Grandangolo in Radioterapia Oncologica
Tumori della mammella – Tumori del polmone

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Ospedale Bellaria, Bologna

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Tumori della mammella

Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials

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

	Number of trials available*	Years trials began	Women	Deaths	Woman-years at risk						
					Median/ woman	Total (thousands)	Distribution by years since diagnosis (thousands)				
							<5	5–9	10–14	15–19	20+
Trial category†											
(A) Lumpectomy, original trials[6–11]	6	1976–86	4398	1982	11·8	52·9	20·3	16·0	10·1	4·8	1·7
(B) Sector resection or quadrantectomy[12–15]	4	1981–91	2399	708	12·4	29·4	11·6	10·3	6·0	1·4	0·1
(C) Lumpectomy in low-risk women[16–22]	7	1989–99	4004	453	6·6	26·9	17·9	7·9	1·1	0·0	0·0
Pathological nodal status											
Negative (pN0)	..	..	7287	1801	9·7	73·7	34·0	23·3	11·3	3·9	1·2
Positive (pN+)	..	..	1050	585	10·3	11·8	4·6	3·2	2·2	1·3	0·5
Unknown	..	..	2464	757	8·8	23·6	11·3	7·6	3·7	1·0	0·0
All women	17	1976–99	10 801	3143	9·5	109·1	49·8	34·1	17·2	6·3	1·7

*Only unconfounded trials are considered—ie, trials in which there was no difference between the treatment groups in the type or extent of surgery or in the use of systemic therapy. Two further eligible trials,[23,24] both category A with a total of 133 women, were identified but data were unavailable. Details of the 17 available trials are given in webappendix pp 4, 45–47. †Elsewhere, these trial categories are abbreviated to: (A) Lumpectomy: original; (B) >Lumpectomy; (C) Lumpectomy: low risk. In category A, 55% were pathologically node negative, 5% were aged 70+ years, 10% had low-grade tumours, 54% had T1 tumours (1–20 mm), 81% had oestrogen-receptor (ER)-positive disease or unknown status, and 44% were in trials in which tamoxifen was used in both trial groups. In category B, 81% were pathologically node negative, 10% were aged 70+ years, 9% had low-grade tumours, 89% had T1 tumours, 86% had ER positive disease or unknown status, and 6% were in trials in which tamoxifen was used in both trial groups. In category C, 73% were pathologically node negative, 40% were aged 70+ years, 33% had low-grade tumours, 90% had T1 tumours, 98% had ER positive disease or unknown status, and 88% were in trials in which tamoxifen was used in both trial groups.

Table 1: **Availability of data from randomised trials of radiotherapy after breast-conserving surgery for invasive cancer that began before the year 2000**

Lancet, October 2011

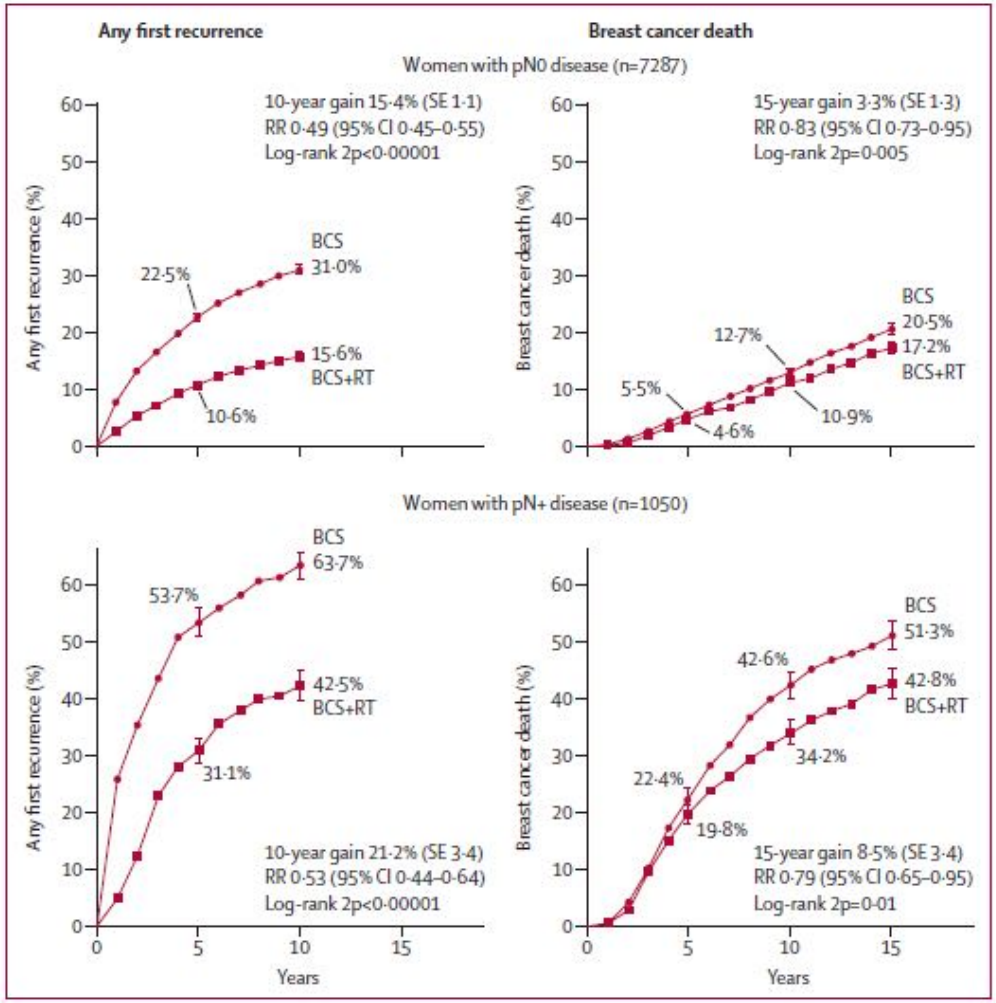

Figure 2: Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 10-year risk of any (locoregional or distant) first recurrence and on 15-year risk of breast cancer death in women with pathologically verified nodal status

Pazienti N0:

- Riduzione RL 15,4% a 10 aa.
- Aumento sopravvivenza 3,3% a 15 aa

Pazienti N+:

- Riduzione RL 21,2% a 10 aa.
- Aumento sopravvivenza 8,5% a 15 aa

Lancet, October 2011

Pz. N0 (7287 pz.)

	Number allocated BCS+RT/BCS	10-year risk of a locoregional or distant recurrence (%)			Test for trend/heterogeneity in absolute reduction	
		BCS+RT	BCS	Absolute reduction with RT (95% CI)	2p unadjusted*	2p adjusted*
(a) Entry age (years)					<0·00001	0·0002
<40	189/174	36·1	60·7	24·6 (13·2 to 36·0)		
40–49	576/582	20·8	41·4	20·6 (15·1 to 26·1)		
50–59	1093/1028	15·0	29·7	14·7 (10·8 to 18·6)		
60–69	1138/1167	14·2	28·3	14·1 (10·4 to 17·8)		
70+	679/661	8·8	17·7	8·9 (4·0 to 13·8)		
(b) Tumour grade					<0·00001	<0·00001
Low	750/757	11·0	22·4	11·4 (6·3 to 16·5)		
Intermediate	816/843	16·4	31·6	15·3 (10·4 to 20·2)		
High	448/431	28·6	53·3	24·7 (17·6 to 31·8)		
Grade unknown	1661/1581	14·7	28·2	13·5 (10·4 to 16·6)		
(c) Tumour size					0·02	0·06
T1 (1–20 mm)	2942/2920	12·4	27·5	15·1 (12·7 to 17·5)		
T2 (21–50 mm)	513/487	30·7	50·0	19·3 (12·6 to 26·0)		
Various/unknown	220/205	24·9	32·6	7·6 (–1·8 to 17·0)		
(d) ER status and trial policy of tamoxifen use†					<0·00001	0·003
ER-poor	448/427	28·9	43·8	14·9 (8·0 to 21·8)		
ER-positive no tamoxifen	1686/1626	18·6	36·0	17·4 (14·3 to 20·5)		
ER-positive with tamoxifen	1541/1559	8·7	22·0	13·3 (10·0 to 16·6)		
(e) Trial policy of using additional therapy†					0·06	0·45
No	1498/1471	15·8	31·6	15·8 (12·7 to 18·9)		
Yes	2127/2085	16·1	31·8	15·6 (12·3 to 18·9)		
Some/unknown	50/56	..	..	..		
(f) Trial category‡					<0·00001 (A *vs* C); 0·90 (A+C *vs* B)	0·16 (A *vs* C); 0·00003 (A+C *vs* B)
(A) Lumpectomy: original	1223/1197	27·8	47·9	20·1 (16·0 to 24·2)		
(B) >Lumpectomy	986/970	14·3	25·9	11·6 (7·9 to 15·3)		
(C) Lumpectomy: low risk	1466/1445	6·3	19·9	13·6 (9·7 to 17·5)		
Total	3675/3612	15·6	31·0	15·4 (13·2 to 17·6)		

Information about numbers of events and woman-years is in webappendix p 26. Results for 5-year risks are in webappendix p 31. ER=oestrogen receptor. *Unadjusted: each factor alone. Adjusted: each factor adjusted for all other factors by means of regression modelling. Categories including unknowns excluded from test for trend or heterogeneity. †A trial policy of tamoxifen use gives tamoxifen to both treatment groups if the disease is ER positive (or ER unknown, here counted with ER positive); additional therapy could be chemotherapy (usually cyclophosphamide, methotrexate, fluorouracil [CMF]) for both treatment groups, or additional RT (nodal RT or a boost or both) for those allocated BCS+RT. ‡Definitions of trial categories A, B, and C are in table 1.

Table 2: **Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 10-year risk of any (locoregional or distant) first recurrence in women with pathologically node-negative disease (n=7287), subdivided by patient and trial characteristics**

Pazienti N0
Vantaggio della RT (riduzione numero di eventi) apprezzabile in tutte le categorie di pazienti, anche in quelle a rischio più basso (età > 70 aa, G1, T1, ER+).

Lancet, October 2011

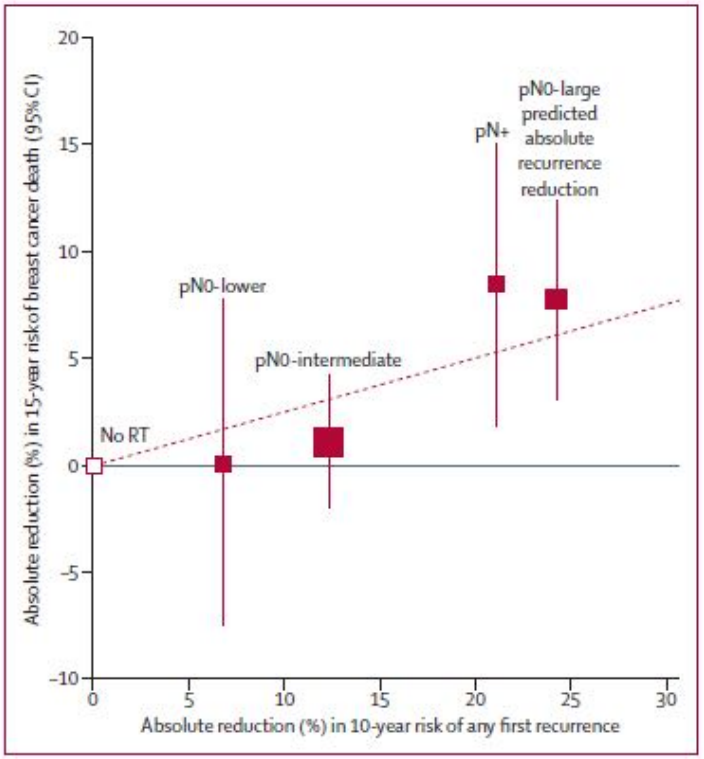

Figure 5: **Absolute reduction in 15-year risk of breast cancer death with radiotherapy (RT) after breast-conserving surgery versus absolute reduction in 10-year risk of any (locoregional or distant) recurrence**

Women with pN0 disease are subdivided by the predicted absolute reduction in 10-year risk of any recurrence suggested by regression modelling (pN0-large ≥20%, pN0-intermediate 10–19%, pN0-lower <10%; further details are in webappendix pp 35–39). Vertical lines are 95% CIs. Sizes of dark boxes are proportional to amount of information. Dashed line: one death from breast cancer avoided for every four recurrences avoided. pN0=pathologically node-negative. pN+=pathologically node-positive.

- Nonostante la riduzione del rischio relativo di eventi sia assai evidente, il beneficio assoluto in termini di sopravvivenza globale è, in alcuni gruppi di pazienti, modesto.

- La scelta terapeutica deve tenere in considerazione questi dati allo scopo di fornire alle pazienti un'informazione adeguata .

- La possibilità di identificare sulla base dei principali fattori anatomo-clinici gruppi a rischio diverso deve essere alla base dei futuri studi clinici volti a valutare tecniche meno invasive (IORT, PBI ecc.)

Lancet, October 2011

Review Article

Ultrashort Courses of Adjuvant Breast Radiotherapy

Wave of the Future or a Fool's Errand?

Atif J. Khan, MD[1]; Roger G. Dale, PhD[2]; Douglas W. Arthur, MD[3]; Bruce G. Haffty, MD[1]; Dorin A. Todor, PhD[3]; and Frank A. Vicini, MD[4]

In accelerated partial breast irradiation (APBI), the most commonly used fractionation schemes include 340 or 385 centigrays delivered in a twice daily administration. A further progression of the APBI literature has been the recent interest in extremely short courses of adjuvant radiotherapy, usually delivered by intraoperative radiotherapy techniques. This newer area of single-fraction radiotherapy approaches remains highly contentious. In particular, the recently reported TARGIT trial has been the subject of both praise and scorn, and a critical examination of the trial data and the underlying hypotheses is warranted. Short-term outcomes of the related Italian ELIOT approach have also been reported. Although the assumptions of linear quadratic formalism are likely to hold true in the range of 2 to 8 grays, equating different schedules beyond this range is problematic. A major problem of current single-fraction approaches is that the treatment doses are chosen empirically, or are based on tolerability, or on the physical dose delivery characteristics of the chosen technology rather than radiobiological rationale. This review article summarizes the current data on ultrashort courses of adjuvant breast radiotherapy and highlights both the promise and the potential pitfalls of the abbreviated treatment. ***Cancer* 2011;000:000–000.** © *2011 American Cancer Society.*

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Accelerated partial breast irradiation using external beam conformal radiation therapy: A review

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Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial

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Summary

Background After breast-conserving surgery, 90% of local recurrences occur within the index quadrant despite the presence of multicentric cancers elsewhere in the breast. Thus, restriction of radiation therapy to the tumour bed during surgery might be adequate for selected patients. We compared targeted intraoperative radiotherapy with the conventional policy of whole breast external beam radiotherapy.

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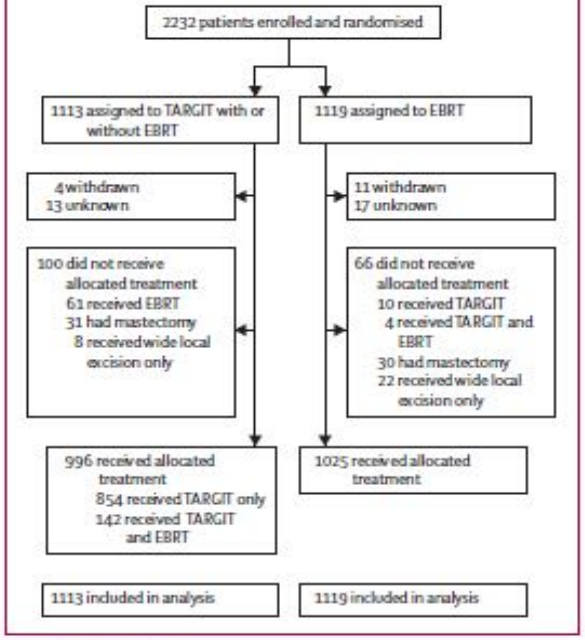
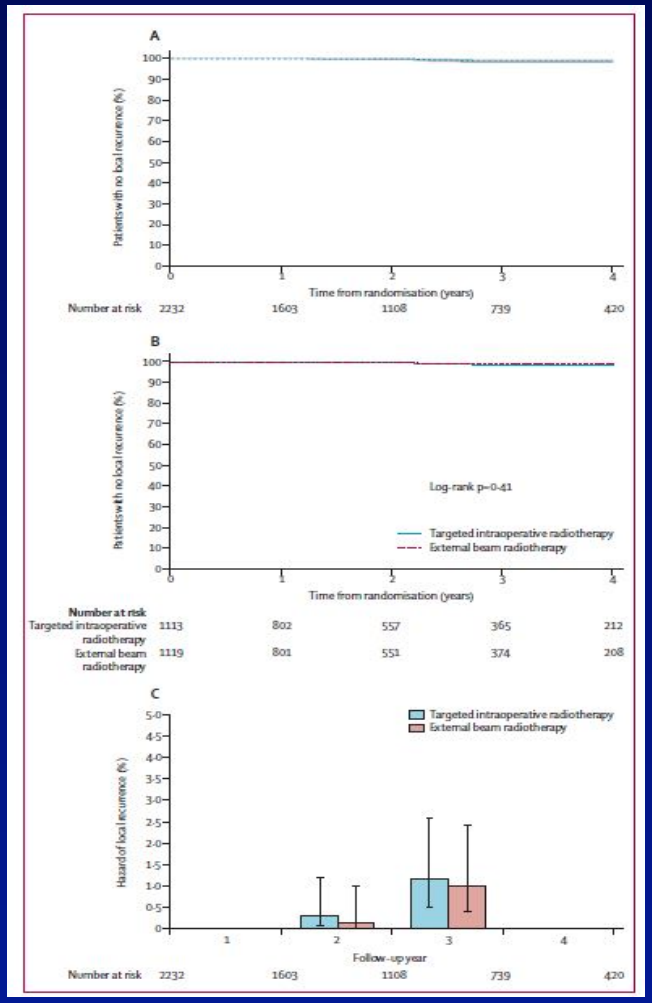


Figure 3: Trial profile
TARGIT=targeted intraoperative radiotherapy. EBRT=external beam radiotherapy. Data for number of patients screened for eligibility are not available from all centres.



	Targeted intraoperative radiotherapy (n=1113)	External beam radiotherapy (n=1119)	p value
Haematoma needing surgical evacuation	11 (1·0%)	7 (0·6%)	0·338
Seroma needing more than three aspirations	23 (2·1%)	9 (0·8%)	0·012
Infection needing intravenous antibiotics or surgical intervention	20 (1·8%)	14 (1·3%)	0·292
Skin breakdown or delayed wound healing*	31 (2·8%)	21 (1·9%)	0·155
RTOG toxicity grade of 3 or 4†	6 (0·5%)	23 (2·1%)	0·002
Major toxicity‡	37 (3·3%)	44 (3·9%)	0·443

Data are number of patients (%). RTOG=Radiation Therapy Oncology Group. *Some of the patients in the first three rows (haematoma needing surgical evacuation, seroma needing more than three aspirations, infection needing intravenous antibiotics or surgical intervention) could be included in the fourth row (skin breakdown or delayed wound healing). †No patient had grade 4 toxicity. ‡Defined as skin breakdown or delayed wound healing and RTOG toxicity grade of 3 or 4).

Table 5: Clinically significant complications

- Follow up mediano 2 aa.
- Nel braccio IORT 203/1113 pz hanno ricevuto anche EBRT; 31 sottoposte a mastectomia dopo IORT

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Clinical Investigation

How do the ASTRO Consensus Statement Guidelines for the Application of Accelerated Partial Breast Irradiation Fit Intraoperative Radiotherapy? A Retrospective Analysis of Patients Treated at the European Institute of Oncology

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1822 pts., trattate tra il 2000 e il 2008 con quadrantectomia + SLD/AD e IORT (e -, 21 Gy)

Table 3 Five-year clinical outcomes for breast cancer patients treated with full-dose intraoperative radiotherapy with electrons categorized according to the American Society for Radiation Oncology (ASTRO) consensus statement

	ASTRO consensus statement						
	Suitable		Cautionary		Unsuitable		
Patients	294		691		812		
Person-years	1,009		2,416		2,837		
Outcome	Events	Rate* (%)	Events	Rate* (%)	Events	Rate* (%)	Log-rank *p*
Ipsilateral breast tumor recurrence	3	1.5	21	4.4	50	8.8	0.0003
Regional lymph node failure	3	1.5	9	1.9	6	1.1	0.55
Distant metastases	3	1.5	8	1.7	22	3.9	0.047
Breast cancer related event	14	6.9	46	9.5	87	15.3	0.0025
Progression free survival	17	91.6	58	88.0	109	80.8	0.0005
Cause-specific survival	2	99.1	7	98.7	22	96.5	0.026
Overall survival	3	98.6	13	97.5	30	95.2	0.039

ASTRO group was not assessable for 25 patients.

* Five-year rate (%) assuming constant rate during the first 5 years.

Table 5 Multivariate analysis of clinical outcomes for patients with breast cancer treated with full-dose intraoperative radiotherapy with electrons categorized according to the American Society for Radiation Oncology (ASTRO) consensus statements

Variable	Ipsilateral breast tumor recurrence		Regional lymph node failure		Distant metastases	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age, year						
<50	1.00		1.00		1.00	
50–59	0.48 (0.28–0.84)	0.01	4.40 (0.54–35.6)	0.16	0.87 (0.28–2.71)	0.80
60+	0.41 (0.23–0.72)	0.002	4.13 (0.51–32.3)	0.18	2.27 (0.83–6.20)	0.11
Tumor size, cm						
≤2	1.00		1.00		1.00	
>2 to ≤3	1.45 (0.81–2.60)	0.21	2.87 (1.06–7.82)	0.04	1.30 (0.57–2.97)	0.53
>3	1.31 (0.39–4.41)	0.66	–	–	–	–
Margins						
Negative	1.00		1.00		1.00	
Close	1.82 (0.55–6.08)	0.33	–	–	1.61 (0.20–12.9)	0.65
Positive	3.52 (0.46–27.2)	0.23	–	–		
Tumor grade						
1	1.00		1.00		1.00	
2	2.72 (1.04–7.13)	0.04	0.67 (0.11–4.16)	0.67	1.80 (0.38–8.58)	0.46
3	5.38 (1.97–14.7)	0.001	5.39 (1.10–26.4)	0.04	7.64 (1.63–35.9)	0.01
LVI						
Absent	1.00		1.00		1.00	
Focal	1.49 (0.75–2.96)	0.25	1.61 (0.44–5.86)	0.47	1.71 (0.62–4.75)	0.30
Diffuse	2.03 (1.03–3.99)	0.04	0.83 (0.10–7.32)	0.87	2.31 (0.86–6.25)	0.10
ER status						
Positive	1.00		1.00		1.00	
Negative	1.56 (0.84–2.94)	0.16	0.54 (0.15–2.01)	0.36	1.44 (0.62–3.35)	0.39
Focality						
Monocentric/focal	1.00		1.00		1.00	
Multicentric/focal	1.50 (0.67–3.38)	0.33	3.85 (0.84–17.6)	0.08	0.51 (0.07–3.81)	0.51
Histology						
Ductal	1.00		1.00		1.00	
Lobular	1.97 (1.00–3.90)	0.05	–	–	1.58 (0.45–5.55)	0.48
Other histologies	0.79 (0.25–2.50)	0.69	–	–	0.92 (0.16–5.21)	0.92
EIC						
Absent/focal	1.00		1.00		1.00	
Extensive	0.59 (0.31–1.14)	0.11	0.68 (0.15–2.99)	0.61	0.78 (0.30–2.07)	0.62
Lymph node status						
Negative	1.00		1.00		1.00	
pN1mi or pN1a (by ALND)	1.29 (0.69–2.40)	0.43	0.32 (0.07–1.50)	0.15	2.05 (0.79–5.36)	0.14
pNx; ≥pN2a (≥4 positive nodes)	1.80 (1.01–3.22)	0.047	0.57 (0.15–2.17)	0.41	3.92 (1.71–8.97)	0.001

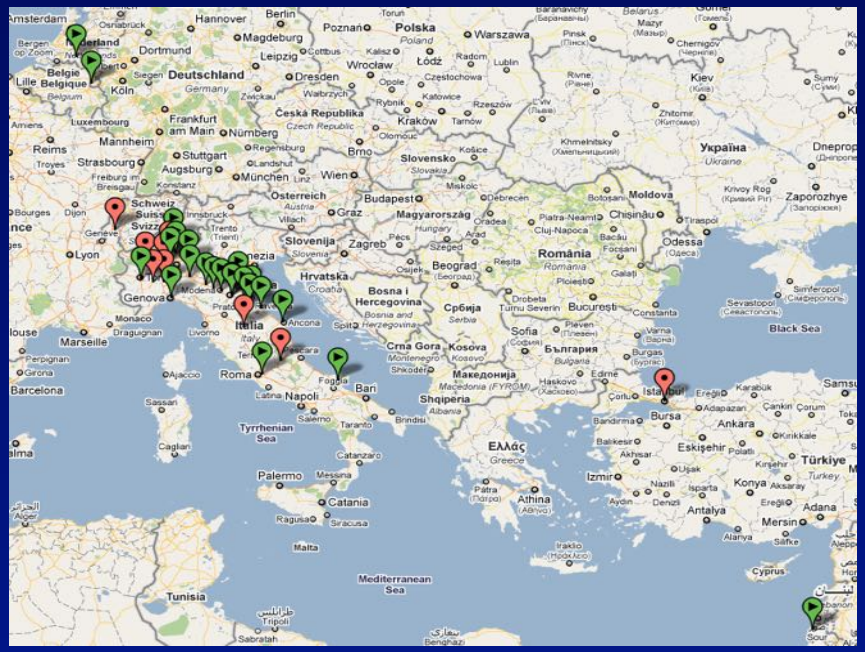
Abbreviations: ALND = axillary lymph node dissection; CI = confidence interval; EIC = extensive intraductal component; ER = estrogen receptor; HR = hazard ratio; LVI = lymph-vascular invasion.

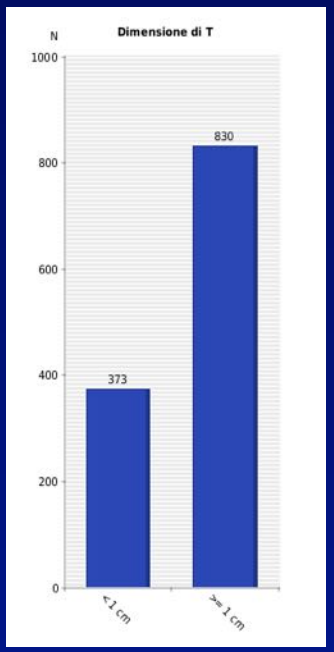
Criteri di selezione!!!

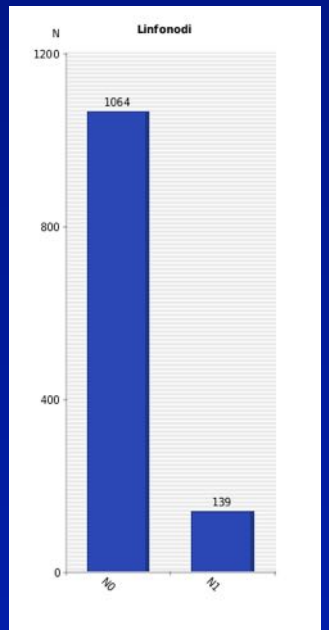
Ongoing studies of partial breast irradiation after conservative surgery

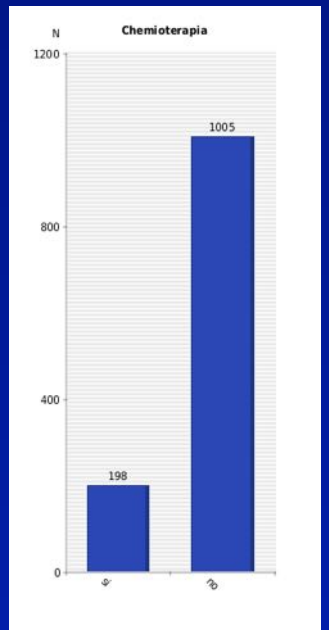
Criteria	Targit	ELIOT	IMPORT	RAPID	NSABP/ RTOG	GEC/ ESTRO	IRMA
N° pts.	2232	1200	2100	2128	4300	1170	3300
Age	>40	>48	>50	>40	>18	>40	>49
T size (mm)	<30	<25	<20	<30	<30	<30	<30
Number N+	0	0	0	0	0-3N+	0-1N+	0-3N+
Grade	1-3	1-3	1-2	1-2	1-3	1-3	1-3
Margins (mm)	negative	>10	>2	negative	negative	>2 invasive >5 DCIS	>2
RT technique	Periop. RX 50 KV	Periop. Electrons 6-12 MeV	Postop. IMRT	Postop.RT 3D	Interstitial Brachyther. Mammosite Postop. RT 3D	LDR or HDR brachyther.	Postop. RT 3D
Dose/ fractions	20 Gy 1 fract.	21 Gy 1 fract.	40 Gy in 15 fract.	38,5 Gy 10 fraz biq	RTE 38,5 Gy in 10 f biq Brachi e Mammo 34 Gy	Low DR 50 Gy High DR 34 Gy	38,5 Gy 10 fract. bid

IRMA trial: 25 centri attivi di cui 23 con > 1 paziente









Al 15.06.2012 randomizzati 1203 pazienti. Interim analysis prevista dopo il reclutamento di 1600 pazienti

Clin Exp Metastasis
DOI 10.1007/s10585-012-9515-z

RESEARCH PAPER

Should ACOSOG Z0011 change practice with respect to axillary lymph node dissection for a positive sentinel lymph node biopsy in breast cancer?

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Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis

A Randomized Clinical Trial

JAMA, February 9, 2011—Vol 305, No. 6

Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis

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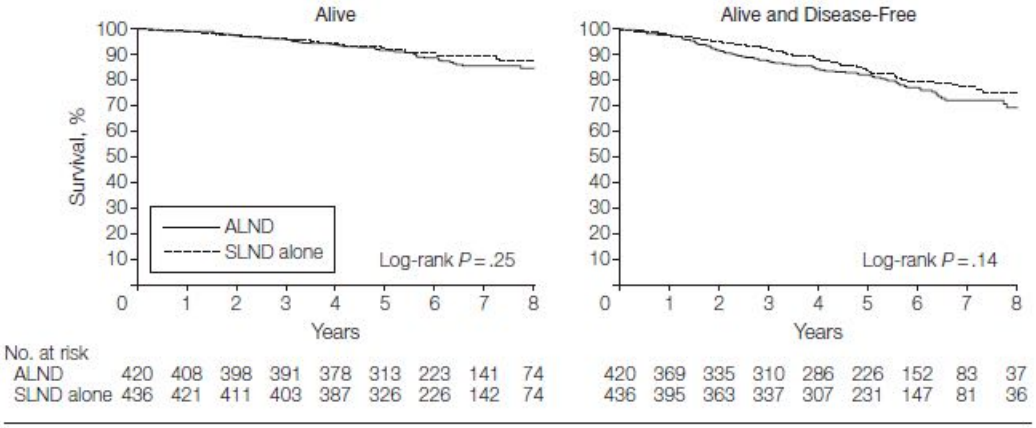
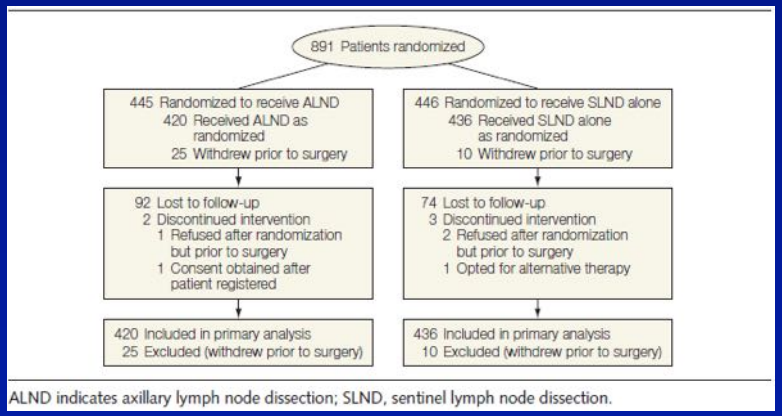
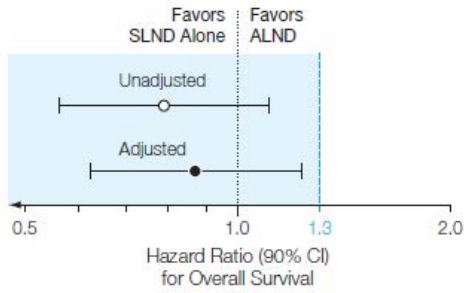
Figure 2. Survival of the ALND Group Compared With SLND-Alone Group





ALND indicates axillary lymph node dissection; SLND, sentinel lymph node dissection.

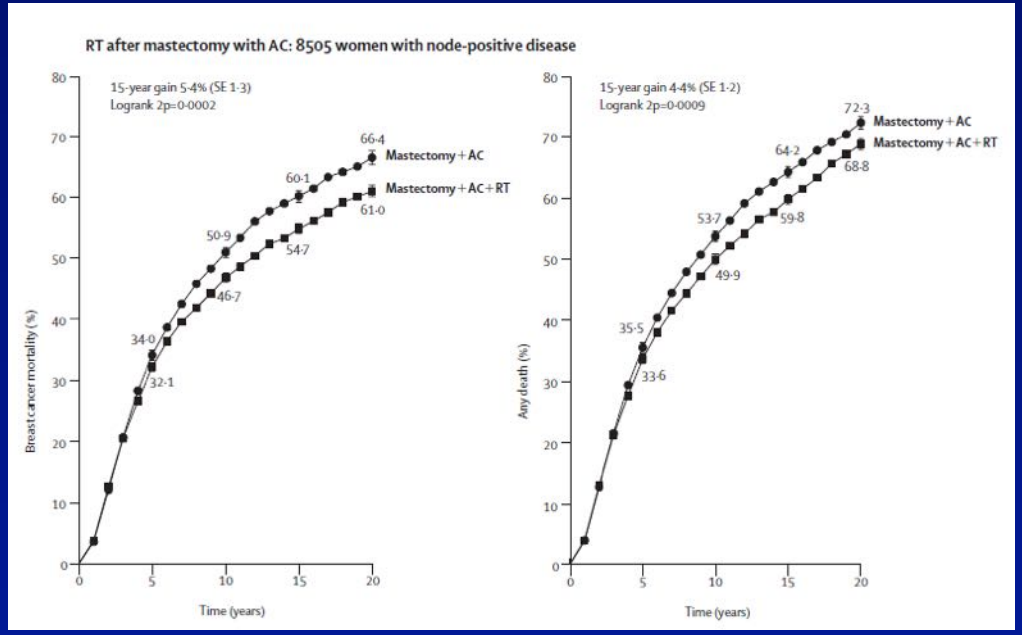
Figure 3. Hazard Ratios Comparing Overall Survival Between the ALND and SLND-Alone Groups



Blue dashed line at hazard ratio=1.3 indicates noninferiority margin; blue-tinted region to the left of hazard ratio=1.3 indicates values for which SLND alone would be considered noninferior to SLND plus ALND. ALND indicates axillary lymph node dissection; CI, confidence interval; SLND, sentinel lymph node dissection.

Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials

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



	5-year local recurrence risk (%) in trials of:			
	(a) RT after BCS (node-negative)		(b) RT after mastectomy and AC (node-positive)	
	RT versus control	Absolute reduction (SE)	RT versus control	Absolute reduction (SE)
Age (years)				
<50	11 vs 33	22 (2)	6 vs 23	17 (1)
50–59	7 vs 23	16 (2)	6 vs 24	18 (2)
60–69	4 vs 16	12 (1)	5 vs 23	18 (2)
≥70	3 vs 13	11 (2)	..	..
Tumour grade				
Well differentiated	4 vs 14	10 (2)	4 vs 22	18 (3)
Moderately differentiated	9 vs 26	17 (2)	4 vs 30	26 (2)
Poorly differentiated	12 vs 34	22 (3)	6 vs 40	34 (4)
Tumour size (T category)				
1–20 mm (T1)	5 vs 20	15 (1)	5 vs 22	17 (2)
21–50 mm (T2)	14 vs 35	21 (3)	6 vs 30	24 (2)
>50 mm (T3 or T4*)	..	..	8 vs 36	28 (4)
ER status				
ER-poor	12 vs 30	18 (3)	8 vs 28	20 (2)
ER-positive	6 vs 25	19 (2)	6 vs 24	18 (2)
Number of involved nodes				
1–3	..	..	4 vs 16	12 (2)
≥4	..	..	12 vs 26	14 (2)
All women	**7 vs 23**	**16 (1)**	**6 vs 23**	**17 (1)**

See webfigures 6a and 6b for more details on characteristics, including separate results for those in whom the relevant characteristic is not known. * T4=tumour of any size with direct extension to skin or chest wall.

Table 3: **Effects of age and tumour characteristics on 5-year risks of local recurrence in trials of radiotherapy (RT) (a) after BCS in women with node-negative disease and (b) after mastectomy and axillary clearance (AC) in women with node-positive disease**

Lancet 2005; 366: 2087–2106

original article

Annals of Oncology 00: 1–7, 2012
doi:10.1093/annonc/mds118

Patterns and risk factors for locoregional failures after mastectomy for breast cancer: an International Breast Cancer Study Group report

P. Karlsson[1*], B. F. Cole[2,3], B. H. Chua[4], K. N. Price[3,5], J. Lindtner[6], J. P. Collins[7], A. Kovács[8], B. Thürlimann[9], D. Crivellari[10], M. Castiglione-Gertsch[11], J. F. Forbes[12], R. D. Gelber[3,5,13], A. Goldhirsch[14,15] & G. Gruber[16] for the International Breast Cancer Study Group

Breast Care

Review Article · Übersichtsarbeit

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Should Postmastectomy Radiotherapy to the Chest Wall and Regional Lymph Nodes Be Standard for Patients with 1–3 Positive Lymph Nodes?

Birgitte V. Offersen[a] Hans-Jürgen Brodersen[b] Mette M. Nielsen[c] Jens Overgaard[d] Marie Overgaard[a], on behalf of the DBCG Radiotherapy Committee

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Influence of Lymphatic Invasion on Locoregional Recurrence Following Mastectomy: Indication for Postmastectomy Radiotherapy for Breast Cancer Patients With One to Three Positive Nodes

Ryoichi Matsunuma, M.D.,*,†††† Masahiko Oguchi, M.D., Ph.D.,† Tomoko Fujikane, M.D., Ph.D.,‡ Masaaki Matsuura, Ph.D.,¶ Takehiko Sakai, M.D., Ph.D.,§ Kiyomi Kimura, M.D.,** Hidetomo Morizono, M.D.,†† Kotaro Iijima, M.D., Ph.D.,‡‡ Ayumi Izumori, M.D.,¶¶ Yumi Miyagi, M.D.,§§ Seiichiro Nishimura, M.D.,*** Masujiro Makita, M.D.,††† Naoya Gomi, M.D., Ph.D.,‡‡‡ Rie Horii, M.D., Ph.D.,¶¶¶ Futoshi Akiyama, M.D., Ph.D.,§§§ and Takuji Iwase, M.D.****

Int J Radiation Oncol Biol Phys, Vol. 83, No. 3, pp. 845–852, 2012

Int J Radiation Oncol Biol Phys, Vol. 83, No. 2, pp. e153–e157, 2012

Locoregional Failure in Early-Stage Breast Cancer Patients Treated With Radical Mastectomy and Adjuvant Systemic Therapy: Which Patients Benefit From Postmastectomy Irradiation?

Marco Trovo, M.D.,* Elena Durofil, R.T.T.,* Jerry Polesel, Sc.D.,† Mario Roncadin, M.D.,* Tiziana Perin, M.D.,‡ Mario Mileto, M.D.,§ Erica Piccoli, M.D.,§ Daniela Quitadamo, Sc.D.,¶ Samuele Massarut, M.D.,§ Antonino Carbone, M.D.,‡ and Mauro G. Trovo, M.D.*

Breast radiotherapy

Increased use of regional radiotherapy is associated with improved outcome in a population-based cohort of women with breast cancer with 1–3 positive nodes ☆

Elaine S. Wai[a,b,c,*], Mary Lesperance[d], Caroline H. Speers[c], Pauline T. Truong[a,b,c], Stuart Jones[a], Scott Tyldesley[b,c,e], Ivo A. Olivotto[a,b,c]

Int J Radiation Oncol Biol Phys, Vol. 83, No. 2, pp. e153–e157, 2012

Clinical Investigation: Breast Cancer

Locoregional Failure in Early-Stage Breast Cancer Patients Treated With Radical Mastectomy and Adjuvant Systemic Therapy: Which Patients Benefit From Postmastectomy Irradiation?

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Table 3 Distribution of patients and local recurrences, hazard ratios (HR), and corresponding 95% confidence intervals (CI), according to selected risk factors

Risk factors	Patients	Local recurrences		Univariate HR (95% CI)*	Multivariate HR (95% CI)†
		n	(%)		
Histology					
Ductal	134	15	(11.2)	1‡	1‡
Lobular	16	2	(12.5)	0.79 (0.17–3.64)	0.16 (0.02–1.10)
T-stage					
1	91	9	(9.8)	1‡	1‡
2	59	8	(13.8)	1.48 (0.56–3.96)	1.69 (0.53–5.43)
N-stage					
0/1mic	94	8	(8.5)	1‡	1‡
1	56	9	(16.1)	1.63 (0.62–4.25)	1.38 (0.52–3.69)
Her2-neu status					
Negative	99	9	(9.1)	1‡	1‡
Positive	29	5	(17.2)	2.22 (0.82–6.07)	1.55 (0.52–4.61)
Menopausal status					
Post	95	7	(7.4)	1‡	1‡
Pre	55	10	(18.2)	4.26 (0.96–18.89)	3.37 (0.66–17.28)
Lymphovascular invasion					
No	106	6	(5.7)	1‡	1‡
Yes	44	11	(24.4)	4.42 (1.58–12.37)	3.49 (1.20–10.15)
Estrogen receptor status					
Positive	120	11	(9.0)	1‡	1‡
Negative	27	6	(24.0)	3.05 (1.06–8.81)	2.18 (0.68–6.96)
Grading					
1–2	82	4	(4.8)	1‡	1‡
3	68	13	(19.4)	4.32 (1.39–13.50)	2.36 (0.69–8.07)
Number of significant risk factors§					
0–1	92	4	(4.4)	1‡	
2	33	5	(15.2)	3.55 (0.94–13.33)	
3	18	5	(27.8)	7.91 (1.92–32.57)	
4	4	3	(75.0)	32.83 (5.44–198.11)	

* Estimated through Cox proportional hazard model, adjusted for age.

† Estimated through Cox proportional hazard model, adjusted for age, plus adjustment for menopausal status, lymphovascular invasion, ER status, and grading, when appropriate.

‡ Reference category.

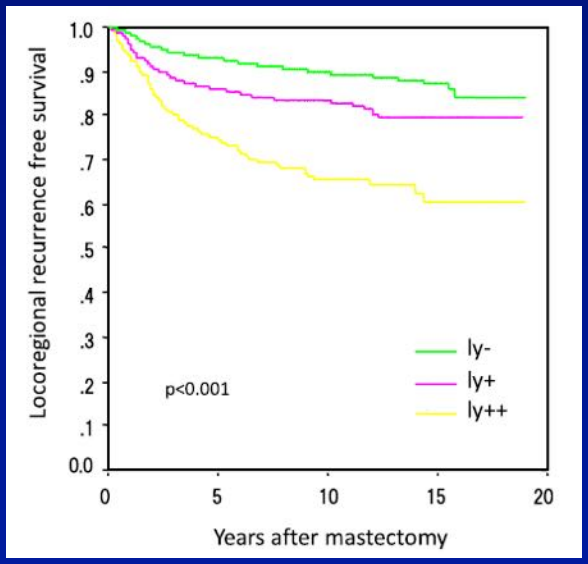
§ Considering menopausal status, lymphovascular invasion, ER status, and grading.

Influence of Lymphatic Invasion on Locoregional Recurrence Following Mastectomy: Indication for Postmastectomy Radiotherapy for Breast Cancer Patients With One to Three Positive Nodes

Ryoichi Matsunuma, M.D.,*,†††† Masahiko Oguchi, M.D., Ph.D.,† Tomoko Fujikane, M.D., Ph.D.,‡ Masaaki Matsuura, Ph.D.,¶ Takehiko Sakai, M.D., Ph.D.,§ Kiyomi Kimura, M.D.,** Hidetomo Morizono, M.D.,†† Kotaro Iijima, M.D., Ph.D.,‡‡ Ayumi Izumori, M.D.,¶¶ Yumi Miyagi, M.D.,§§ Seiichiro Nishimura, M.D.,*** Masujiro Makita, M.D.,††† Naoya Gomi, M.D., Ph.D.,‡‡‡ Rie Horii, M.D., Ph.D.,¶¶¶ Futoshi Akiyama, M.D., Ph.D.,§§§ and Takuji Iwase, M.D.****

Patients with node-positive (1 to 3) (n = 1086)									
ly									
ly−		1.000			1.000			1.000	
ly+	0.088	1.925	0.906–4.090	0.061	1.722	0.976–3.040	0.731	0.943	0.677–1.315
ly++	0.139	2.168	0.779–6.035	0.005	2.762	1.359–5.616	0.411	1.210	0.769–1.904
Number of positive nodes									
n:1		1.000			1.000			1.000	
n:2	0.526	0.760	0.324–1.778	0.263	1.384	0.784–2.444	0.991	0.998	0.716–1.391
n:3	0.303	1.528	0.682–3.421	0.245	1.471	0.767–2.818	0.000	1.813	1.302–2.524
T-stage									
T1		1.000			1.000			1.000	
T2	0.750	1.159	0.468–2.875	0.781	0.914	0.487–1.716	0.629	0.919	0.653–1.294
T3	0.187	2.095	0.698–6.285	0.369	1.448	0.645–3.248	0.265	1.292	0.823–2.028
Age									
≦49		1.000			1.000			1.000	
≧50	0.494	1.269	0.641–2.511	0.428	1.225	0.741–2.025	0.085	1.274	0.967–1.679
ER									
Positive		1.000			1.000			1.000	
Negative	0.464	1.316	0.631–2.741	0.574	1.164	0.686–1.973	0.610	0.928	0.697–1.236
PgR									
Positive		1.000			1.000			1.000	
Negative	0.806	1.092	0.541–2.205	0.455	0.819	0.485–1.383	0.768	1.044	0.784–1.390

Abbrevations: ER = Estrogen receptor; RR = relative risk; PgR = progesterone receptor. ER, PgR evaluated at Enzyme Immuno Assay.



Int J Radiation Oncol Biol Phys, Vol. 83, No. 3, pp. 845–852, 2012

Editorial

Radiation-induced heart morbidity after adjuvant radiotherapy of early breast cancer – Is it still an issue?

Birgitte Offersen *, Inger Højris, Marie Overgaard

Review

Late radiation-induced heart disease after radiotherapy. Clinical importance, radiobiological mechanisms and strategies of prevention

Nicolaus Andratschke [a,*], Jean Maurer [a], Michael Molls [a], Klaus-Rüdiger Trott [b]

Cardiac morbidity

Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden

Paul McGale [a], Sarah C. Darby [a,*], Per Hall [b], Jan Adolfsson [c], Nils-Olof Bengtsson [d], Anna M. Bennet [b], Tommy Fornander [e], Bruna Gigante [f], Maj-Britt Jensen [g], Richard Peto [a], Kazem Rahimi [h], Carolyn W. Taylor [a], Marianne Ewertz [i]

Cardiac morbidity

Cardiac dose estimates from Danish and Swedish breast cancer radiotherapy during 1977–2001

Carolyn W. Taylor [a,*], Dorthe Brønnum [b], Sarah C. Darby [a], Giovanna Gagliardi [c], Per Hall [d], Maj-Britt Jensen [e], Paul McGale [a], Andrew Nisbet [f], Marianne Ewertz [g]

Radiotherapy and Oncology 100 (2011) 157–159

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Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden

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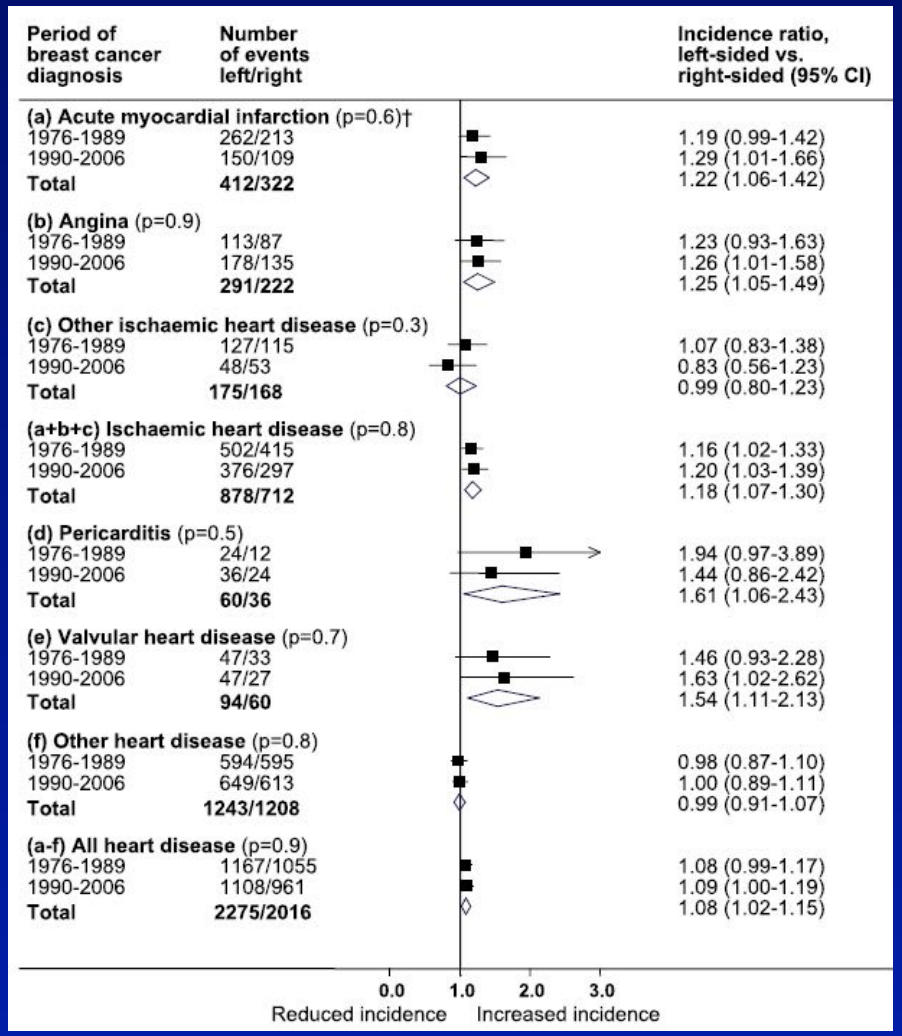

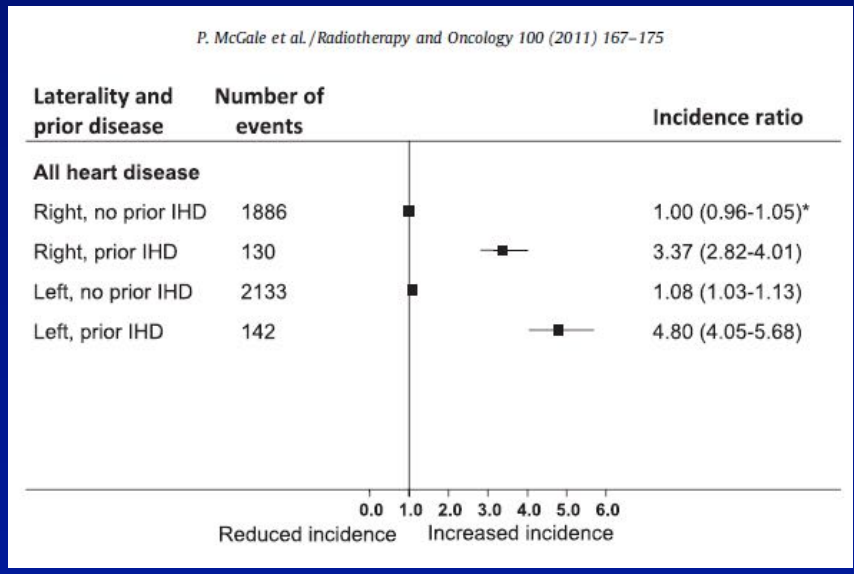

Cardiac morbidity

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Table 2
Cardiac dose estimates for Danish women identified using the Danish Breast Cancer Group database and irradiated for breast cancer since 1977, based on individual radiotherapy charts.

Year of radiotherapy[a]	Number of women evaluated	Average mean dose (standard deviation)									
		Target dose (Gy)	Heart dose (Gy)		Heart BED[b] (Gy_2)		LAD[c] dose (Gy)		RCA[d] dose (Gy)		Circ[e] dose (Gy)	
			Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
1977–1981	199	40.6 (6.3)	6.1 (3.3)	2.9 (1.6)	10.2 (7.9)	4.6 (3.7)	16.4 (9.7)	1.5 (1.2)	4.2 (1.9)	7.7 (4.0)	3.1 (1.4)	1.1 (0.9)
1982–1988	187	48.4 (6.6)	5.7 (2.3)	2.9 (1.1)	8.4 (5.9)	3.9 (2.5)	16.3 (7.2)	1.4 (0.8)	4.2 (1.5)	8.2 (3.3)	2.8 (1.0)	0.9 (0.6)
1989–2001	295	53.8[f] (5.1)	5.8 (1.2)	2.1 (0.5)	10.1 (3.2)	2.4 (0.8)	20.9 (5.3)	1.3 (0.3)	3.0 (1.3)	5.3 (2.8)	2.8 (0.6)	0.9 (0.2)

Regimens were reconstructed on a representative patient with typical anatomy.

[a] Women were grouped according to the years that breast cancer protocols changed in Denmark. The DBCG77 protocol was mainly used between 1977 and 1981; the DBCG82 protocol between 1982 and 1988 and the DBCG89 protocol between 1989 and 2001.

[b] The biologically effective dose (BED) takes into account the fraction size as well as dose and is given by $BED = [nd(1 + d/(\alpha/\beta)]$ where n is number of fractions and d is dose per fraction in Gy. α/β was assumed to be 2 Gray. It was possible to calculate BEDs for 97% of the women studied. It was not possible to calculate BED for the other 3% women who received unusual techniques such as iridium wire radiotherapy.

[c] Left anterior descending coronary artery.

[d] Right coronary artery.

[e] Circumflex coronary artery.

[f] Target dose includes boost radiotherapy.

Breast Cancer Res Treat (2010) 120:273–284
DOI 10.1007/s10549-009-0655-z

EDITORIAL

Recommendations for research priorities in breast cancer by the coalition of cancer cooperative groups scientific leadership council: imaging and local therapy

Joseph A. Sparano · Etta D. Pisano · Julia R. White · Kelly K. Hunt · Eleftherios P. Mamounas · Edith A. Perez · Gabriel N. Hortobagyi · Julie R. Gralow · Robert L. Comis

Table 4 Research recommendations and high priority studies in radiation therapy

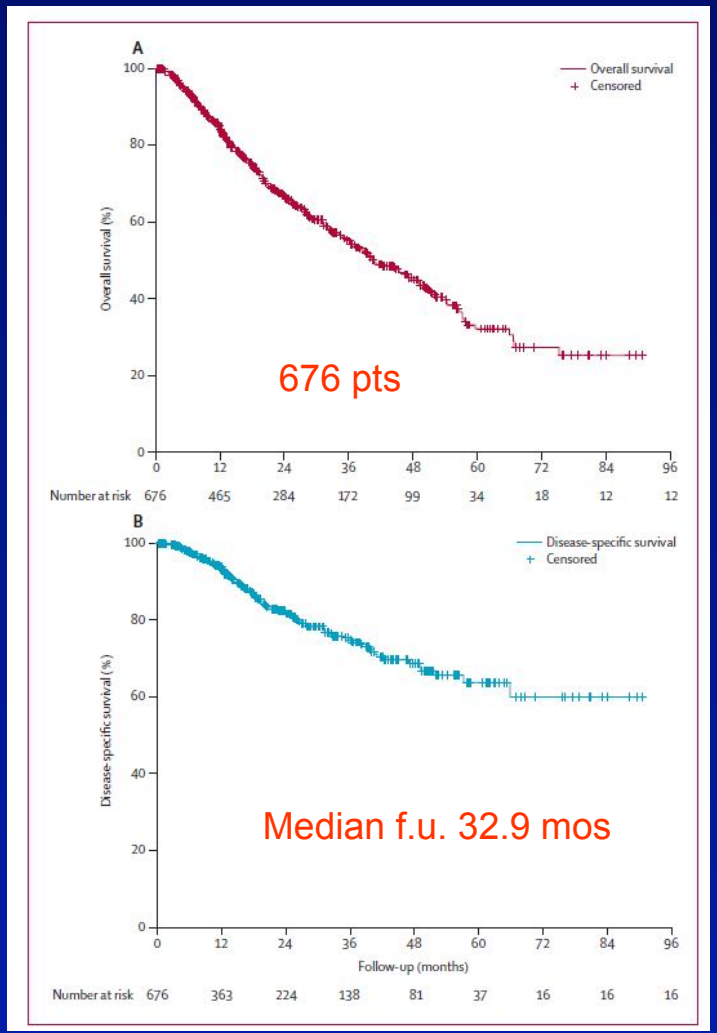
Optimal breast volume to irradiate after lumpectomy. The RTOG 0413/NSABP B-39 trial is under way to examine the best way to define optimal breast volume to irradiate after lumpectomy.
Incorporate translational studies. There is a need to identify biological and genetic markers for tumor response and patient toxicity to improve individualization of BC treatment. How can we best identify patients who benefit from radiation therapy prior, or after, surgery?
Evolving radiation technologies and modalities. How do we implement novel radiation technologies and modalities? Should they be implemented? Does utilization of these modalities improve patient outcomes?

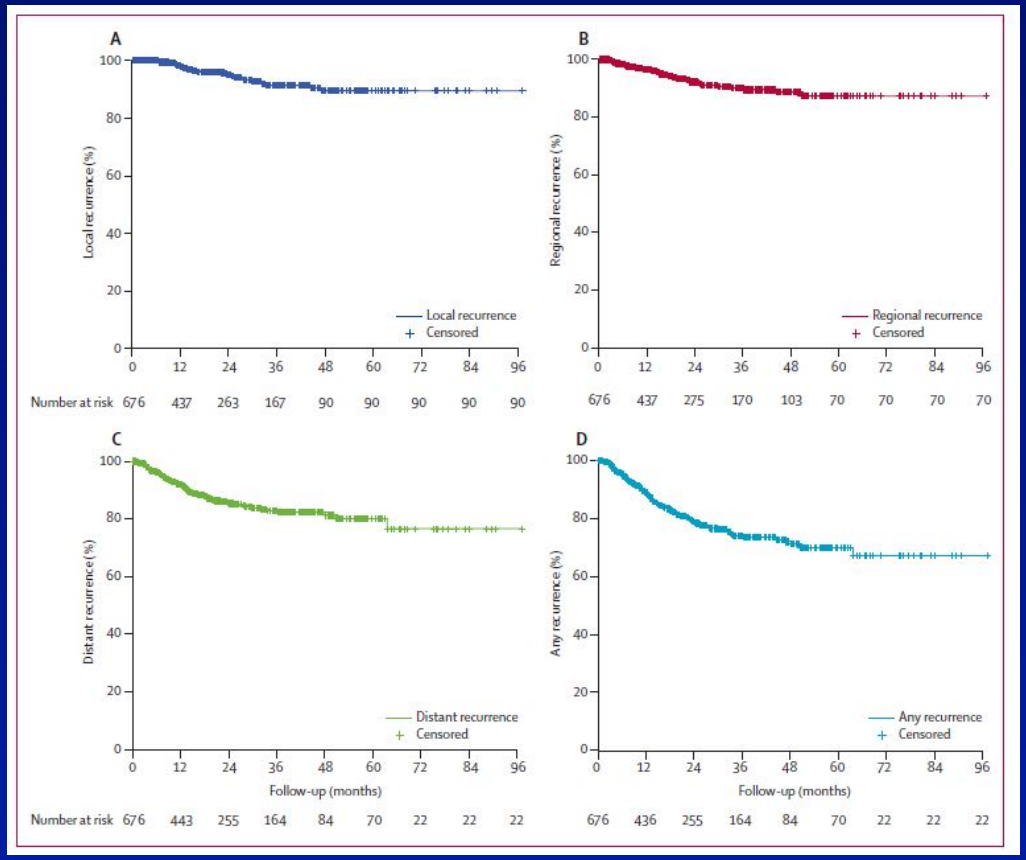
Tumori del polmone

Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis

Sashendra Senthi, Frank J Lagerwaard, Cornelis J A Haasbeek, Ben J Slotman, Suresh Senan

Lancet Oncol 2012; 13: 802–09





Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis

Sashendra Senthi, Frank J Lagerwaard, Cornelis J A Haasbeek, Ben J Slotman, Suresh Senan

	Patients (n=676)	All (n=676; %)	Recurrence (n=124; %)	Distant recurrence (n=82; %)	Median time to recurrence (months; 95% CI)
Any recurrence	124	18%	100%	..	11·4 (9·5–13·2)
Local recurrence					
Isolated LR	18	3%	15%	..	13·5 (8·3–18·7)
LR and RR	2	<1%	2%	..	..
LR and DR	6	<1%	5%	..	..
LR, RR, and DR	4	<1%	3%	..	..
Any LR	30	4%	24%	..	14·9 (11·4–18·4)
Regional recurrence					
Isolated RR	22	3%	18%	..	10·9 (6·1–15·8)
RR and DR	15	2%	12%	..	..
Any RR	43	6%	35%	..	13·1 (7·9–18·3)
Distant recurrence					
Isolated DR	57	8%	46%	..	8·3 (6·4–10·2)
Any DR	82	12%	66%	..	9·6 (6·8–12·4)
Locoregional without DR	42	6%	34%	..	13·1 (9·7–16·5)
Initial DR site					
Pulmonary	36	..	..	44%	..
Pleuritis or lymphangitis	10	..	..	12%	..
Bone	17	..	..	21%	..
Brain	15	..	..	18%	..
Liver	12	..	..	15%	..
Distant nodal	5	..	..	6%	..
Adrenal	2	..	..	2%	..
Skin	1	..	..	1%	..
Second lung primary					
All	42	6%	..	..	18·0 (12·5–23·5)
Ipsilateral	19	3%	..	..	20·0 (17·0–23·0)
Same lobe	8	1%	..	..	20·4 (17·5–23·4)
Different lobe	11	1%	..	..	18·0 (5·5–30·6)
Contralateral lobes	23	4%	..	..	15·9 (9·9–21·3)

LR=local recurrence. RR=regional recurrence. DR=distance recurrence.

Table 2: **Disease recurrence after stereotactic ablative radiotherapy**

- Local recurrences are uncommon (4%)
- Regional recurrences are not frequent (6%)
- The most predominant pattern is out of field isolated distant recurrence presenting early, despite initial PET staging (8%)

Table Patient characteristics (n = 177)

Characteristic	No. of patients (% of total)
Gender	
Male	101 (57)
Female	76 (43)
Median age	76 years (range 50–91 years)
Stage	
IA	106 (60)
IB	71 (40)
Median tumor diameter	26 mm (range 10–70 mm)
Fractionation scheme	
20 Gy × 3 (18 Gy × 3 Gy as of 2008)	61 (34)
12 Gy × 5 (11 Gy × 5 Gy as of 2008)	82 (46)
7.5 Gy × 8	34 (19)
Smoking	
Current or former smoker	168 (95)
Never smoked	9 (5)
GOLD class	
No COPD	65 (37)
Class I	37 (21)
Class II	75 (42)
Charlson morbidity score	
0	18 (10)
1	59 (33)
2	38 (22)
3	39 (22)
4	16 (9)
5	7 (4)
Pathological confirmation	
Yes	60 (33)
No	117 (66)
Histology (n = 60 patients)	
Adenocarcinoma	20 (33)
Squamous cell carcinoma	16 (27)
Undifferentiated NSCLC	24 (38)

Abbreviations: GOLD = Global initiative for chronic Lung Disease; COPD = chronic obstructive pulmonary disease.

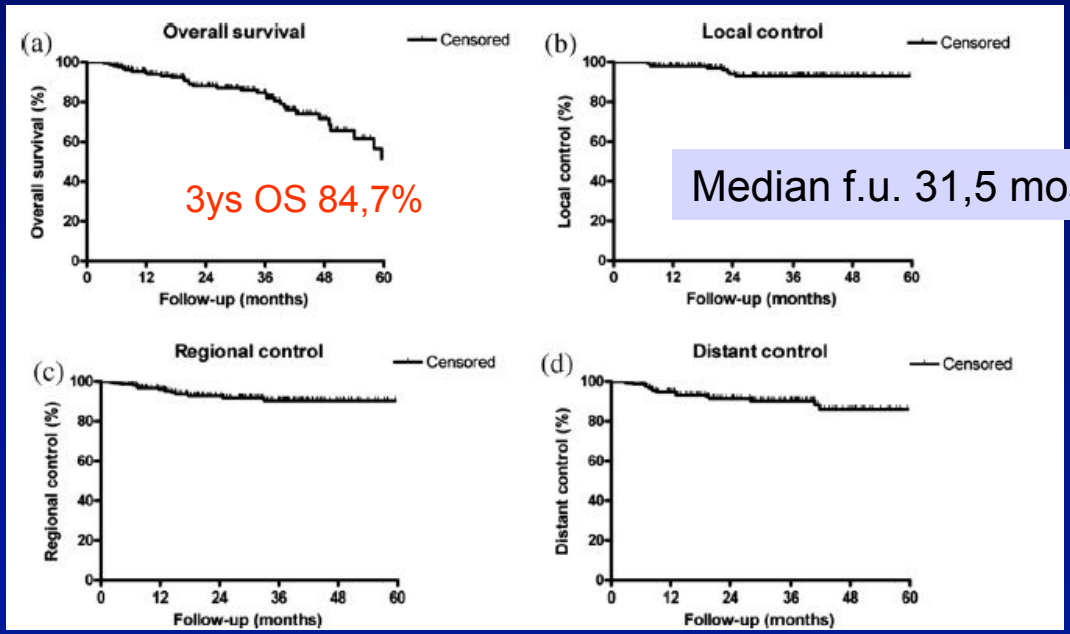
Int J Radiation Oncol Biol Phys, Vol. 83, No. 1, pp. 348–353, 2012

Clinical Investigation: Thoracic Cancer

Outcomes of Stereotactic Ablative Radiotherapy in Patients With Potentially Operable Stage I Non-Small Cell Lung Cancer

Frank J. Lagerwaard, M.D., Ph.D.,* Naomi E. Verstegen, B.Sc.,* Cornelis J.A. Haasbeek, M.D., Ph.D.,* Ben J. Slotman, M.D., Ph.D.,* Marinus A. Paul, M.D., Ph.D.,† Egbert F. Smit, M.D., Ph.D.,‡ and Suresh Senan, Ph.D., F.R.C.R., M.R.C.P.*

*Departments of *Radiation Oncology, †Thoracic Surgery, and ‡Pulmonary Medicine, VU University Medical Center, Amsterdam, The Netherlands*



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American College of Surgeons Oncology Group Z4099/Radiation Therapy Oncology Group 1021: A randomized study of sublobar resection compared with stereotactic body radiotherapy for high-risk stage I non–small cell lung cancer

Hiran C. Fernando, MD,[a] and Robert Timmerman, MD[b]

(J Thorac Cardiovasc Surg 2012;■:1-4)

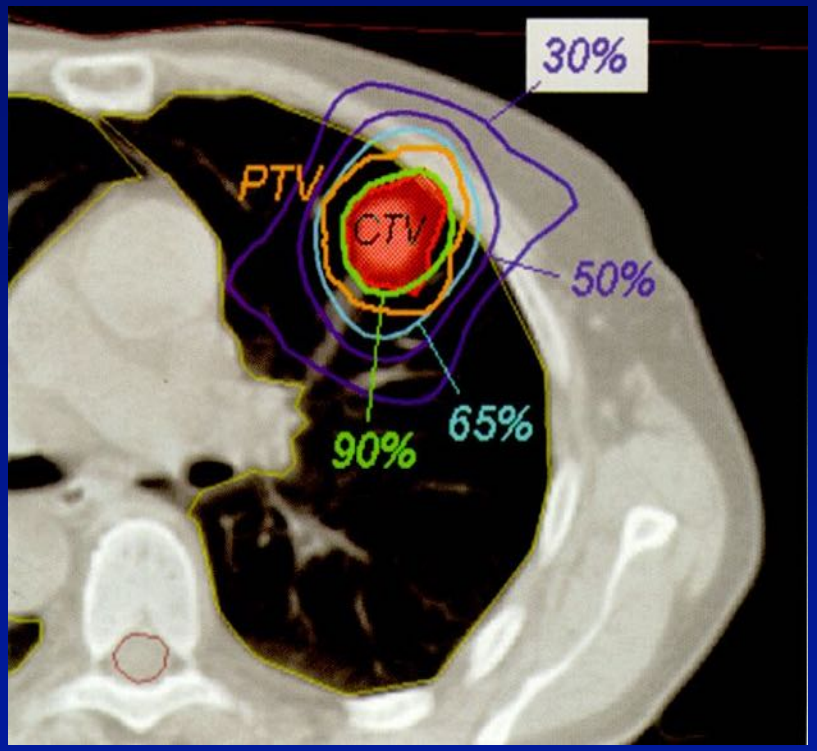
Stereotactic Ablative Body Radiotherapy (SABR)

High precision image guided radiation therapy characterized by:

- accurate target definition
- reproducible patient/tumor positioning,
- multiple fixed beams or arc delivery

Features of SBRT delivery:

- Very high biological doses
- Delivery in 3-8 sessions
- Steep dose gradients



Overall Survival according BED_{10}

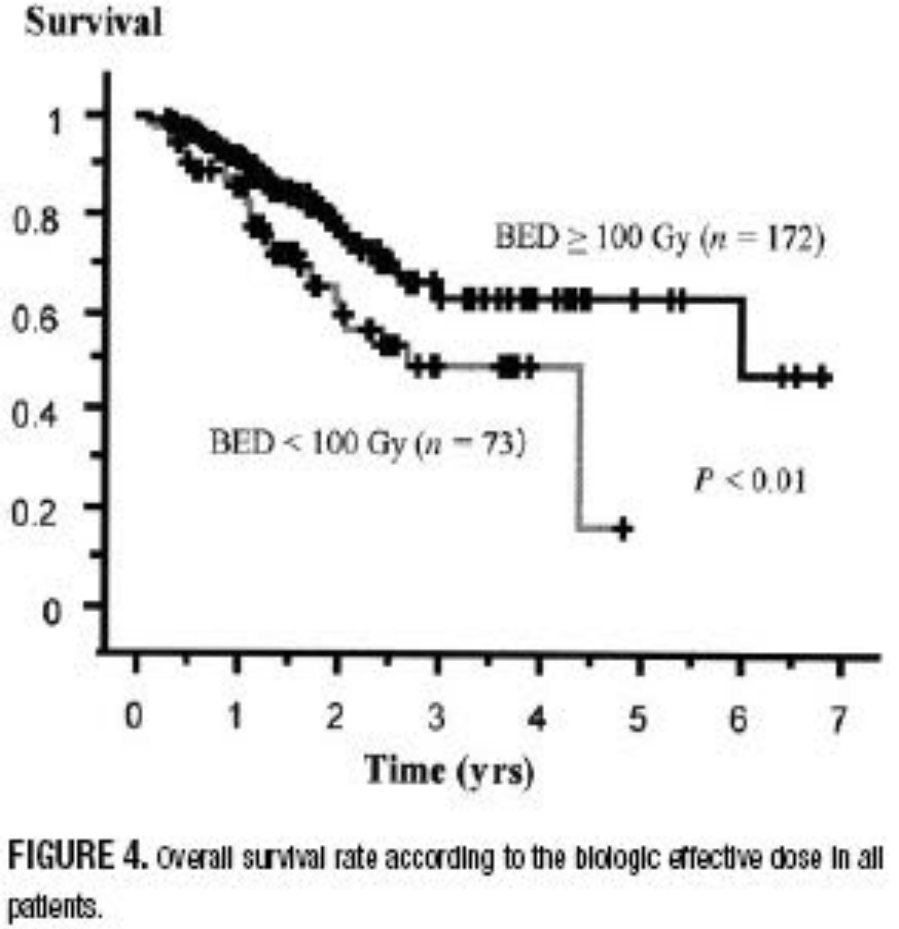


FIGURE 4. Overall survival rate according to the biologic effective dose in all patients.

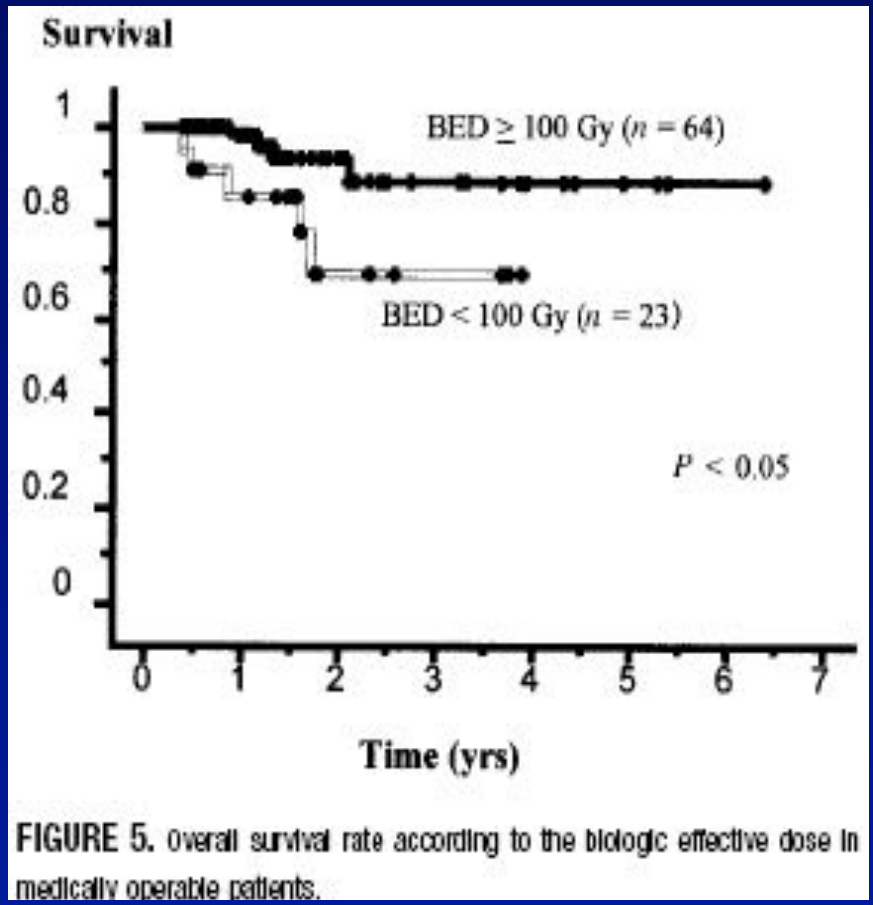


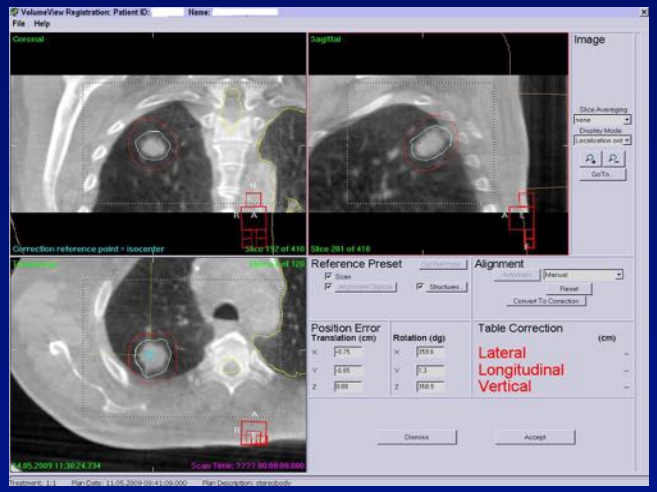
FIGURE 5. Overall survival rate according to the biologic effective dose in medically operable patients.

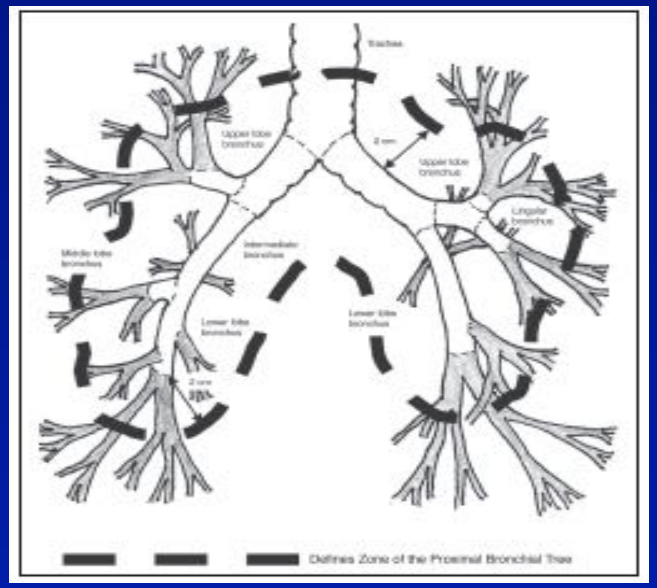
"Japanese Multiinstitutional Study" Onishi et al. Cancer (2004): 101, 1623-1631

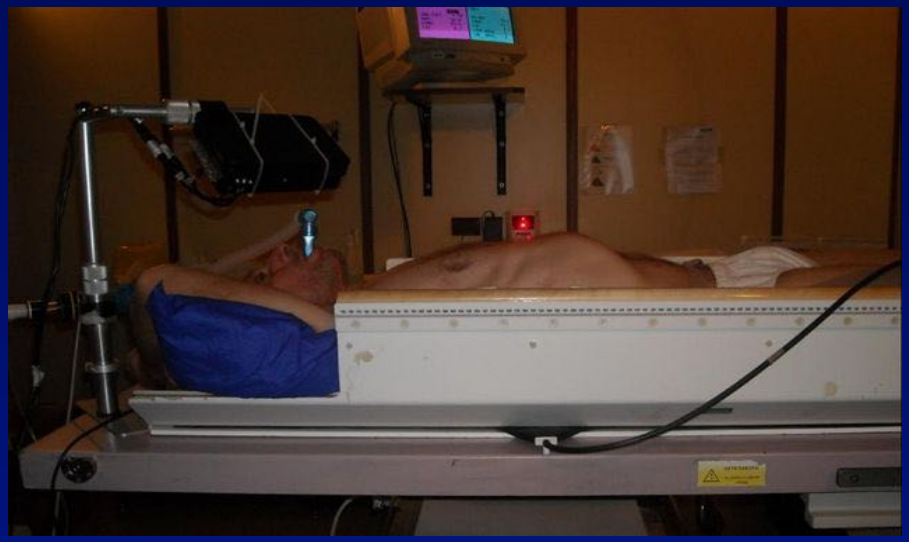
Risk adapted SBRT protocols

- T1 (< 3 cm) tumors without extensive contact with thoracic wall or mediastinum: 3 fractions of 18 Gy @ 80% (BED: 151)
- T1 tumors with broad contact with mediastinum or thoracic wall, T2 tumors:

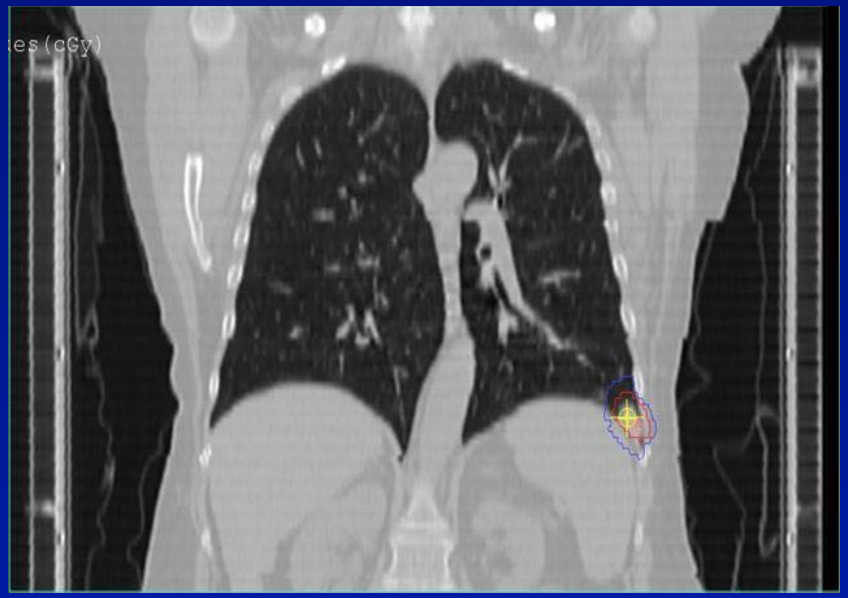
  5 fractions of 12 Gy @ 80% (BED: 132)
- Tumors adjacent to pericardium or hylus: 8 fractions of 7,5 Gy @ 80% (BED 105)

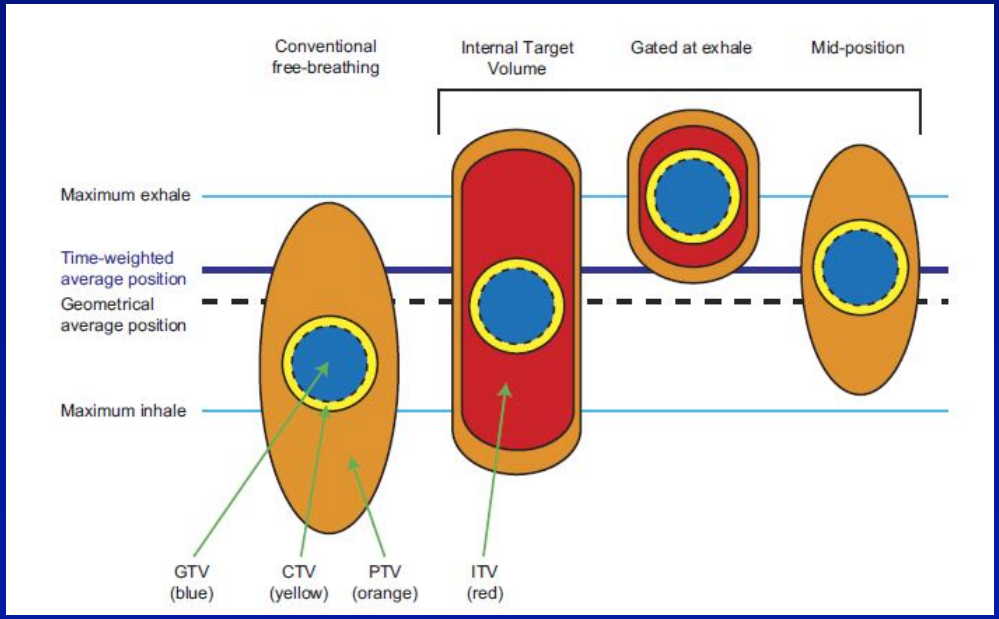







Wednesday, September 19, 2001
1 second per division
Press spacebar to terminate breath-hold.
10




Conventional free-breathing
Internal Target Volume
Gated at exhale
Mid-position
Maximum exhale
Time-weighted average position
Geometrical average position
Maximum inhale
GTV (blue)
CTV (yellow)
PTV (orange)
ITV (red)

CONSIDERATION OF DOSE LIMITS FOR ORGANS AT RISK OF THORACIC RADIOTHERAPY: ATLAS FOR LUNG, PROXIMAL BRONCHIAL TREE, ESOPHAGUS, SPINAL CORD, RIBS, AND BRACHIAL PLEXUS

FENG-MING (SPRING) KONG, M.D., PH.D.,* TIMOTHY RITTER, PH.D.,* DOUGLAS J. QUINT, M.D.,† SURESH SENAN, M.D.,‡ LAURIE E. GASPAR, M.D.,§ RITSUKO U. KOMAKI, M.D.,¶ COEN W. HURKMANS, PH.D.,‖ ROBERT TIMMERMAN, M.D.,# ANDREA BEZJAK, M.D.,** JEFFREY D. BRADLEY, M.D.,†† BENJAMIN MOVSAS, M.D.,‡‡ LON MARSH, C.M.D.,* PAUL OKUNIEFF, M.D.,§§ HAK CHOY, M.D.,# AND WALTER J. CURRAN, JR., M.D.¶¶

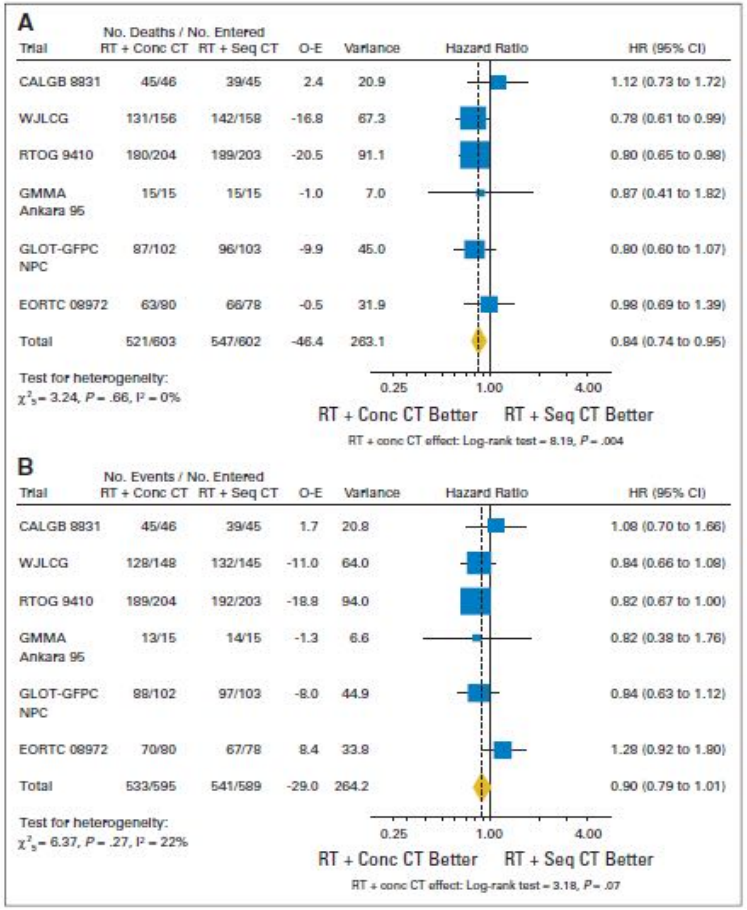
Table 1. Dosimetric limits for thoracic organs at risk

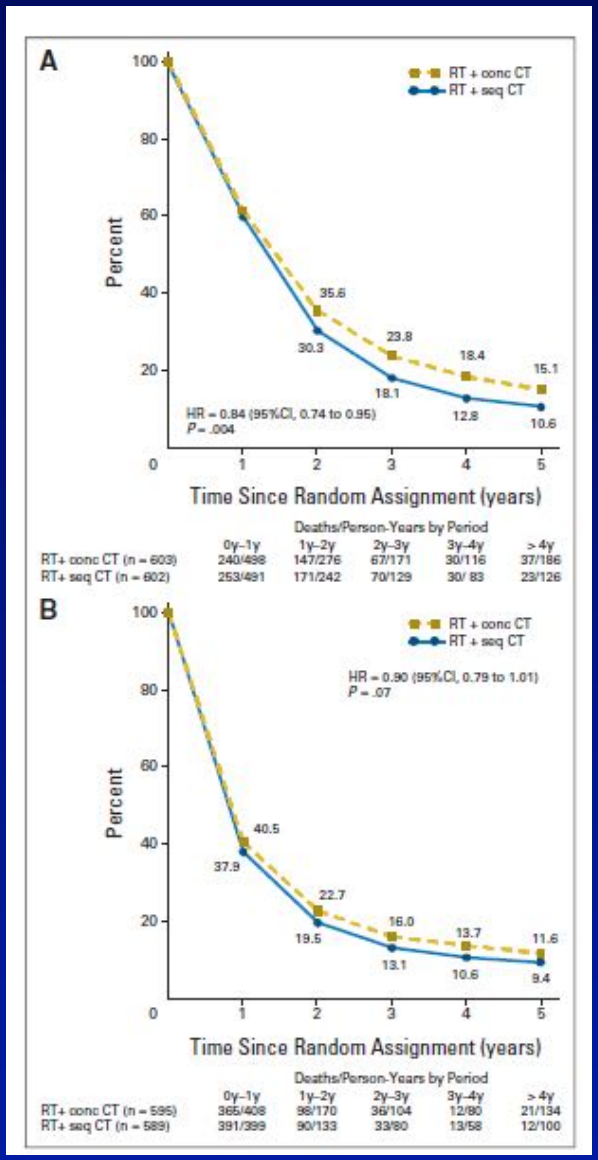
Dose limits for OARs	3D-CRT (RTOG 0617)	3D-CRT (RTOG 0972/CALGB 36050)	SBRT (RTOG 0618, 3 fx)	SBRT (ROSEL European trial, 3 or 5 fx)
Spinal cord (point dose)	Point dose ≤50.5 Gy	Any portion ≤50 Gy	≤18 Gy (6 Gy/fx)	18 Gy (3 fx) 25 Gy (5fx)
Lung	Mean lung dose ≤20 Gy, V_{20} ≤37%	V_{20} ≤35%	V_{20} ≤10%*	V_{20} <5–10%†
Esophagus	Mean dose ≤34 Gy	Not limited	≤27 Gy (9 Gy/fx)	24 Gy (3 fx) 27 Gy (5 fx)
Brachial plexus (point dose)	≤66 Gy	Not limited	≤24 Gy (8 Gy/fx)	24 Gy (3 fx) 27 Gy (5 fx)
Heart‡	≤60, ≤45, ≤40 Gy for 1/3, 2/3, 3/3 of heart	≤60, ≤45, ≤40 Gy for 1/3, 2/3, 3/3 of heart	≤30 Gy (10 Gy/fx)	24 Gy (3 fx) 27 Gy (5 fx)
Trachea, bronchus	Not limited	Not limited	≤30 Gy (10 Gy/fx)	30 Gy (3 fx) 32 Gy (5 fx)
Ribs	Not limited	Not limited	Not limited§	Not limited
Skin	Not limited	Not limited	≤24 Gy (8 Gy/fx)	Not limited

Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 5, pp. 1442–1457, 2011

Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced Non–Small-Cell Lung Cancer

Anne Aupérin, Cecile Le Péchoux, Estelle Rolland, Walter J. Curran, Kiyoyuki Furuse, Pierre Fournel, Jose Belderbos, Gerald Clamon, Hakki Cuneyt Ulutin, Rebecca Paulus, Takeharu Yamanaka, Marie-Cecile Bozonnat, Apollonia Uitterhoeve, Xiaofei Wang, Lesley Stewart, Rodrigo Arriagada, Sarah Burdett, and Jean-Pierre Pignon





VOLUME 28 · NUMBER 13 · MAY 1 2010
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Amini et al. Radiation Oncology 2012, 7:33
http://www.ro-journal.com/content/7/1/33

RADIATION ONCOLOGY

RESEARCH Open Access

Accelerated hypofractionated radiation therapy compared to conventionally fractionated radiation therapy for the treatment of inoperable non-small cell lung cancer

Arya Amini[1,3], Steven H Lin[1,4*], Caimiao Wei[2], Pamela Allen[1], James D Cox[1] and Ritsuko Komaki[1]

Table 1 Patient/Treatment Characteristics

Variable		ACRT (45 Gy) n = 119	STRT1 (60-63 Gy) n = 90	STRT2 (> 63 Gy) n = 91	Total	*p*-value
Age	median(range)	68(41,100)	67(44,88)	73(47,95)	69.5(41,100)	< 0.001
Gender	Female	48(40.3%)	43(47.8%)	50(54.9%)	141(47.0%)	0.108
	Male	71(59.7%)	47(52.2%)	41(45.1%)	159(53.0%)	
Smoking Status	Never	8(6.8%)	2(2.2%)	4(4.4%)	14(4.7%)	0.224
	Quit	70(59.8%)	45(50.6%)	53(58.2%)	168(56.6%)	
	Current	39(33.3%)	42(47.2%)	34(37.4%)	115(38.7%)	
Karnofsky Performance Status score	90	3(2.5%)	5(5.6%)	6(6.6%)	14(4.7%)	< 0.001
	80	35(29.4%)	58(64.4%)	40(44.0%)	133(44.3%)	
	70	47(39.5%)	23(25.6%)	38(41.8%)	108(36.0%)	
	≤ 60	34(28.6%)	4(4.4%)	7(7.7%)	45(15.0%)	
Presenting Weight	No	56(51.4%)	67(75.3%)	61(67.8%)	184(63.9%)	0.002
loss ≥ 5%	Yes	53(48.6%)	22(24.7%)	29(32.2%)	104(36.1%)	
Tumor Stage	IIIA	37(31.1%)	50(55.6%)	57(62.6%)	144(48.0%)	< 0.001
	IIIB	82(68.9%)	40(44.4%)	34(37.4%)	156(52.0%)	
Tumor Histology	Adenocarcinoma	37(31.4%)	31(35.2%)	41(45.6%)	109(36.8%)	0.142
	Squamous	42(35.6%)	34(38.6%)	32(35.6%)	108(36.5%)	
	NSC-NOS	39(33.1%)	23(26.1%)	17(18.9%)	79(26.6%)	
Tumor Grade	Well	3(2.5%)	0(0%)	4(4.4%)	7(2.3%)	0.069
	Moderate	11(9.2%)	12(13.3%)	10(11.0%)	33(11.0%)	
	Poor	37(31.1%)	42(46.7%)	29(31.9%)	108(36.0%)	
	Unclear	68(57.1%)	36(40.0%)	48(52.7%)	152(50.7%)	
Tumor Size (cm)	median(range)	5(1,11.5)	5(1.5,10.5)	4.2(1,9)	5(1,11.5)	0.039
Induction	No	96(80.7%)	29(32.2%)	64(70.3%)	189(63.0%)	< 0.001
Chemotherapy	Yes	23(19.3%)	61(67.8%)	27(29.7%)	111(37.0%)	
Adjuvant	No	105(88.2%)	85(94.4%)	86(94.5%)	276(92.0%)	0.15
Chemotherapy	Yes	14(11.8%)	5(5.6%)	5(5.5%)	24(8.0%)	

ACRT: accelerated radiotherapy; STRT1: standard radiation therapy 1 (60-63 Gy); SBRT2: standard radiation therapy 2 (> 63 Gy); NSC-NOS: Non-Small Cell-Not Otherwise Specified

300 pz. NSCLC stadio III
No CT concomitante
119 pz 45 Gy / 15 fx
67 pz 60 Gy / 2Gy fx
73 pz. >63 Gy / 2 Gy fx

Amini et al. Radiation Oncology 2012, 7:33
http://www.ro-journal.com/content/7/1/33

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Arya Amini[1,3], Steven H Lin[1,4*], Caimiao Wei[2], Pamela Allen[1], James D Cox[1] and Ritsuko Komaki[1]

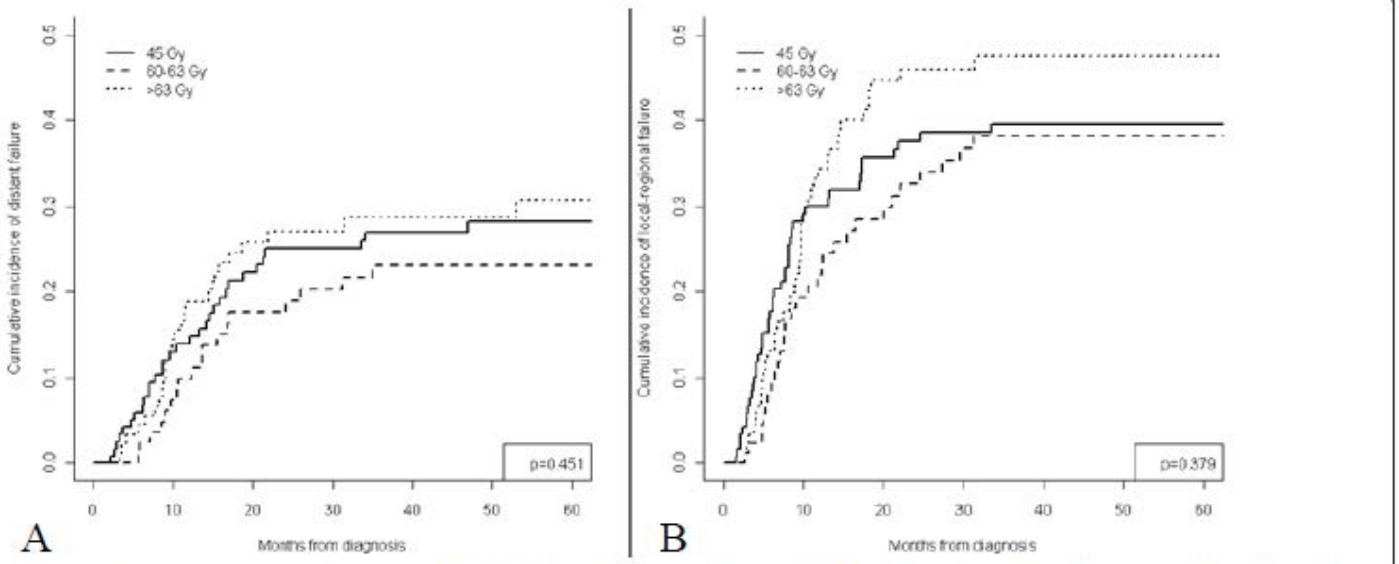

Figure 1 Cumulative incidence representing rate of local-regional recurrence (Figure 1A) and distant failure (Figure 1B) for all patients based on radiation treatment groups.

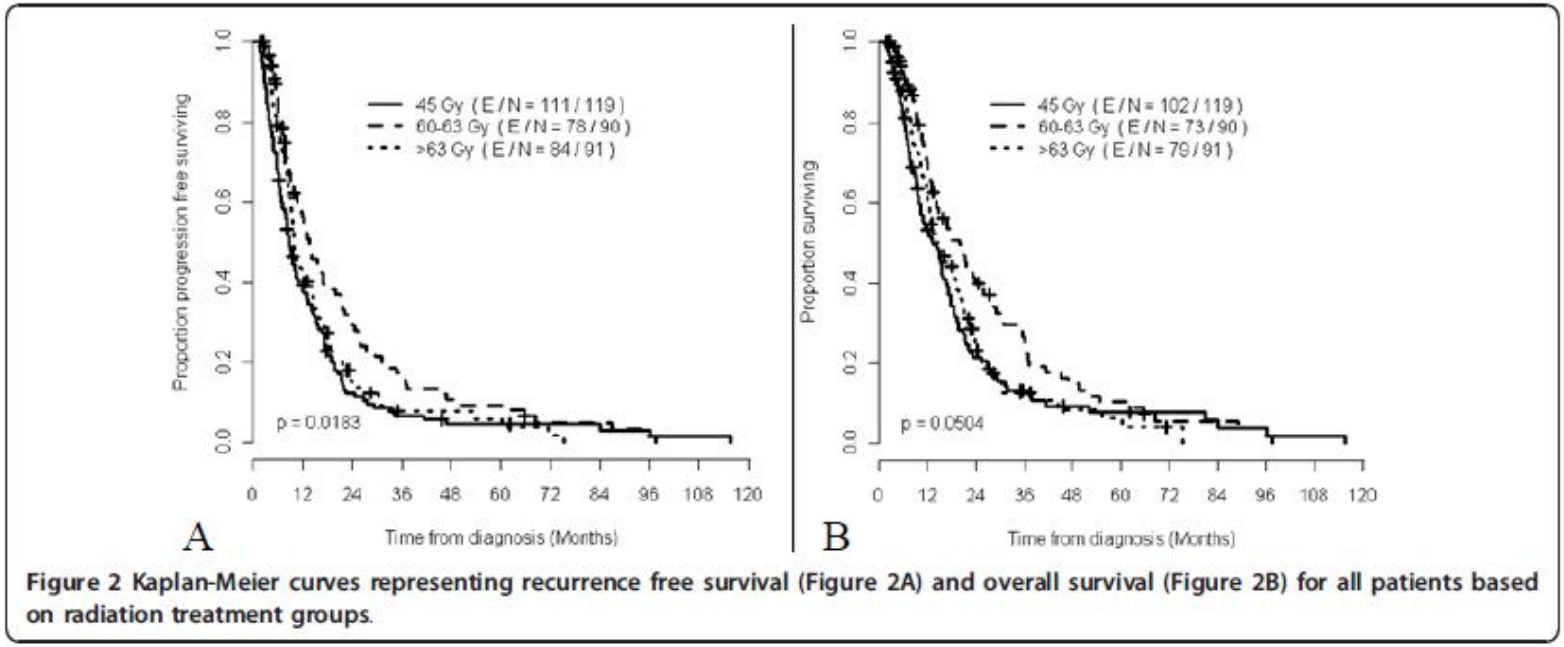

Figure 2 Kaplan-Meier curves representing recurrence free survival (Figure 2A) and overall survival (Figure 2B) for all patients based on radiation treatment groups.

Amini et al. Radiation Oncology 2012, 7:33
http://www.ro-journal.com/content/7/1/33

RADIATION ONCOLOGY

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Accelerated hypofractionated radiation therapy compared to conventionally fractionated radiation therapy for the treatment of inoperable non-small cell lung cancer

Arya Amini[1,3], Steven H Lin[1,4*], Caimiao Wei[2], Pamela Allen[1], James D Cox[1] and Ritsuko Komaki[1]

$$BED = (nd)(1 + d/[\alpha/\beta]) - 0.693.t/\alpha.Tpot$$

Conclusions

Our findings suggest that accelerated radiotherapy for patients with inoperable tumors is a safe, convenient and effective treatment option. Although this study is limited by the retrospective nature of the analysis, these are hypothesis-generating results which can serve as a basis of a prospective study comparing hypofractionated regimen with conventionally fractionated radiotherapy. However, with similar rates of efficacy in high-risk individuals as seen from these results, a shortened treatment time interval will reduce overall treatment cost and improve patient convenience. We believe this treatment approach will be a viable treatment option for unresectable lung cancers in the future in combination with sequential systemic therapies.

Mature results of a phase II trial on individualised accelerated radiotherapy based on normal tissue constraints in concurrent chemo-radiation for stage III non-small cell lung cancer ☆

Angela van Baardwijk [a,*], Bart Reymen [a], Stofferinus Wanders [a], Jacques Borger [a], Michel Öllers [a], Anne-Marie C. Dingemans [b], Gerben Bootsma [c], Wiel Geraedts [d], Cordula Pitz [e], Ragnar Lunde [f,h], Frank Peters [g], Philippe Lambin [a], Dirk De Ruysscher [a]

Patient, tumor and treatment characteristics.

Characteristic	No. of patients	(%)
Age (median in years and range)	63.2	(40–80)
Sex		
Male	88	(64.2)
Female	49	(35.8)
WHO-PS		
0	68	(49.6)
1	58	(42.3)
2	10	(7.3)
3	1	(0.7)
Histology		
Squamous cell carcinoma	40	(29.2)
Adenocarcinoma	22	(16.1)
Large cell/undifferentiated	73	(53.2)
Unknown	2	(1.5)
Clinical stage		
IIB	1	(0.7)
IIIA	50	(36.5)
IIIB	86	(62.8)
Type of concurrent chemotherapy		
Cisplatin–etoposide	94	(68.6)
Cisplatin–vinorelbine	39	(28.5)
Carboplatin based	4	(2.9)
Gross tumour volume		
Median (range) total tumour load in cc	76.4	(3.7–518.9)
Prescribed TTD		
Median (range) in Gy	65.0	(51–69)
$EQD_{2,T}$ corrected for proliferation		
Median (range) in Gy	53.9	(43.1–63.1)
MLD		
Median (range) in Gy	16.3	(4.4–21.0)
OTT		
Median (range) in days	35	(18–48)

137 pz., IIIA e IIIB

Carboplatino + Gemcitabina x 2

RT + CDDP +VNR o CDDP + VP 16

45 Gy in 3 settimane (1,5 Gy x 2/die) + 2 Gy x frazione (1 fx/die) fino a Dmax per OAR

Dose media: 65 Gy (range 51-69 Gy)

Durata media del trattamento 5 settimane (range: 18-48 giorni)

European Journal of Cancer (2012)

Mature results of a phase II trial on individualised accelerated radiotherapy based on normal tissue constraints in concurrent chemo-radiation for stage III non-small cell lung cancer ☆

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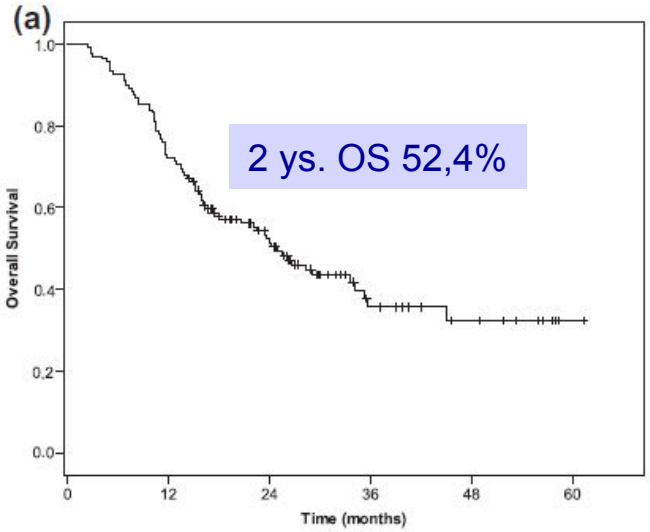
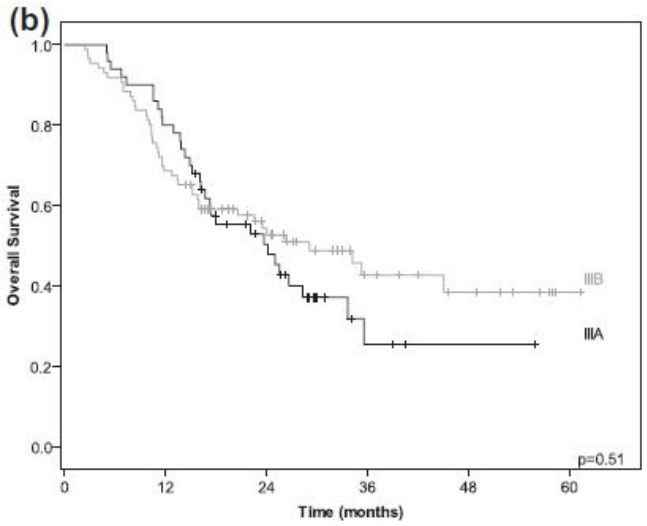
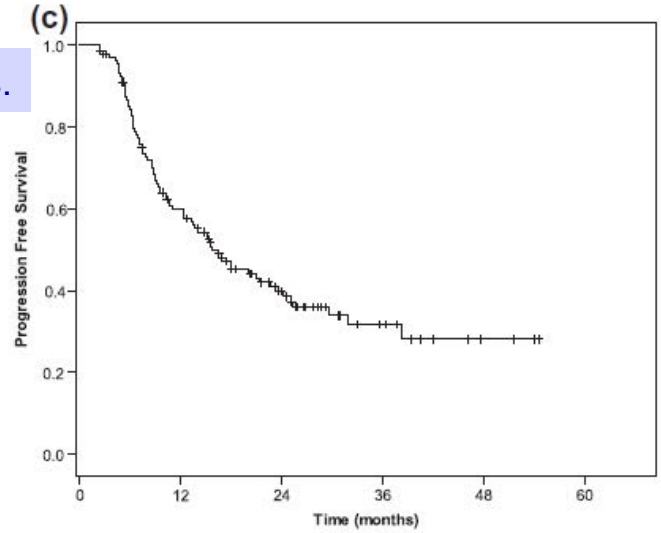


2 ys. OS 52,4%



Median f.u. 30.9 mos.



European Journal of Cancer (2012)

Hyperfractionated or Accelerated Radiotherapy in Lung Cancer: An Individual Patient Data Meta-Analysis

Audrey Mauguen, Cécile Le Péchoux, Michele I. Saunders, Steven E. Schild, Andrew T. Turrisi, Michael Baumann, William T. Sause, David Ball, Chandra P. Belani, James A. Bonner, Aleksander Zajusz, Suzanne E. Dahlberg, Matthew Nankivell, Sumithra J. Mandrekar, Rebecca Paulus, Katarzyna Behrendt, Rainer Koch, James F. Bishop, Stanley Dische, Rodrigo Arriagada, Dirk De Ruysscher, and Jean-Pierre Pignon

Table 1. Description of Included Trials

Trial	No. of Patients Randomly Assigned	Inclusion Period	Median Follow-Up (years)	Histology	RT Total Dose (Gy)	No. of Fractions	Duration (weeks)	BED St/EXP	CT Dose	Patient Characteristic
ECOG 3588[24]	417	1989-1992	13.0	SCLC	Standard: 45	25	5	39.5	Cisplatin 60 mg/m² day 1	PS 0-2
					Experimental: 45	30	3 BID	43.9	Etoposide 120 mg/m² days 1-3 4 cycles (3 weeks)	
NCCTG 892052[25]	268	1990-1996	9.3	SCLC	Standard: 50.4	28	5.5	43.8	Cisplatin 30 mg/m² days 1-3	PS 0-2
					Experimental: 48	32	5.5 SC* BID	39.5	Etoposide 130 mg/m² days 1-3 6 cycles† (4 weeks)	
RTOG 8808-ECOG 4588[26]	326	1989-1992	6.8	NSCLC	Standard: 60 Gy	30	6	55.5	None	KPS ≥ 70
					Experimental: 69.6	58	6 BID	61.9		Stage II-III
PMCI 88C091[27]	101	1989-1995	Not reached	NSCLC	Standard: 60	30	6	55.5	None	PS 0-1
					Experimental: 60	30	3 BID	64.2		Stage I-III
PMCI 88C091 CT[27]	107	1989-1995	Not reached	NSCLC	Standard: 60	30	6	55.5	Carboplatin 70 mg/m² days 1-5	PS 0-1
					Experimental: 60	30	3 BID	64.2	+ Carboplatin 70 mg/m² days 29-33 in standard arm	Stage I-III
CHART[28]	563‡	1990-1995	6.9	NSCLC	Standard: 60	30	6	55.5	None	PS 0-1
					Experimental: 54	36	1.5 TID	57.2		Stage I-III
NCCTG 902451[29]	74	1992-1993	8.1	NSCLC	Standard: 60	30	6	55.5	None	PS 0-2
					Experimental: 60	40	6 SC§ BID	52.5		Stage III
NCCTG 942452[30]	246	1994-1999	7.3	NSCLC	Standard: 60	30	6	55.5	Cisplatin 30 mg/m² days 1-3, 28-30	PS 0-1
					Experimental: 60	40	6 SC§ BID	52.5	Etoposide 100 mg/m² days 1-3, 28-30	Stage III
CHARTWEL[31]	300	1997-2005	4.9	NSCLC	Standard: 66	33	6.5	60.6	None	PS 0-1
					Experimental: 60	40	2.5 TID	61.6		Stage I-III
CHARTWEL CT[31]	106	1997-2005	3.5	NSCLC	Standard: 66	33	6.5	60.6	Induction CT—dependent on institution's choice	PS 0-1
					Experimental: 60	40	2.5 TID	61.6		Stage I-III
ECOG 2597[32]	119	1998-2001	6.7	NSCLC	Standard: 64	32	6.5	58.7	Carboplatin AUC 6 day 1	PS 0-1
					Experimental: 57.6	36	2.5 TID	60.2	Paclitaxel 225 mg/m² day 1 2 cycles‖ (3 weeks)	Stage III
Gliwice 2001[33]	58	2001-2006	5.3	NSCLC	Standard: 72	40	8	62.7	None	PS 0-1
					Experimental: 72	40	5.5	68.5		Stage II-III

Abbreviations: BED, biologic effective dose; BID, RT given twice a day; CT, chemotherapy; if not specified, the chemotherapy is concomitant to the radiotherapy; CHART, Continuous Hyperfractionated Accelerated Radiation Therapy; CHARTWEL, CHART Week-End Less; ECOG, Eastern Cooperative Oncology Group; Exp, experimental; (K) PS, (Karnofsky) performance status; NCCTG, North Central Cancer Treatment Group; NSCLC, non–small-cell lung cancer; PCMI, Peter MacCallum Institute; RT, Radiotherapy; RTOG, Radiation Therapy Oncology Group; SC, split course; SCLC, small-cell lung cancer; St, standard; TID, RT given three times a day.

*Two series of 8 days with a break of 2.5 weeks.

†Three cycles induction, two cycles concomitant, and one after RT; etoposide dose was reduced to 100 mg/m² for cycles 4 to 6.

‡Patients were randomly allocated in a 3:2 ratio to CHART or conventional radiotherapy.

§Two series of 2 weeks with a break of 2 weeks.

‖Induction chemotherapy.

VOLUME 30 · NUMBER 22 · AUGUST 1 2012

JOURNAL OF CLINICAL ONCOLOGY

Hyperfractionated or Accelerated Radiotherapy in Lung Cancer: An Individual Patient Data Meta-Analysis

Audrey Mauguen, Cécile Le Péchoux, Michele I. Saunders, Steven E. Schild, Andrew T. Turrisi, Michael Baumann, William T. Sause, David Ball, Chandra P. Belani, James A. Bonner, Aleksander Zajusz, Suzanne E. Dahlberg, Matthew Nankivell, Sumithra J. Mandrekar, Rebecca Paulus, Katarzyna Behrendt, Rainer Koch, James F. Bishop, Stanley Dische, Rodrigo Arriagada, Dirk De Ruysscher, and Jean-Pierre Pignon

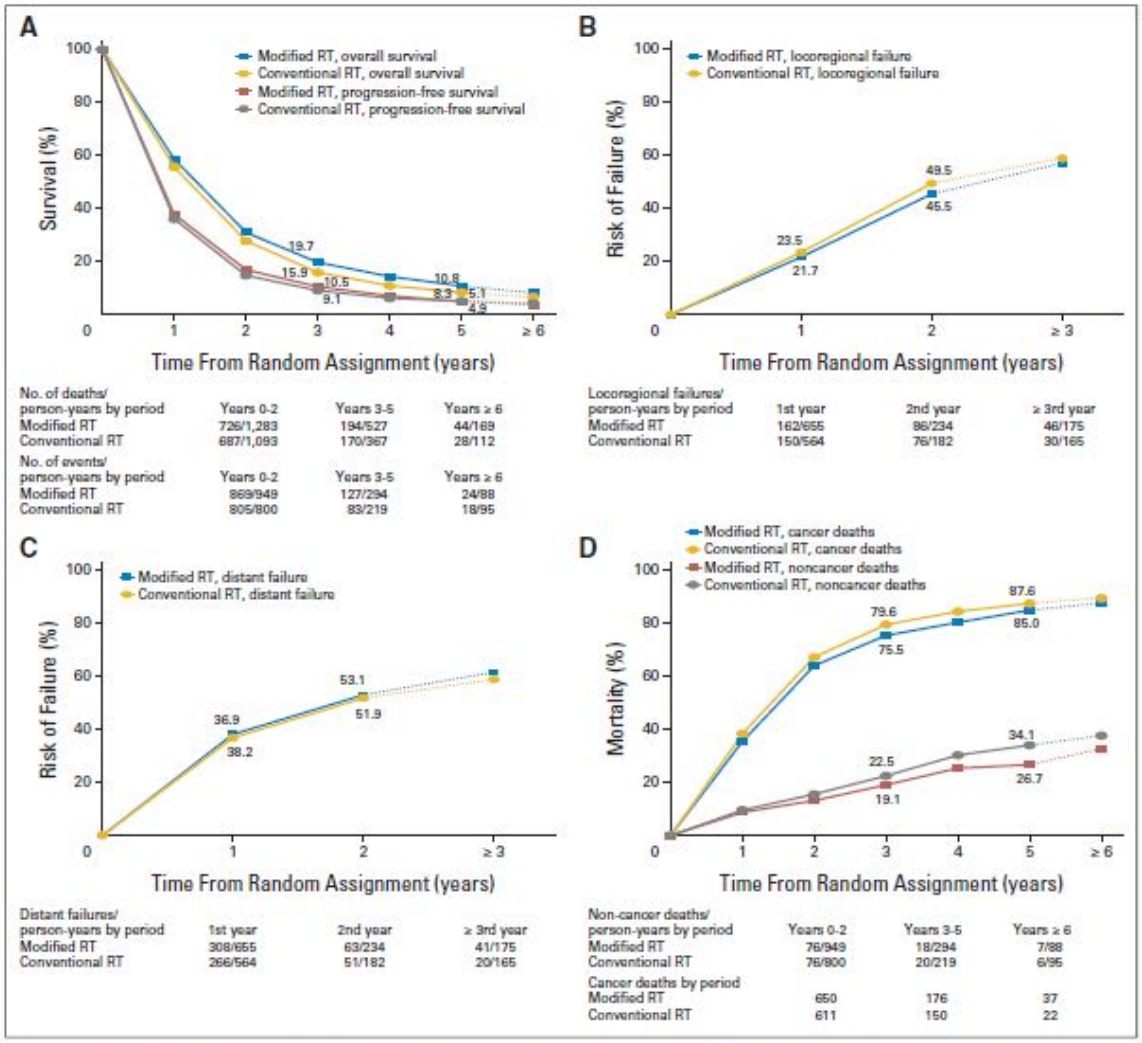


Fig 3. Survival curves for the non–small-cell lung cancer trials: (A) overall and progression-free survival; (B) locoregional failure; (C) distant failure; (D) lung and non–lung cancer mortality. RT, radiotherapy.

2000 pz.
10 trials; RT +/- CT:
+ 2,5% OS a 5aa
per RT iperfrazionata
o accelerata

Concomitant chemoradiotherapy is at present considered the standard regimen for locally advanced lung cancer. The integration of optimized conformal RT to improve local control as well as the combination with systemic agents to reduce systemic failures using modified RT regimens should be reconsidered. The search for biologic predictive factors that could enable us to better individualize the optimal treatment for patients with lung cancer is also warranted, as this meta-analysis seems to show that there are different possibilities to improve curability of lung cancer. Further research is needed to identify the optimal schedule of modified fraction RT, including new techniques in target volume definition, treatment techniques, and delivery, such as positron emission tomography scans, intensity-modulated RT, and dose-guided RT.[40]

VOLUME 30 · NUMBER 22 · AUGUST 1 2012
JOURNAL OF CLINICAL ONCOLOGY

Anti-Tumour treatment

Cancer Treatment Reviews 38 (2012) 626–640

Targeted agents in non-small cell lung cancer (NSCLC): Clinical developments and rationale for the combination with thoracic radiotherapy

Pek Keng Koh [a,*], Corinne Faivre-Finn [a,1], Fiona H. Blackhall [b,2], Dirk De Ruysscher [c,3]

REVIEW Open Access

A review of clinical trials of cetuximab combined with radiotherapy for non-small cell lung cancer

Carsten Nieder[1,2*], Adam Pawinski[1], Astrid Dalhaug[1] and Nicolaus Andratschke[3]

Radiation Oncology 2012, **7**:3

frontiers in ONCOLOGY

REVIEW ARTICLE
published: 10 April 2012
doi: 10.3389/fonc.2012.00031

Radiotherapy and erlotinib combined: review of the preclinical and clinical evidence

Therapy	Study	Phase	Stage, clinical setting	Treatment schedule	RT	Clinical end point	Target recruitment
Cilengitide	NCT01118676	I	Stage III	Cilengitide → cisplatin/vinorelbine + RT + cilengitide	66 Gy in 33 daily fractions	Primary: MTD Secondary: Response, Survival free of metastases, OS, Toxicity, biomarkers	24
Bortezomib	NCT00093756	I/II	Stage III	Carboplatin/paclitaxel + RT + bortezomib (Phase I closed 2009)	60 Gy in 30 daily fractions	Primary: MTD (Phase 1), Survival at 1 yr (Phase 2) Secondary: Tolerability, Response Rate, PFS, OS, biomarkers	99
Everolimus	NCT01167530	I	Stage III and symptomatic Stage IV	1st Phase: once weekly Everolimus → RT + everolimus → everolimus(RAD001) → chemo 2nd Phase: daily Everolimus → RT + everolimus → everolimus(RAD001) → chemo Chemo = cisplatin/vinorelbine	66 Gy in 33 daily fractions	Primary: DLT Secondary: PFS, OS, Response	36
Vorinostat	NCT01059552	I	Stage III	RT + Cisplatin/pemetrexed + vorinostat	70 Gy in 35 daily fractions	Primary: Safety and MTD Secondary: PFS, Response Rate, biomarkers	22
	NCT00662311	I/II	Stage III	RT + Paclitaxel + vorinostat	N/A	Primary: MTD Secondary: Response, PFS, OS, Safety and Toxicity	35
Selumetinib (AZD6244)	NCT01146756	I	Stage III and symptomatic Stage IV	RT + Selumetinib	66 Gy in 33 daily fractions	Primary: Recommended Phase II Dose, DLT Secondary: Safety, Dose delivery, Response, biomarkers	33
Veliparib (ABT-888)	NCT01386385	I/II	Stage III	Phase I and Arm I: chemo + veliparib → chemoRT + veliparib Arm II: chemo + placebo → chemoRT + placebo Chemo = carboplatin/paclitaxel	7 weeks RT	Primary: DLT, MTD (Ph1), PFS (Ph2) Secondary: Response, Toxicity, Time to progression, PFS, OS, biomarkers	122
Bevacizumab + erlotinib	NCT00280150	I/II	Stage III, squamous histology with no haemoptysis, non-central tumors	Cohort 1:ChemoRT + bevacizumab Cohort 2 and 3: ChemoRT + bevacizumab + erlotinib Consolidation bevacizumab + erlotinib (closed 2008) Chemo = carboplatin/paclitaxel	74 Gy	Primary: MTD (Phase I, closed 2008), safety Secondary: Feasiblity and tolerability of consolidation therapy, Toxicity, Response, Survival	50
Sunitinib	NCT00437372	Ib	Solid tumors, including of the thorax	RT + sunitinib	N/A, 2–8 weeks	Primary: Safety and Toxicity Secondary: biomarkers	60
Vandetanib (ZD6474)	NCT00745732	I/II	Unresectable or inoperable Stage I-IV	Vandetanib → RT + Vandetanib	Phase I: 45 Gy in 15 fractions Phase II: 45 Gy or 70 Gy in 35 daily fractions	Primary: MTD Secondary: Response, biomarkers	48
Endostatin (Endostar)	RT0902 NCT01158144	II	Stage III	ChemoRT + Endostar → chemo x2 + Endostar chemo = carboplatin/paclitaxel	66 Gy in 33 daily fractions	Primary: Tumor Response Rate Secondary: OS	134

Cetuximab	RTOG-0617 NCT00533949	III	Stage III	Arm I: chemoRT 60GY Arm II: chemoRT 74 Gy (closed) Arm III: chemoRT 60 Gy + cetuximab Arm IV: chemoRT 74 Gy + cetuximab (closed) Chemo = carboplatin/paclitaxel	Arm I + III: 60 Gy in 30 daily fractions Arm II + IV: 74 Gy in 37 daily fractions	Primary: OS Secondary: PFS, Locoregional failure, Grade 3–5 AE, QoL, Quality adjusted survival, biomarkers	500
	NCT00985855	II: randomised	Stage III	Arm I: chemo → chemoRT + cetuximab Chemo Arm 1 = cisplatin/vinorelbine Arm II:chemo → chemoRT + cetuximab Chemo Arm 2 = cisplatin/etoposide	66 Gy in 33 daily fractions	Primary: Grade 3 toxicity	62
	RADITUX NTR2230	I/II	Stage II/III	Cisplatin + RT ± cetuximab	66 Gy in 24 daily fractions	Primary: Local control Secondary: Safety, OS, PFS, Response, AE	110
	NCT00492206	II	Stage III	RT + cetuximab → paclitaxel/carboplatin × 3 cycles + (cetuximab weekly for 26 weeks)	63 Gy	Primary: Response rate Secondary: PFS, Safety, Baseline tumor EGFR and biomarkers	36
	NCT01102231	II	Stage III, non-squamous	RT + Cisplatin + pemetrexed + cetuximab	66 Gy in 33 daily fractions	Primary: Disease control rate Secondary: OS	100
	NCT00673738	II	Stage IIA to IIIA	RT + cetuximab → docetaxel × 3 cycles + cetuximab	63 Gy	Primary: PFS Secondary: OS/Response rate, feasibility, tolerance, QoL, profile that predicts response/prognosis	27
Panitumumab	RTOG-0839 NCT00979212	II	Stage IIIA, N2+, potentially operable	Arm I: induction chemoRT → (surgery) → chemotherapy Arm II: Induction chemoRT + panitumumab → (surgery) → chemotherapy (consolidation cetuximab closed) Chemo = carboplatin + paclitaxel	60 Gy in 30 daily fractions	Primary: Mediastinal nodal clearance Secondary: OS, first failure, acute and late AE, surgical morbidities, Response rate, biomarkers	97
Gefitinib	NCT01391260	II	Stage III or Stage IV, non-squamous EGFR mutation positive	RT + gefitinib	upto 66 Gy in 33 daily fractions	Primary: Response Secondary: PFS, OS, QoL	30
Erlotinib	CALGB 30605 NCT00553462	II	Stage III, poor risk	Carboplatin/paclitaxel → RT + erlotinib	66 Gy in 33 daily fractions	Primary: OS at 12 months Secondary: Response, PFS	76
	NCT00563784	II	Stage III	RT + Carboplatin/paclitaxel + erlotinib	63 Gy in 35 daily fractions	Primary: Feasibility, Safety Secondary: association between EGFR expression and reponse/toxicity, OS, Time to Disease Progression, Response	48
	TARLAL NCT00888511	II	Stage IIB to IIIB	RT + erlotinib	66 Gy in 33 daily fractions	Primary: Local Failure Free Survival at 9 months after the start of RT Secondary: Toxicity, Local tumor control, Response, biomarkers, OS, DFS, Late Toxicity	57

Anti-Tumour treatment

Targeted agents in non-small cell lung cancer (NSCLC): Clinical developments and rationale for the combination with thoracic radiotherapy

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Perspective

At present, none of the targeted agents we have identified as being investigated in clinical studies have shown proven benefit when combined with RT, either in the curative or in the palliative setting. There is only one phase III study in progress of RT combined with cetuximab, and early closure due to toxicity has hampered progress for both EGFR TKIs and antiangiogenics. Crucial to successful development of targeted agent and RT combinations is cooperation between early phase trialists, clinical pharmacologists, radiobiologists and radiation oncologists. Heterogeneity arising from factors such as RT delivery, dose and normal tissue dose constraints needs to be minimised in the same way that rigorous criteria for clinical factors such as performance status and end organ function apply to early phase trials. This does mean that the NSCLC population eligible for such trials is relatively rare among all potential patients eligible for RT and emphasises the importance of prioritising trials based on a biological rationale backed by preclinical data. Much therefore remains to be learned about the combination of RT with targeted agents, in spite of its huge potential.

- Al momento attuale nessuno degli agenti biologici testati insieme a RT ha mostrato di poter dare un significativo beneficio
- La chiusura anticipata di alcuni trials di fase II con TKI e antiangiogenetici per eccesso di tossicità ha determinato una battuta di arresto nello sviluppo di nuovi progetti di ricerca
- Attualmente è in corso un solo studio di fase III con RT + CT +/- Cetuximab

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TUMORI DEL POLMONE
Prospettive

- La SBRT ha un ruolo fondamentale nel trattamento dei pazienti con NSCLC in stadio iniziale non operabili. Sono in corso studi che confrontano SBRT e chirurgia in pazienti operabili

- Per i pazienti in stadio localmente avanzato lo standard rimane la radiochemioterapia concomitante. In questo momento appare importante definire quale sia il regime di radioterapia più efficace (accelerazione del trattamento?)

- L'associazione tra farmaci biologici e radioterapia rimane di grande interesse, ma al momento attuale è ancora oggetto di ricerca.