La Radioterapia Stereotassica Ablativa: Neoplasia polmonare

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Standard treatment for early stage NSCLC

The current standard of care for small volume tumors is surgical resection in medically fit patients.

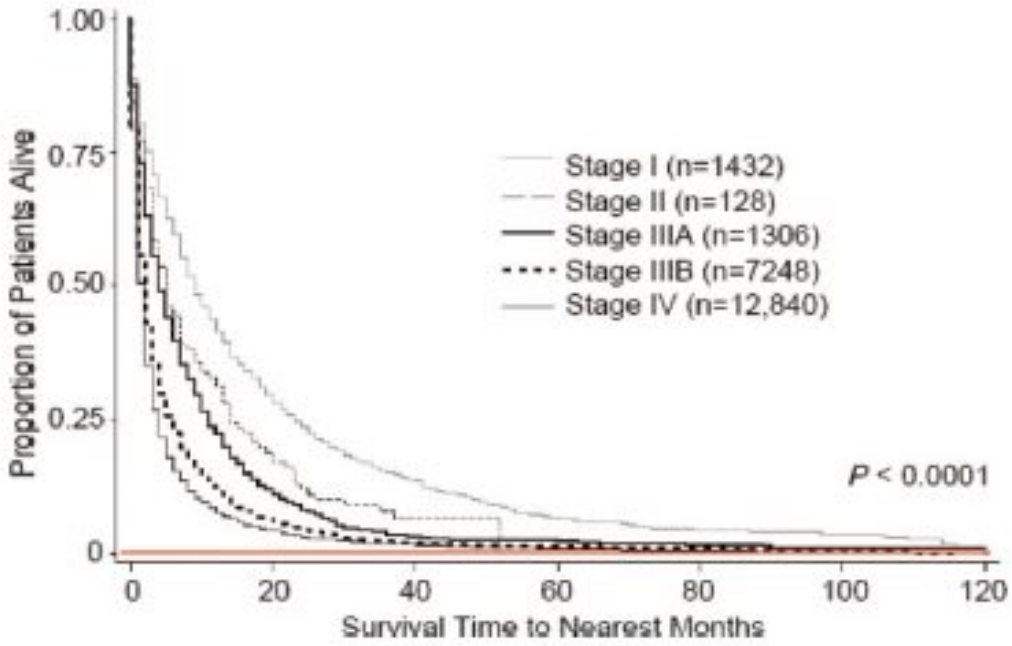
Surgery offers the potential of local tumor control in up to 96% of patients.

However surgical resection is not possible in a substantial proportion of patients (about 20% of all patients with stage I NSCLC).

Guckenberger M, Strahl Onkol 2014; 190(1): 26-33

Turning Gray: The Natural History of Lung Cancer Over Time

Frank C. Detterbeck, MD, and Christopher J. Gibson, BA†*



Detterbeck FC, JTO 2008;3(7):781-92

Natural History of Untreated Early stage NSCLC

Study	Accrual Years	N	How Found	Clinical Stage	Environment	Comments	Overall Survival MST (mo)	% 1-yr	% 2-yr	% 5-yr	Death Due to Ca
Vrdoljak et al.[68]	80–87	50	Routine	cI, II	Croatia	—	13	56	13	0	—
Chadha et al.[70]	90–01	39	Routine	cI, II	USA	Registry	12	26	0	0	49
Kyasa et al.[71]	91–98	70	Routine	cI, II	VA	—	11	44	17	0	86
[a]Wisnivesky et al.[20]	91–99	1,052	Routine	cI, II	SEER	M > 65 yr	6	30	14	3	~90[b]
[a]Wisnivesky et al.[20]	91–99	1,292	Routine	cI, II	SEER	F > 65 yr	9	40	19	5	~90[b]
Average			**Routine**	**cI, II**			**10**	**39**	**13**	**2**	**~80**
[a]Henschke et al.[72]	88–94	131	Routine	cIa	SEER	6–15 mm diam	(24)[c]	(81)[c]	(48)[c]	(39)[c]	—
[a]Raz et al.[36]	89–03	571	Routine	cIa	USA	Registry	13	53	33	9	—
Sobue et											81
[a]Raz et a											84
[a]Wisnive											73
Chadha c											~50[b]
McGarry et al.[35]	94–99	49	Routine	cI[e]	VA	All M	14	62	38	—	53
[f]Motohiro et al.[14]	82–91	584	Routine	cI	Japan	—	(17)[b,f]	(69)[b,f]	(36)[b,f]	(14)[b,f]	—
Vrdoljak et al.[68]	80–87	19	Routine	cIb	Croatia	—	17	80	20	0	—
[a]Raz et al.[36]	89–03	861	Routine	cIb	USA	Registry	8	46	18	5	—
[a]Raz et al.[36]	89–03	128	Routine	cII	USA	Registry	5	33	13	3	—
[a]Wisnivesky et al.[73]	88–04	140	Routine	cII	SEER	—	(14)[c]	(37)[c]	(20)[c]	(10)[c]	78
Vrdoljak et al.[68]	80–87	31	Routine	cIIb	Croatia	—	11	40	8	0	—
[g]**Average**			**Routine**	**cI, cII**			**11**	**49**	**22**	**4**	**70**
[h]Flehinger et al.[15]	73–78	29	CXR screen	cI	USA	—	(25)[c,h]	(88)[c,h]	(57)[c,h]	(9)[c,h]	—
Sobue et al.[13]	82–84	42	CXR screen	cI	Japan	—	25	76	48	14	80
[f]Motohiro et al.[14]	82–91	215	CXR screen	cI	Japan	—	(27)[f]	(80)[f]	(56)[f]	(24)[f]	—
[g]**Average**			**CXR screen**	**cI**			**25**	**76**	**48**	**14**	**80**

UNTREATED EARLY STAGE NSCLC have a poor survival
(MST 10 months, 1-yr OS 39%, 5-yr OS 2%)

Detterbeck FC, JTO 2008;3(7):781-92

STEREOTACTIC HIGH DOSE FRACTION RADIATION THERAPY OF EXTRACRANIAL TUMORS USING AN ACCELERATOR

Clinical experience of the first thirty-one patients

HENRIC BLOMGREN, INGMAR LAX, INGEMAR NÄSLUND and RUT SVANSTRÖM

"Our impression at present is that SRT with high-dose fractions may not only be of clinical value for patients with intracranial metastases but also for some patients with extracranial lesions".

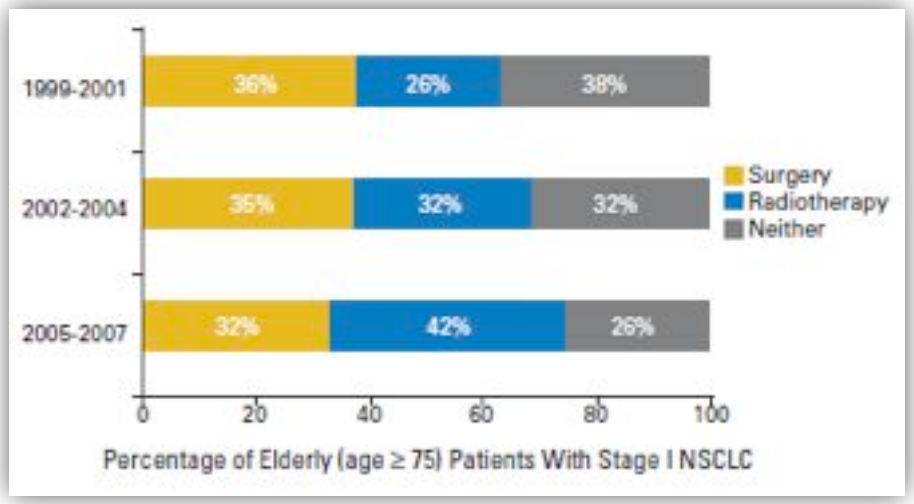
Blomgren H, Acta Oncol 1995; 34(6): 861-70

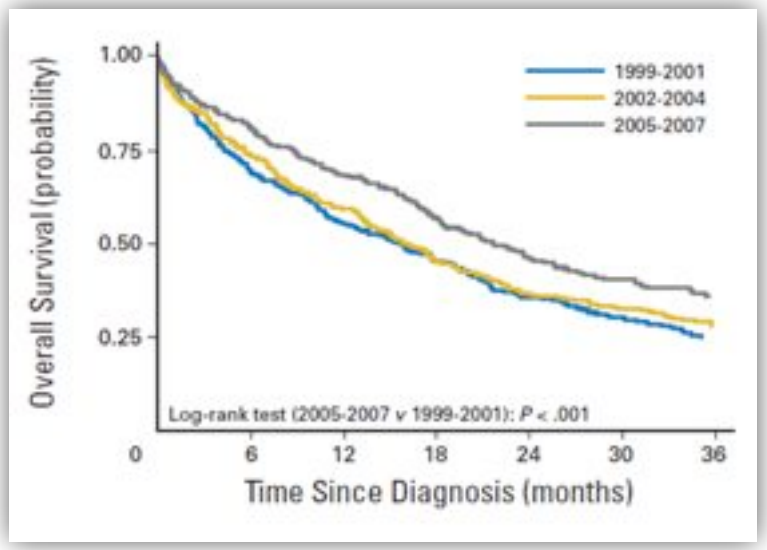
Impact of Introducing Stereotactic Lung Radiotherapy for Elderly Patients With Stage I Non–Small-Cell Lung Cancer: A Population-Based Time-Trend Analysis

David Palma, Otto Visser, Frank J. Lagerwaard, Jose Belderbos, Ben J. Slotman, and Suresh Senan

875 elderly patients

- Surgery: 299 pts (34%)
- Radiotherapy: 299 pts (34%)
- Neither: 277 pts (32%)

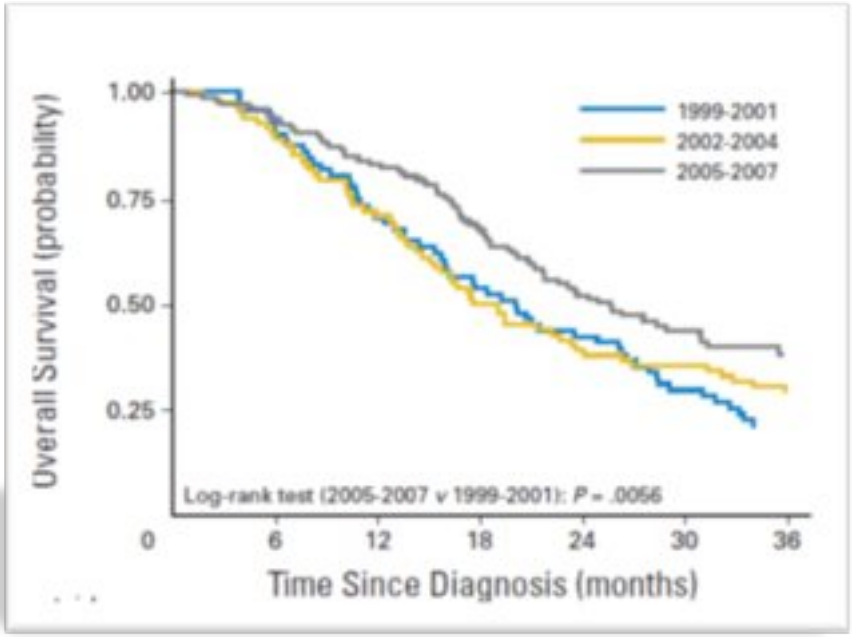




Palma D, JCO 2010;28 (35):5153-9

The introduction of SBRT coincided with a 12% absolute decrease in the number of untreated patients.

The improvement in OS was confined to RT patients (HR 0.70; 95% CI, 0.49 to 0.99), whereas no significant survival improvements were seen in the other groups.



Palma D, JCO 2010;28 (35):5153-9

Meta-analysis

Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: A meta-analysis

Janneke P.C. Grutters [a,*], Alfons G.H. Kessels [b], Madelon Pijls-Johannesma [a], Dirk De Ruysscher [a], Manuela A. Joore [b,1], Philippe Lambin [a,1]

30 studies

Treatment	5-year Overall Survival
Conventional Radiotherapy (CRT)	20%
Stereotactic Radiotherapy (SBRT)	42%
Proton Therapy	40%
Carbon-ion Therapy	42%

Survival rates for SBRT were higher than those for CRT, but similar to particle therapy in stage I inoperable NSCLC.

Grutters JP, Radiother Oncol 2010; 95:32-40

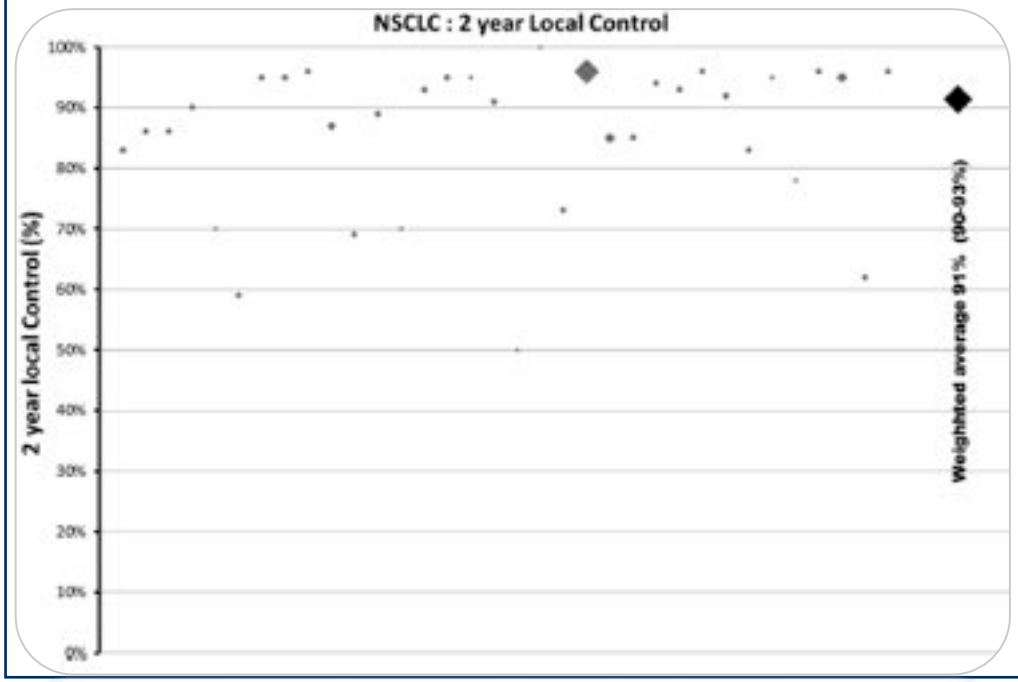
Retrospective studies on SABR in inoperable NSCLC

	N pts	*Median Fup (months)*	*Dose Gy / fx*	*Local Control*	*OS*
Uematsu et al. 2001	50	36	50-60 Gy / 5-10 fx	94%	3-yr 66%
Wulf et al. 2004	20	11	26-37.5 Gy / 1-3 fx	92%	2-yr 32%
Onishi et al. 2004	35	13	60 Gy / 10 fx	88%	2-yr 64%
Onimaru et al. 2008	28	27	48 Gy / 4 fx	64%	IA 3-yr 82% IB 3-yr 32%
Takeda et al. 2009	63	31	50 Gy / 5 fx	95%	IA 3-yr 90% IB 3-yr 63%

Stereotactic radiotherapy (SABR) for the treatment of primary non-small cell lung cancer; Systematic review and comparison with a surgical cohort

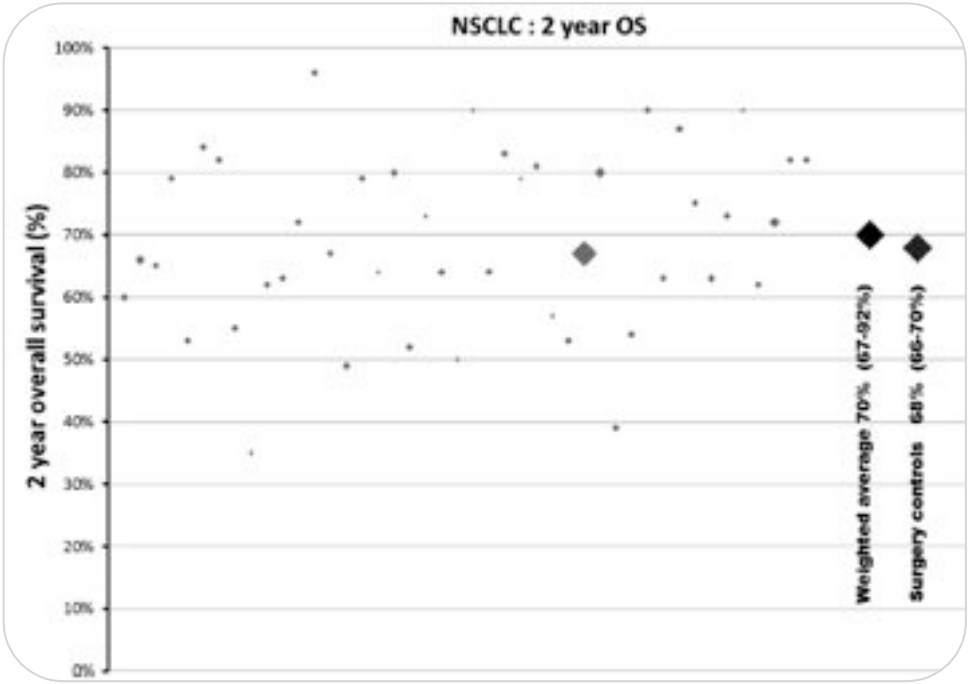
Francesca Soldà [a], Mark Lodge [b], Sue Ashley [c], Alastair Whitington [d], Peter Goldstraw [e], Michael Brada [f,*]

45 reports containing 3771 patients treated with SABR



The 2-year Local Control was 91% (95% CI: 90-93%)

Soldà F, Radiother Oncol 2013; 109:1-7



The 2-year Overall Survival was 70% (95% CI: 67-72%)

Staging	*No. patients*	*2-year OS (%)*	*95% CI*
Stage IA	792	73	70-76
Stage IB	1246	64	62-67
Stage II A	455	57	52-61
Stage II B	1625	50	47-52
Stage I	2038	68	66-70
Stage II	2080	51	49-53

The 2-year Overall Survival was 68% in the surgically treated clinical stage I

(from IASLC database)

Soldà F, Radiother Oncol 2013; 109:1-7

Thirty-four of the 45 studies covering 91% of the patients used a linear accelerator (Linac) and 11 (14%) a robotic mounted linac (Cyberknife).

There was non survival or local PFS difference with different radiotherapy technologies used for SABR

Soldà F, Radiother Oncol 2013; 109:1-7

Stereotactic Ablative Radiotherapy for stage I histologically proven non-small cell lung cancer: An Italian multicenter observational study

196 patients (median age 75 yrs)

Stage IA: 79.1%
Stage IB: 20.9%

Median follow-up time: 30 months

3-yr LRFS: 89.7%

Dose	*No (%)*
48 Gy / 4 fr	72 (36.7)
45 Gy / 3 fr	65 (33.2)
50 Gy / 5 fr	34 (17.3)
55 Gy / 5 fr	10 (5.1)
60 Gy / 8 fr	8 (4.1)
54 Gy / 3 fr	7 (3.6)

OVERALL SURVIVAL		
1-year: 94%	2-year: 81.6%	3-year: 68%

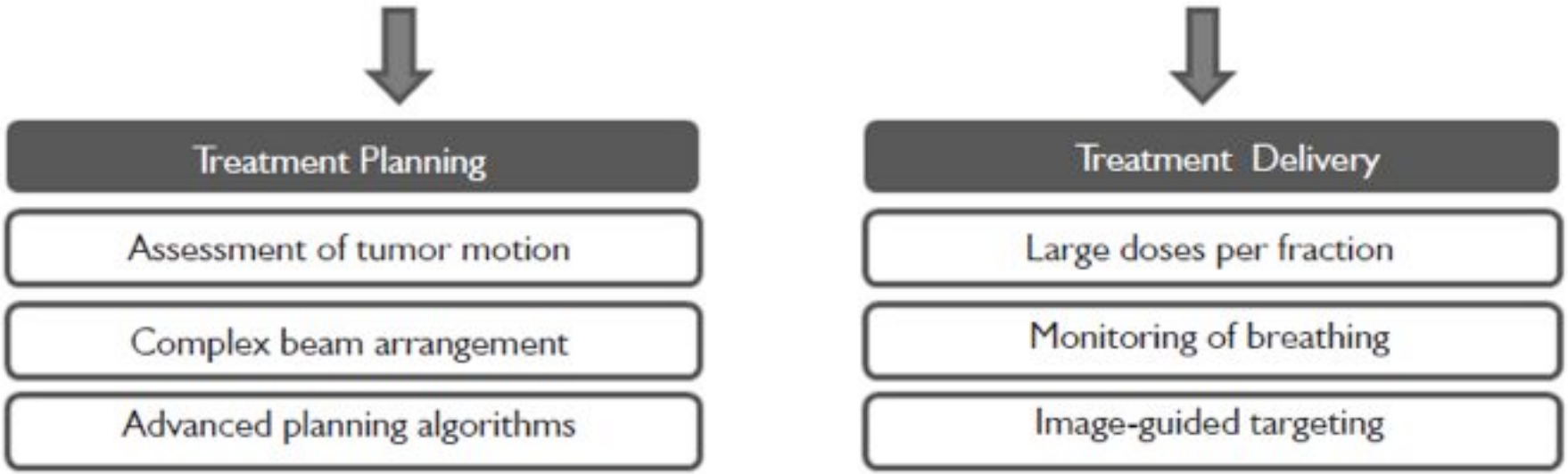
Multivariate analysis	LR *p*	DFS *p*	OS *p*	CSS *p*
Stage IB vs IA	0.69	0.001	0.007	0.003

Ricardi U, Lung Cancer 2014; 84:248-253

Prospective phase II studies on SABR in NSCLC

	N pts	*Median Fup*	*SABR dose*	*Local Control*	*OS*
Nagata et al. 2005	45	30 months	12 Gy x 4 fr @ isocenter	30mo 98%	3-yr 75%
Baumann et al. 2009	57	35 months	15 Gy x 3 fr @ 65%	3-yr 92%	3-yr 60%
Fakiris et al. 2009	70	50 months	20-22 Gy x 3 fr @ 80%	3-yr 88%	3-yr 43%
Ricardi et al. 2010	62	28 months	15 Gy x 3 fr @ 80%	3-yr 88%	3-yr 51%
Timmerman et al. 2010	54	34 months	18 Gy x 3 fr @ 80%	3-yr 98%	3-yr 38%
Bral et al. 2011	40	16 months	3-4 fr td 60 Gy	2-yr 84%	2-yr 52%

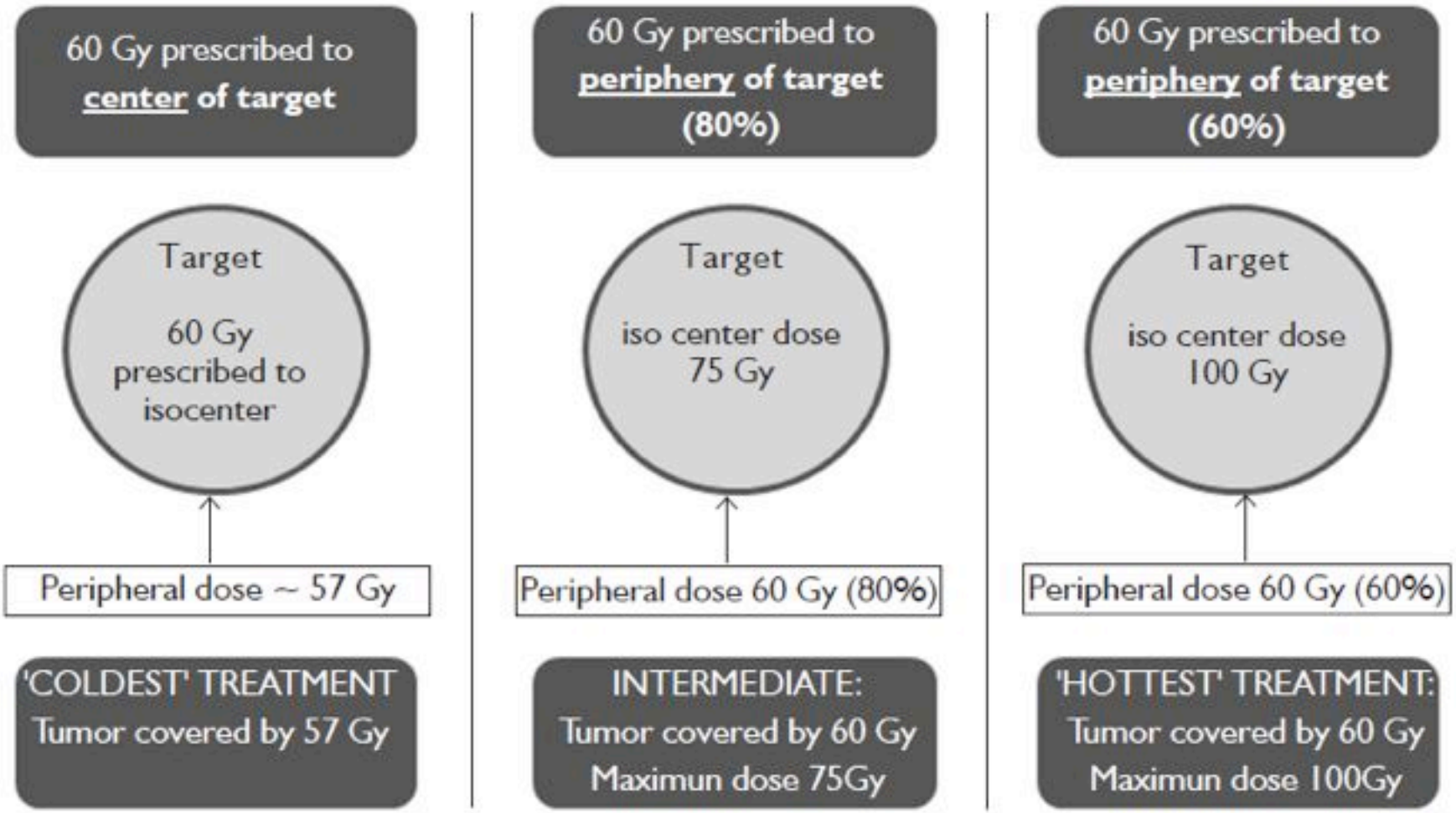
Key features of SABR



Quality Assurance

Senan S, J Thorac Dis 2011; 3:189-196

Dose Prescription in SABR



Senan S, J Thorac Dis 2011; 3:189-196

CLINICAL INVESTIGATION Lung

WHICH IS THE OPTIMAL BIOLOGICALLY EFFECTIVE DOSE OF STEREOTACTIC BODY RADIOTHERAPY FOR STAGE I NON–SMALL-CELL LUNG CANCER? A META-ANALYSIS

Jian Zhang, Ph.D.,*†§ Fujun Yang, M.D.,*†§ Baosheng Li, M.D., Ph.D.,†§ Hongsheng Li, Ph.D.,†§ Jing Liu, Ph.D.,‡ Wei Huang, M.D.,†§ Dongqing Wang, M.D.,†§ Yan Yi, M.D.,†§ and Juan Wang, M.D.†§

34 observational studies (2587 patients)

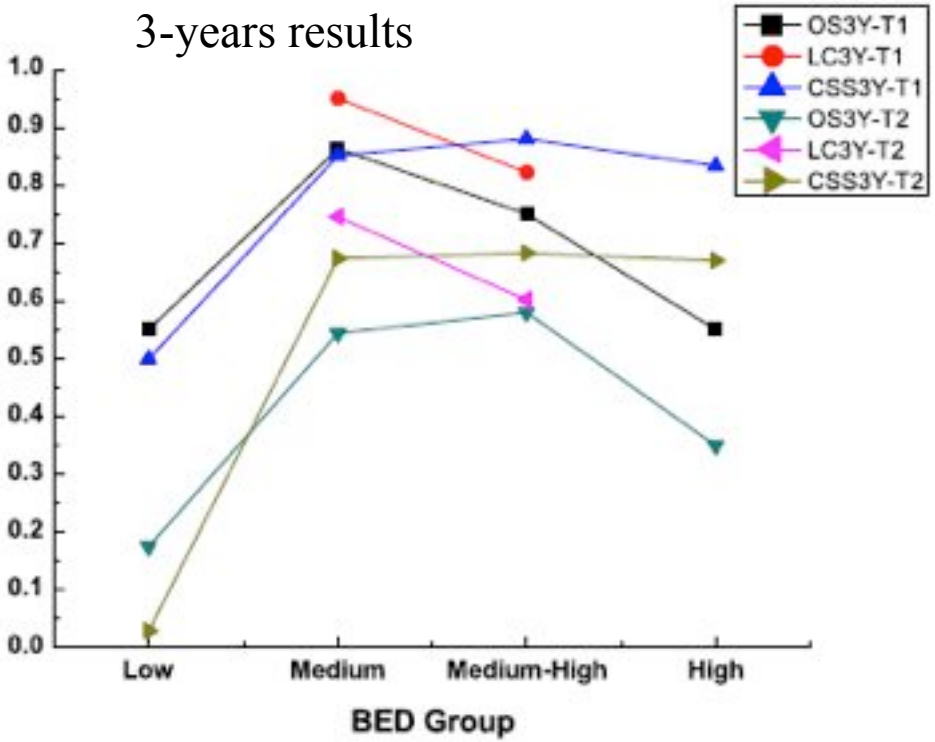
BED group	*range (Gy)*
Low	< 83.2
Medium	83.2 – 106
Medium to High	106 - 146
High	> 146

Overall Survival (OS)

Cancer-Specific Survival (CSS)

Local Control (LC)

Zhang J,IJROBP 2011; 81:305-316



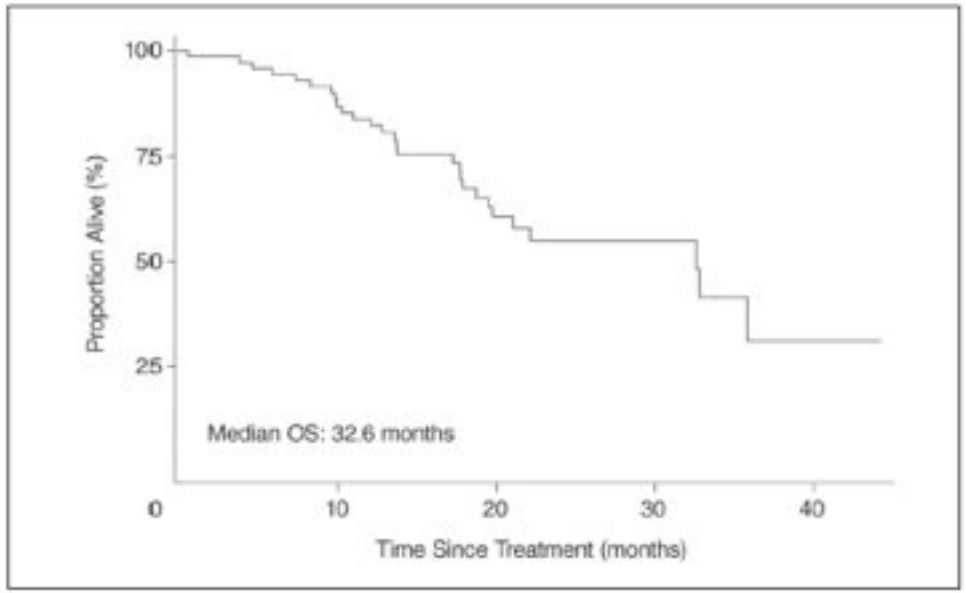
Patients treated with medium or medium to high BED have higher OS than those treated with low or high BED.

Zhang J,IJROBP 2011; 81:305-316

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Excessive Toxicity When Treating Central Tumors in a Phase II Study of Stereotactic Body Radiation Therapy for Medically Inoperable Early-Stage Lung Cancer

All 70 patients enrolled completed therapy as planned
Median follow-up time: 17.5 months



SABR dose 60-66 Gy / 3 fr

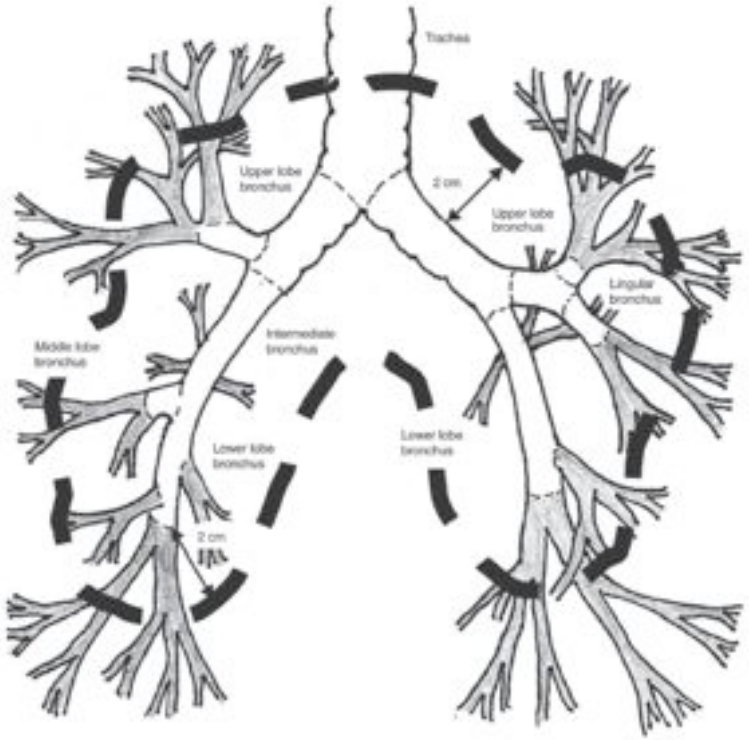
Median OS: 32.6 months

2-year OS: 54.7%

2-year LC: 95%

Timmerman R, JCO 2008; 24:4833-4839

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT



14 patients experienced grade 3 to 5 toxicity

Grade 3 to 4 toxicities:
decline in pulmonary function tests, pneumonias, pleural effusions, apnea, and skin reaction.

Grade 5 toxicities (6 pts):
Bacterial pneumonia, pericardial effusion, massive hemoptysis

Median time to toxicity: 10.5 months

Both univariate and multivariate analysis showed that tumor location (hilar/pericentral *v* peripheral) was a strong predictor of toxicity (*P* .004).

Timmerman R, JCO 2008; 24:4833-4839

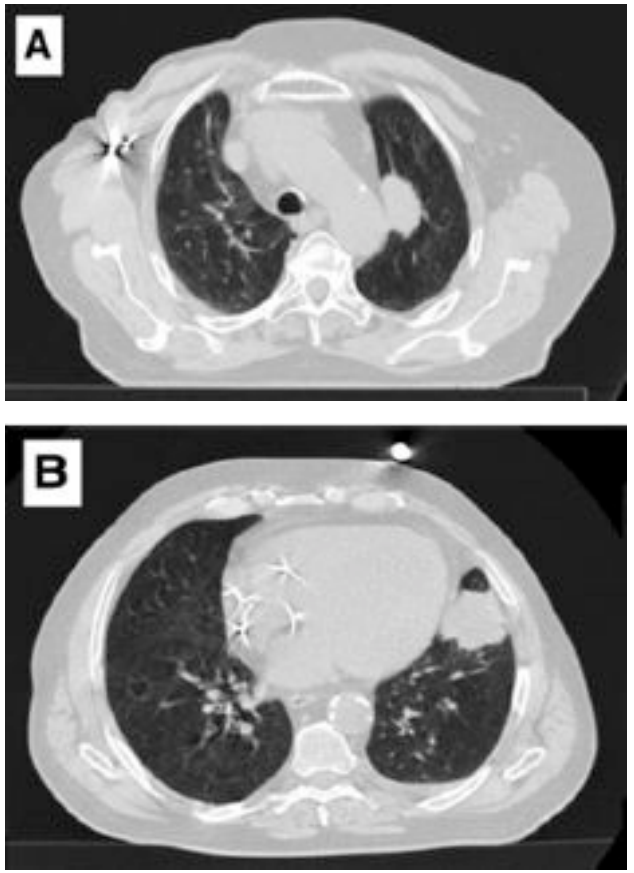
SABR in centrally located NSCLC

	Central NSCLC	*Central other*	*Dose / fx*	*Follow-up*	*LC*	*OS*	*Toxicity grade >3*
Milano et al. 2009	7	56	50 / 5	10 months	2-yr 73%	72%	Pericarditis (n=1)
Chang et al. 2008	27	-	40-50 / 4	17 months	89%	NS	Brachial plexus neuropathy (n=1)
Haasbeek et al. 2011	63	-	60 / 8	35 months	3-yr 93%	3-yr 63%	Chest wall pain (n=2), Dyspnea (n=2)
Nuyttgens et al. 2012	39	17	36-60 / 5	23 months	2-yr 76%	2-yr 60%	Acute pneumonitis (n=4), late pneumonitis (n=6)

Outcomes of Stereotactic Ablative Radiotherapy for Centrally Located Early-Stage Lung Cancer

63 patients (median age 74 yrs)

Tumor Location	*No of pts*
Proximal bronchial tree	37
Pericardium	11
Overlap other mediastinal structures	15
Aorta	6
Near esophagus	2
Other	7

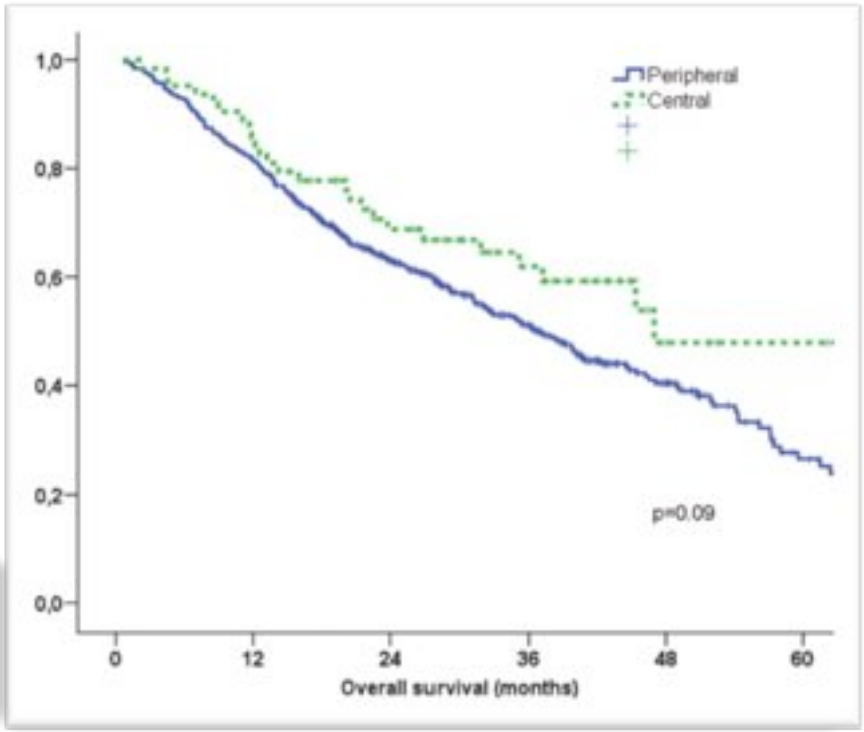


Haasbeek CJ, J Thorac Oncol 2011; 6:2036-2043

SABR schedule: 60 Gy / 8 fr

Overall Survival		
1-yr OS	*2-yr OS*	*5-yr OS*
85.7%	69%	49.5%

3-yr Local Control: 92.6%



Median follow-up: 35 months

No grade 4-5 toxicity was observed

No significant differences in outcomes were observed between these 63 patients and 445 other SABR patients treated for peripheral early-stage lung tumors.

Haasbeek CJ, J Thorac Oncol 2011; 6:2036-2043

Systematic review

Outcomes of stereotactic ablative radiotherapy for central lung tumours: A systematic review

Sashendra Senthi *, Cornelis J.A. Haasbeek, Ben J. Slotman, Suresh Senan

20 publications, reporting outcomes for 563 central lung tumours

Author (year)	BED_{10}	Overall survival	Cause-specific survival	Local control
Chang [26] (2008)	113	–		Crude rate 89%
Song [36] (2009)	106	50% at 2 years	–	89% at 2 years
Milano [27] (2009)	100	72% at 2 years	–	73% at 2 years
Fakiris [24] (2009)	180	Median 24 months	–	–
Unger [28] (2010)	72	–	–	63% at 1 year
Oshiro [29] (2010)	80	–	–	60% at 2 years
Baba [35] (2010)	90	72% at 3 years	82% at 3 years	66% at 3 years
Bradley [32] (2010)	86	75% at 2 years[a,b]	90% at 2 years[a,b]	86% at 2 years
Andratschke [34] (2011)	60	29% at 3 years	–	64% at 3 years
Haasbeek [32] (2011)	105	64% at 3 years	–	93% at 3 years
Bral [23] (2011)	150	–	–	Crude rate 94%
Olsen [38] (2011)	100	–	–	100% at 2 years[c]
Rowe [37] (2012)	114	–	–	94% at 2 years
Nuyttens [30] (2012)	132	53% at 3 years[b]	3 years 80%	76% at 2 years
Janssen [31] (2012)	77	–	–	87% at 1 year[a]

Senthi S, Radiother Oncol 2013; 106:276-282

Author (year)	Simulation	Target volumes	Image guidance	Prescription	Heterogeneity correction	Total dose gray/ fractions
Onimura [15] (2003)	Inspiration, expiration, standard CT	ITV + PBM = PTV	Orthogonal x-rays	Isocentre, PTV got 80%	No	48/8
Xia [22] (2006)	Slow CT and fluoroscopy	GTV + 10 mm = PTV	Not reported	50% Isodose covering 95% PTV	No	50/10
Chang [26] (2008)	4-Dimentional CT	ITV + 8 mm = CTV + 3 mm = PTV	CT-on-rails and orthogonal X-ray	75–90% Isodose covering PTV	Yes	50/4
Song [36] (2009)	Standard CT with fluoroscopy	GTV + PBM = PTV	Conebeam CT	85% Isodose covering 95% PTV	No	48/4[a]
Milano [27] (2009)	Expiratory breath hold CT	GTV + PBM = PTV	Stereoscopic X-ray	Isocentre,PTV got 80%	No	50/5[a]
Fakiris [24] (2009)	Standard CT	GTV = CTV + PBM = PTV	No reported	80% Isodose covering 95% PTV	No	60/3
Guckenberger [40] (2009)	4-Dimentional CT	ITV + 5 mm = PTV	Conebeam CT	65% Isodose covering PTV	Yes	48/8
Unger [28] (2010)	Inhalation breath hold, fiducials	GTV = PTV	Respiratory tracking fiducial markers	70–80% Isodose covering 95% PTV	Yes	40/5
Oshiro [29] (2010)	Expiratory breath hold CT	GTV + PBM = PTV	Gated X-ray	Not reported, likely to isocentre	No	50/5[a]
Baba [35] (2010)	Inspiration, expiration, standard CT	ITV + PBM = PTV	Not reported	Isocentre, 95% of PTV got 80%	Yes	50/4
Bradley [33] (2010)	4-Dimentional CT	ITV + PBM = PTV	Not reported	75–85% Isodose covering 95% PTV	Yes[b]	45/5
Andratschke [34] (2011)	Multiple standard and slow CT	ITV + PBM = PTV	Orthogonal x-rays	60% Isodose covering 100% PTV	Yes	35/5[a]
Haasbeek [32] (2011)	4-Dimentional CT	ITV + 3 mm = PTV	Orthogonal X-ray	80% Isodose covering 99% PTV	No	60/8
Bral [23] (2011)	Planning PET CT and fluoroscopy	ITV + 5 mm = PTV	Stereoscopic X-ray	95% Isodose covering 95% PTV	No	60/4
Olsen [38] (2011)	4-Dimentional CT	ITV + PBM = PTV	Conebeam CT	60–90% Isodose covering 95% PTV	Yes	50/5[a]
Stauder [39] (2011)	4-Dimentional CT	ITV + PBM = PTV	Conebeam CT	100% Isodose covering 95% PTV	Yes[b]	48/4
Rowe [37] (2012)	4-Dimentional CT	ITV + 7 mm = PTV	Conebeam CT	100% Isodose covering 95% PTV	Yes	50/4[a]
Nuyttens [30] (2012)	Standard CT	GTV + 5 mm = PTV	Respiratory tracking fiducial markers	75–90% Isodose covering 95% PTV	Yes	60/5[a]
Taremi [25] (2012)	4-Dimentional CT	ITV + 5 mm = PTV	Conebeam CT	100% Covered 95% of PTV	Yes[b]	60/8
Janssen [31] (2012)	4-Dimentional CT	ITV + 3 mm = CTV + PBM = PTV	Conebeam CT	80% Isodose covering PTV	No	48/8

Tumour location (central vs peripheral) did not impact overall survival.

Grade 3 or 4 toxicities may be more common following SABR for central tumours, but occurred in less than 9% of patients.

Senthi S, Radiother Oncol 2013; 106:276-282

Risk-adapted SABR

Peripheral T1 Lesions: 18-20 Gy x 3 fr
(BED_{10}: 151-180 Gy)

T2 Tumors or T1 near chest wall: 11-12 Gy x 5 fr
(BED_{10}: 115-132 Gy)

Tumors adjacent to hilus, mediastinum, hearth: 7.5 Gy x 8 fr
(BED_{10}: 105 Gy)

Senthi S, Lancet Oncol 2012;13:802-809

Conclusions

- The introduction of SABR was associated with a decline in the proportion of untreated elderly patients.

- High-grade toxicity is uncommon when 'risk-adapted' fractionation schemes are applied.

- Quality Assurance procedures and standardisation in terms of dose prescription and delivery techniques are warranted.