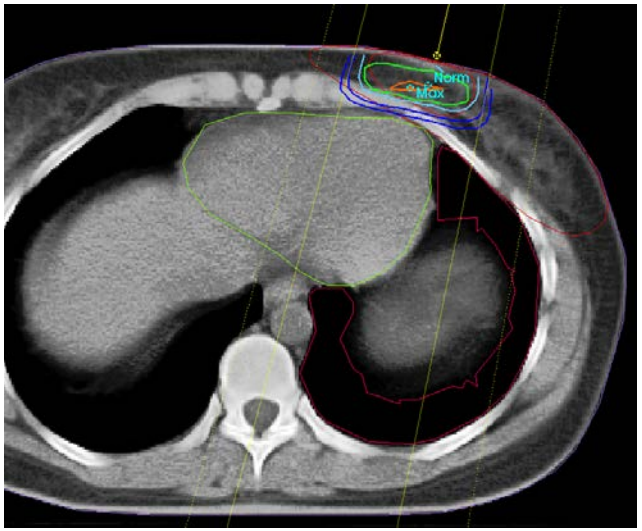


Fibrosis

Boost dose escalation does not improve local control after R1-Resection while late toxicity is increased

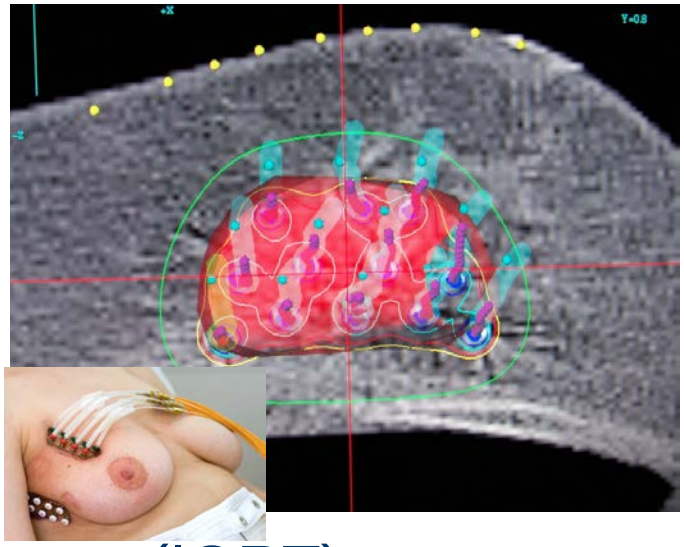
Boost-irradiation of the tumor bed after surgery

Percutanous 3D-planned radiotherapy



Do we hit the target ?

3D-planned brachytherapy



Electrons

Intraoperative radiotherapy (IORT)

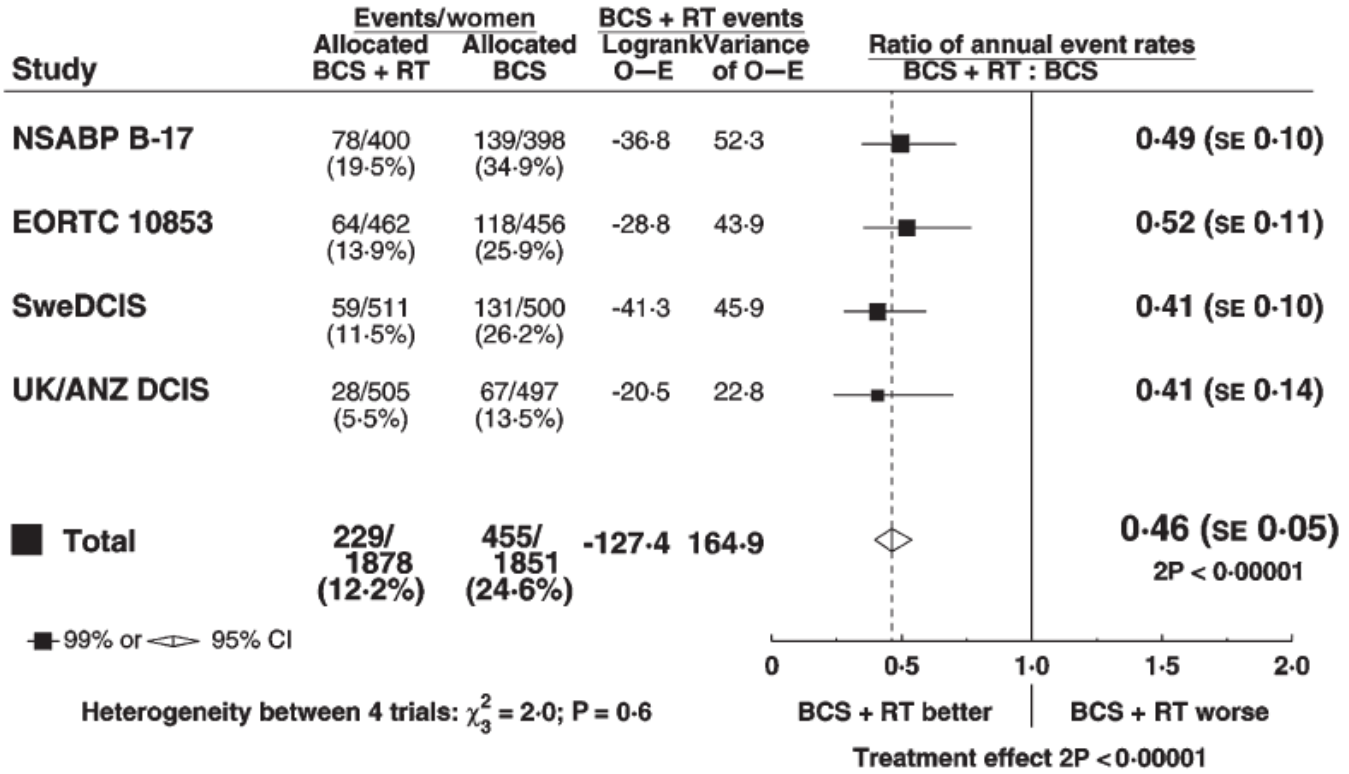
Photons

Adjuvant Radiotherapy DCIS

Is adjuvant RT necessary after BCS for DCIS?

Metaanalysis EBCTCG, 2010:

Journal of the National Cancer Institute Monographs, No. 41, 2010



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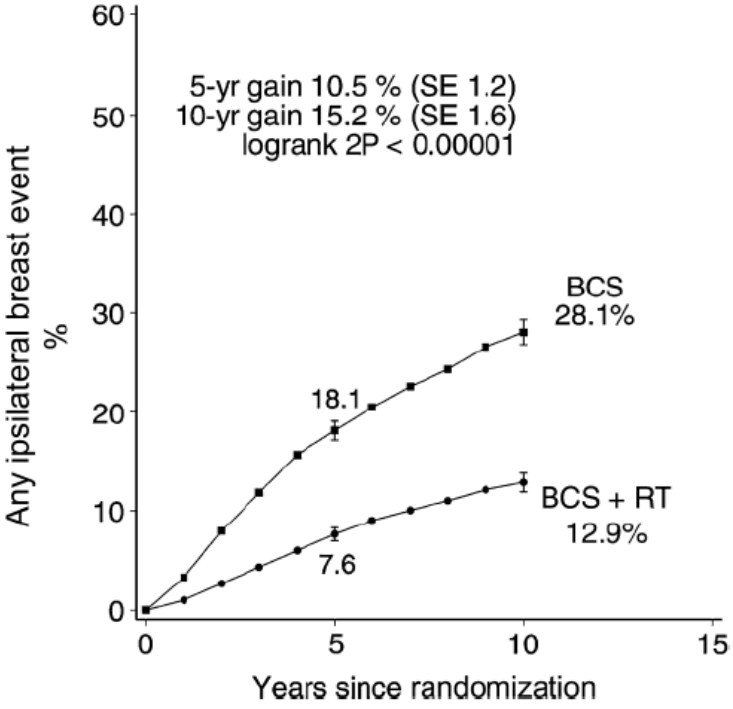

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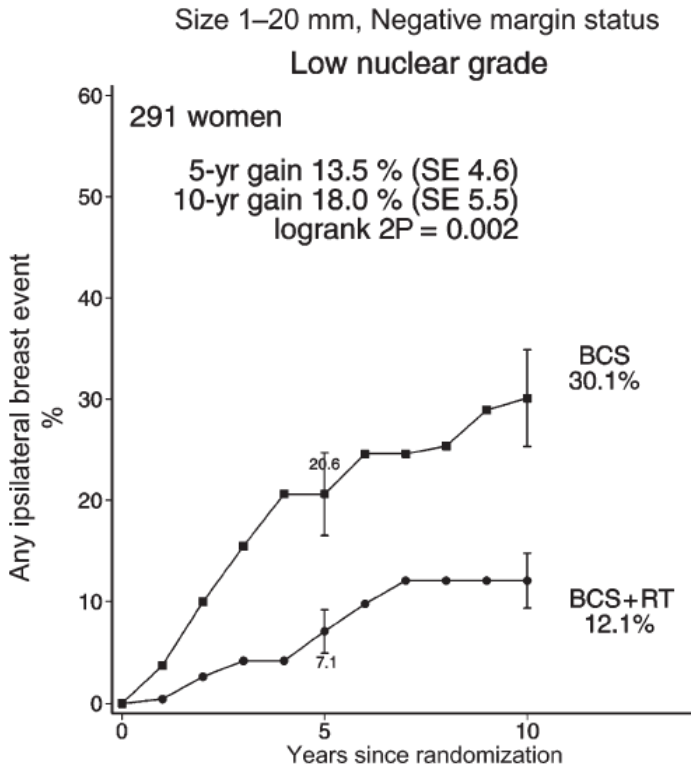


No identification of subgroups that do not profit with respect to local control!

Adjuvant Radiotherapy DCIS

Is adjuvant RT necessary after BCS for DCIS?

Wong et al., JCO, 2006:
Prospectively randomised study: sole BCS vs. BCS+ adjuvant RT
planned patient number: 200

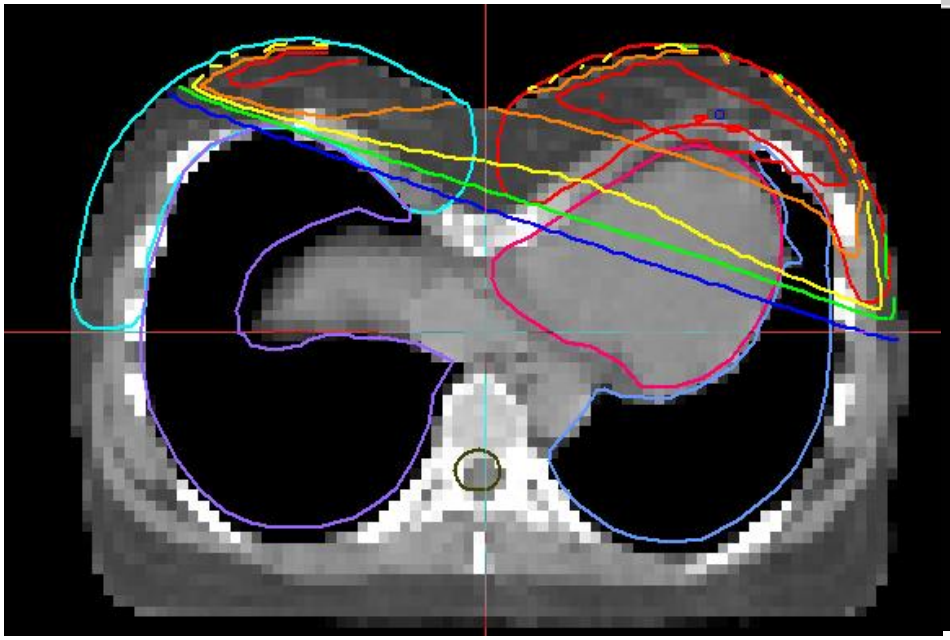
Inclusion criteria:
G1-2
Margins >= 1 cm
Tumor size <= 2,5 cm

Van Nuys Prognostic Index (VNPI) <7

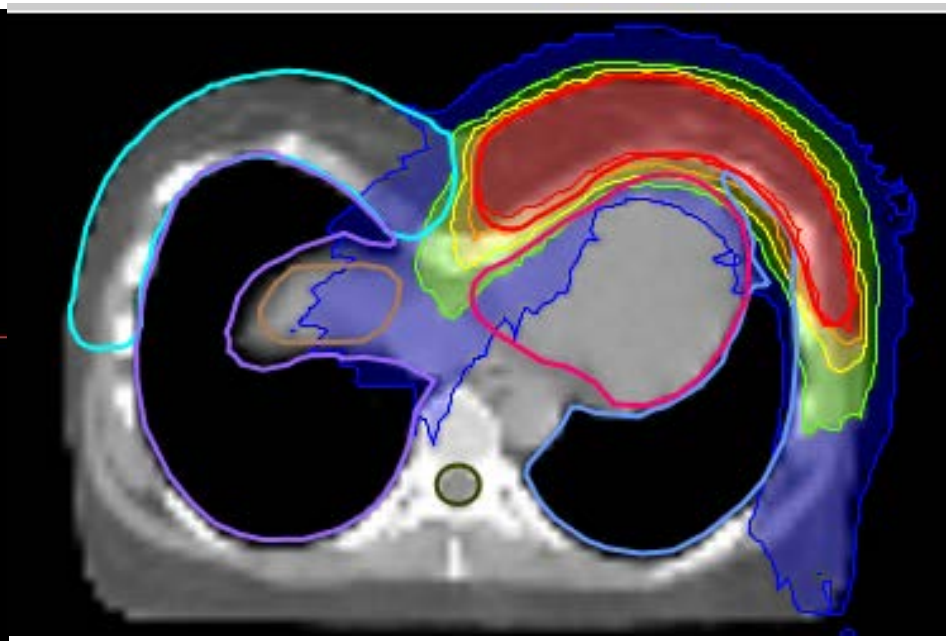
Premature study termination after158 patients because of high recurrence rates!
5-year recurrence rates: approx. 12% (70% DCIS, 30% invasive)

No identification of subgroups without benefit from adjuvant RT!

Technical Developments:
Aim: Better Conformation Of Dose:
Intensity Modulated RadioTherapy (**IMRT**)

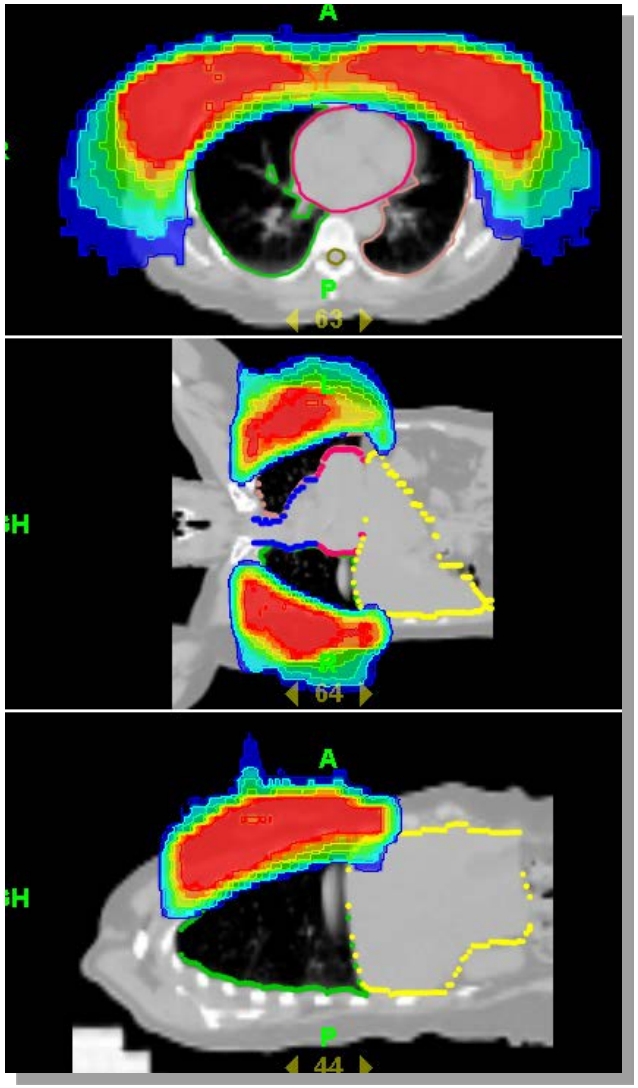


conventional 3D-Plan



IMRT

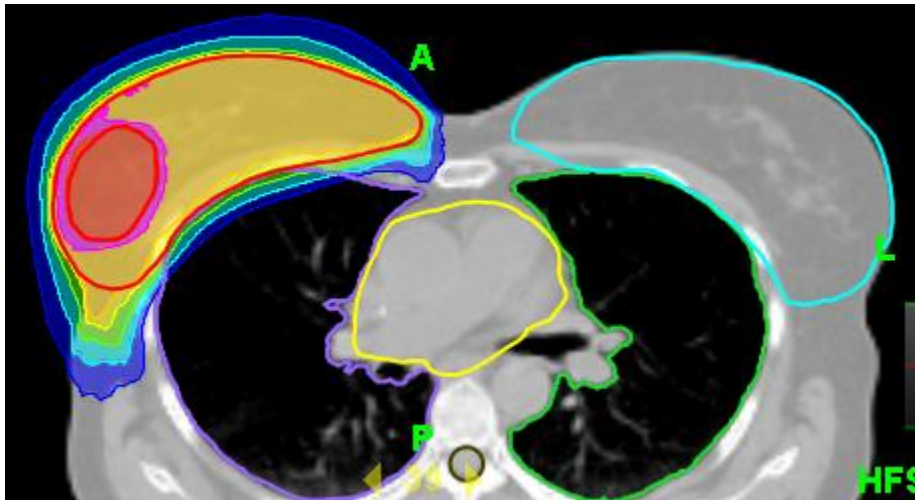
Intensity Modulated RadioTherapy (IMRT)



40 y old patient afterbilateral BCS: sparing of lung and heart tissue

Intensity Modulated RadioTherapy (IMRT)

Integrated Boost



Shortening of overall treatment time

Potentially higher rates of acute and late normal tissue changes by elevated single doses

MINT-Trial

Prospectively randomised, multicentric phase-III study

Hypothesis: no impairment of the outcome despite the shortened treatment

N= 502 patients
Adjuvant RT after BCS

Konv. RT + sequent. Boost

28 + 8 = 36 fractions

IMRT + integrated Boost

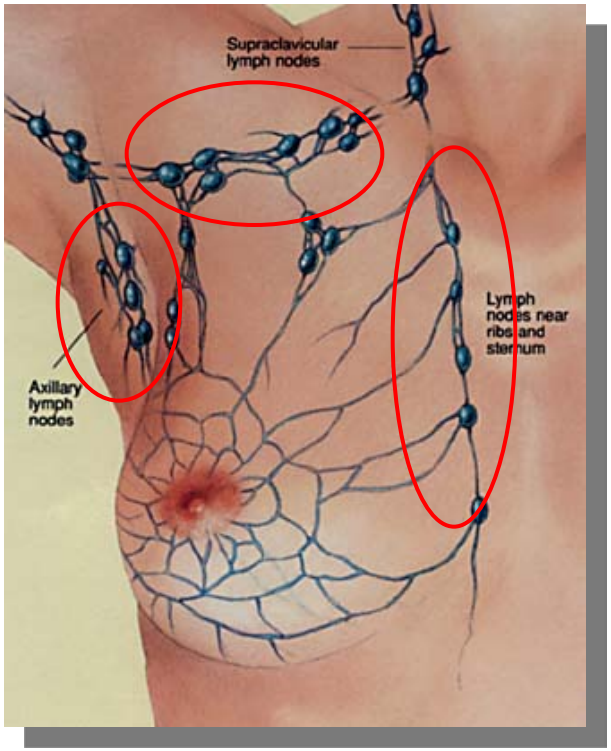
28 fractions

Endpoints: Cosmetics, toxicity and local control

Adjuvant Radiotherapy Regional Lymphatics

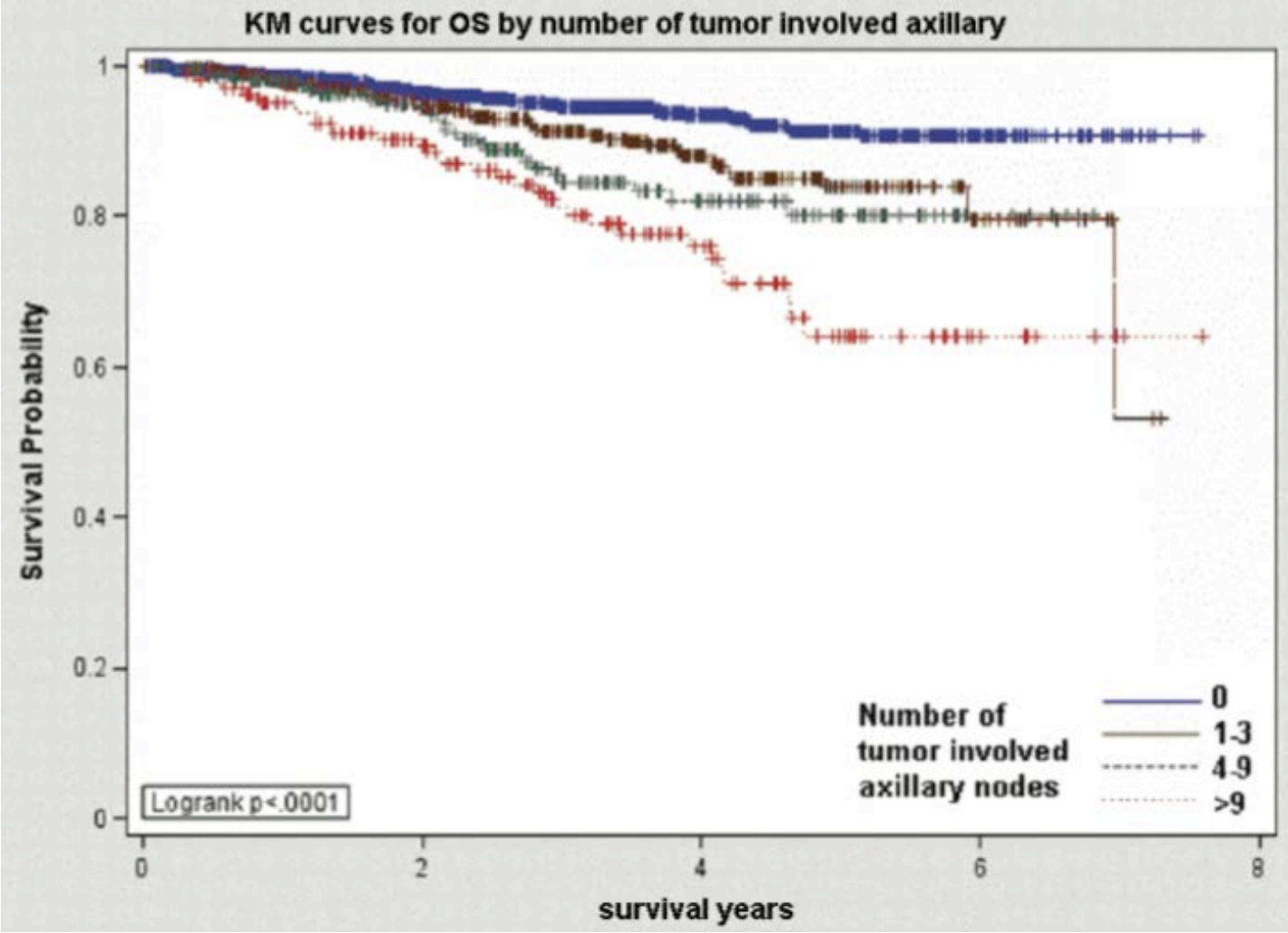
Little evidence by clinical studies on adjuvant RT of the lymphatics to date

Most data result from post-mastectomy trials



The Impact Of Nodal Status On Survival:

Heidelberg Cohort 2003-2009 (N= 3089 all breast cancers)



Heil et al, Breast 2012

Nodal Status Is An Independet Predictor:

Heidelberg Cohort 2003-2009 (N= 2723 inv. breast cancers)

	DFS		DDFS		OS	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
Age	1.01 (0.0288)	1.017 (<0.0004)	1.014 (0.0037)	1.018 (<0.0002)	1.029 (<0.0001)	1.036 (<0.0001)
pT category	2.105 (<0.0001)	1.67 (<0.0001)	2.334 (<0.0001)	1.882 (<0.0001)	2.181 (<0.0001)	1.824 (<0.0001)
Nodal status	1.655 (<0.0001)	1.354 (<0.0001)	1.723 (<0.0001)	1.368 (<0.0001)	1.59 (<0.0001)	1.355 (<0.0001)
Grading	2.502 (<0.0001)	1.673 (<0.0001)	2.701 (<0.0001)	1.759 (<0.0001)	3.215 (<0.0001)	1.804 (<0.0003)
HR status	0.376 (<0.0001)	0.421 (<0.0001)	0.383 (<0.0001)	0.410 (<0.0001)	0.27 (<0.0001)	0.262 (<0.0001)
HER2 status	2.27 (<0.0001)	1.05 (0.7811)	2.117 (<0.0001)	0.968 (0.8586)	2.348 (<0.0001)	0.822 (0.3988)

DFS, disease-free survival; DDFS, distant disease-free survival; OS, overall survival; HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

Heil et al, Breast 2012

Adjuvant Radiotherapy Axillary Lymphatics

Is additional therapy of the axilla mandatory in positive sentinel node?

Tjan-Heijnen, ASTRO abstract 2009:

retrospective, 2592 pat., no macro mets, only pN0(i-), pN0(i+) or pN1mi

Treatment: **SN only** *or* **completion ALND** *or* **axillary RT**

	n	5-year AR(%)	HR AR (95%CI)*
pN0(i-)(sn) cALND	113	1.9	1.00
pN0(i-)(sn) SN	722	2.2	1.07 (0.23 - 4.94)
pN0(i+)(sn) cALND or ax RT	459	1.1	1.00
pN0(i+)(sn) SN	340	1.7	2.14 (0.57 - 7.96)
pN1mi(sn) cALND or ax RT	828	1.2	1.00
pN1mi(sn) SN	130	6.2	4.45 (1.46 - 13.54)

Significantly higher axillary recurrence rate in pN1mi when no further treatment (surgery or RT) is performed

Adjuvant Radiotherapy Axillary Lymphatics

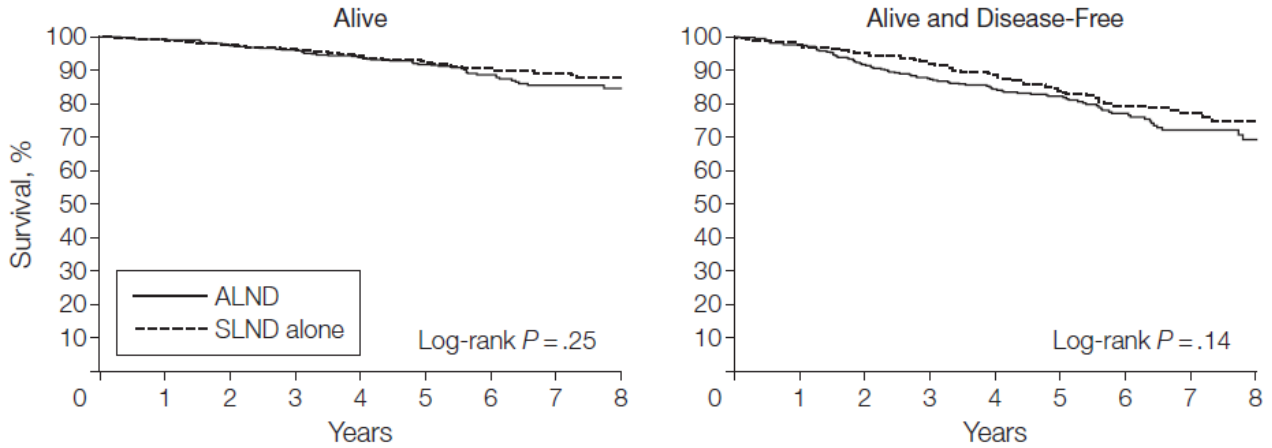
Is additional therapy of the axilla mandatory after positive SLND?

Giuliano et al., JAMA 2011: ACOSOG Z0011 trial

randomized, closed prematurely: 856 of 1900 planned patients
T1-2, cN0, sentinel node biopsy positive (1-2 SNB+)

Treatment: **BCS, adjuvant tangential RT (breast only, not axilla)**

Randomisation: completion ALND vs. no further dissection



Adjuvant Radiotherapy Axillary Lymphatics

Is additional therapy of the axilla mandatory after positive SLND?

Giuliano et al., JAMA 2011: ACOSOG Z0011 trial

Conclusion: „in patients with limited positive SLN disease, treated with breast conservation +/- systemic therapy, the use of SLND alone compared with ALND did not result in inferior survival“

But:

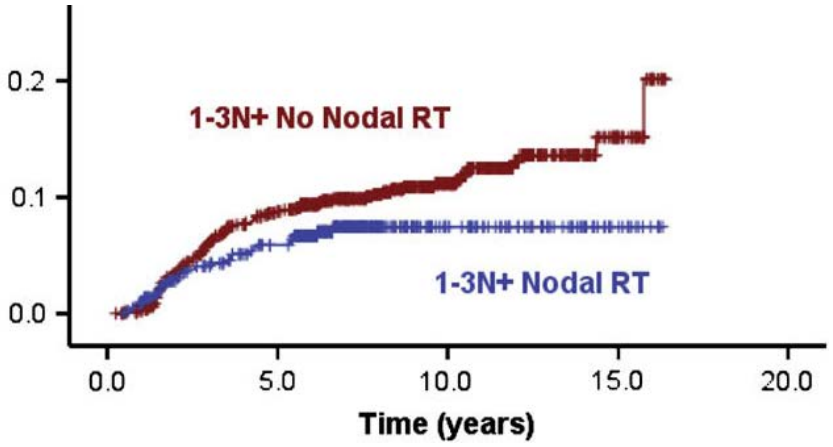
- Study not powered for the limited patient number
- Primary endpoint overall survival, not locoregional recurrence
- Short follow-up (median 6.3 y) for detection of survival differences
- Radiotherapy not further specified, espec. concerning inclusion of axilla

Results should be interpreted very carefully

Adjuvant Radiotherapy Supraclavicular Lymphatics

Irradiation of the supraclavicular lymphatics even in less than 4 affected axillary nodes?

Truong et al. 2009: retrospective, 5699 Pat., T1/2, N0-1a, M0



1-3 pos. ax. LN: **age<50** *or* **G3** *or* **ER-neg**.: locoregional recurrence risk **15-20 %**

significant reduction of regional recurrence by supraclavicular RT

Adjuvant Radiotherapy Supraclavicular Lymphatics

Irradiation of the supraclavicular lymphatics even in less than 4 affected axillary nodes?

Whelan, ASCO Abstract 2011: **Intergroup / NCIC-CTG MA.20 trial**

Prospective, multicenter, 1832 pts., high-risk N0 (10%) or **N+ (85% N1a)**

Whole-breast RT (50 Gy)

Whole-breast RT (50 Gy)
+
regional nodal RT
(SCLV/internal mammary/axillary apex) (45 Gy)

Impact of WBI+RNI on :
- isolated locoregional 5-yr DFS: 96.8% vs 94.5% (SS)
- distant DFS: 92.4% vs 87.0% (SS)
- DFS: 89.7% vs 84.0% (SS)
- OS: 92.3% vs 90.7% (trend p=0.07)

Summary

- **Invasive carcinoma:** Adjuvant RT improves local control and overall survival
  further improvement of local control by Boost-RT
- **In-situ carcinoma:** Adjuvant RT after BCS improves local control
  no identification of subgroups not profiting to date
- **IMRT:** improved dose conformality and normal tissue sparing
  possibility of integrated boost concept
- **Regional lymphatics:** SLN+: omission of cALND only in selected cases
  1-3N+: RT of supraclavicular lymphatics (G3,<50y,ER/PR -)
  4-N+: supraclavicular RT generally recommended