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Meta-analysis

Is high-dose stereotactic body radiotherapy (SBRT) for stage I non-small cell lung cancer (NSCLC) overkill? A systematic review

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ABSTRACT

Background and purpose: For stereotactic body radiotherapy (SBRT), typically a scheme of 60 Gy in 3–8 fractions is applied, producing local tumour control rates around 90%. The dose specification is in one point only and ignores possible underdosages at the edge of the planning target volume (PTV). We investigated the doses at the edge of the PTV and correlated this with local tumour control with the aim to shed light on the radiation dose needed to eradicate stage I NSCLC.

Materials and methods: Published data on the freedom from local progression (FFLP) data from SBRT and accelerated high-dose conventional radiotherapy series for stage I NSCLC with a follow up of at least 30 months were included. The $EQD_{2,T}$ was calculated from the dose at the periphery of the PTV.

Results: Fifteen studies for SBRT (1076 patients) showed a median FFLP of 88.0 ± 10.4% with a median $EQD_{2,T}$ of 76.9 ± 17.4 Gy. The median FFLP was 87.6 ± 6.0% for the accelerated schedules with an $EQD_{2,T}$ of 86.9 ± 39.1 Gy, respectively. No significant relation was found between FFLP and the $EQD_{2,T}$ ($p = 0.23$).

Conclusions: Several fractionated and accelerated schedules with equal biological doses achieve the same tumour control rates as SBRT. Lower, but more uniform doses to the whole PTV may be sufficient to achieve similar control rates, with the possibility to deliver SBRT in adapted schedules, beneficial to centrally located tumours in the vicinity of critical structures like the oesophagus and great vessels.

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The incidence of cancer is increasing in Europe, with an estimated number of 3.2 million new cases a year. Lung cancer ranks third in terms of incidence, but is the main cause of cancer-related death. About 25% of lung cancer patients present with early stage disease [1]. For patients with clinical stages I and II disease with no medical contraindications, surgery is the first treatment of choice showing 5-year survival rates of about 60–80% for stage I and 40–50% for stage II, respectively [1]. However for patients who are medically or technically unfit for surgery and for patients refusing surgery, stereotactic body radiotherapy (SBRT), also called stereotactic ablative radiotherapy (SABR), is an alternative with local control rates >90% at 3 years [2–7]. Most guidelines recommend doses of 48–60 Gy in 3–8 fractions delivered in about 3 weeks [8]. However, these hypo-fractionation schedules might be too toxic with regard to late side effects if critical structures, such as main bronchi or large vessels are within the planning target volume (PTV). In a single institution phase II study by Timmerman and colleagues including 70 patients with early stage, inoperable NSCLC tumours located anywhere within the lung, including centrally located tumours [9]. In the analysis of high-grade toxicity (grade 3–5), tumour location (hilar or pericentral versus peripheral) was a strong predictor for grade 3–5 toxicity ($p = 0.004$). Patients treated for tumours in the peripheral lung had 2-year freedom from severe toxicity estimated at 83% as compared with 54% in patients with central tumours. Therefore, centrally located tumours often 'conventional' radiotherapy fractionation, commonly consisting of 60–66 Gy given in 2 Gy per day, 5 days a week is chosen. However, reported local control rates are poor and highly variable, varying between 6% and 70% [7,10,11], although there seems to be a trend for better local control with higher biologically-effective doses [12,13]. This should not be surprising in view of the data of Martel et al., showing that the D_{50} (which is the dose needed to achieve 50% tumour control) at 30 months would be 84.5 Gy, delivered in once-daily 2 Gy per fraction [14]. A similar biologically effective dose may be delivered using accelerated schedules with multiple daily fractions or with hypo-fractionation [15–19]. Another strategy for centrally located early stage tumours is the use of more "risk-adaptive strategies" for SBRT [20–22]. Haasbeek and colleagues reported on a SBRT scheme, in which the number of fractions and total dose used is dependent on the T-stage, the localisation of the tumour and therefore the risk of normal tissue toxicity [23]. In 9 out of 63 patients with centrally located tumours treated with 60 Gy in 8 fractions,

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it could not be excluded that their death had a cardiopulmonary cause. Early results with Cyber Knife technology in patients with central tumours showed no severe toxicities [24].

Published SBRT studies vary considerably with regard to clinical target volume (CTV) and planning target volume (PTV) margins, methods of dose prescription, fractionation schemes, planning parameters, dose calculation algorithms used, planning techniques, use of 4D CT scans, quality assurance during treatment; all of which might influence the outcome [25]. As an example, the dose at the edge of the PTV ranges widely between studies as well as the degree of dose inhomogeneity within the target volume to achieve a steep dose falloff. Furthermore, with regard to calculation algorithms some series have been reported using type A dose calculation algorithms, i.e. models that are primarily based on electronic path length (EPL) scaling for in-homogeneity corrections, whereas others have used type B models that in an approximate way consider changes in lateral electron transport. The more advanced type B models should be used for dose calculations for lung tumour treatments [26]. As a consequence, the reported doses are not comparable between series. We hypothesise that the absorbed dose in the PTV will be significantly less than the reported dose at the dose specification point for most studies. As a consequence, the dose required to eradicate stage I tumours, especially small T1 tumours, may be overestimated based on the doses reported. Avoiding this "overkill" may be beneficial and may result in an even better therapeutic ratio that would allow one to treat central lesions with hypo-fractionation.

Here, accelerated high-dose conventional radiotherapy with larger margins was compared with several SBRT schemes, to investigate which hypo-fractionated schedule would have the best therapeutic ratio, and hence be applicable for central lesions without loss of efficacy.

Methods and materials

In this systematic review, a literature search from January 1, 1995 to December 31st, 2011 was performed using PubMed to select studies for SBRT/SABR and/or accelerated radiotherapy for stage I NSCLC (cT1-2N0M0 according to the UICC 7th Edition). Studies were included if they: (1) provided 3 year freedom from local progression (FFLP) data, (2) had a median follow-up of at least 30 months, (3) were published in English, (4) accepted or published as full text paper or meeting abstract, and (5) doses to the edge of the tumour should be described or could be estimated according to the allowed dose inhomogeneity.

Additional information was obtained through personal correspondence with the authors. The biologically equivalent dose in 2 Gy fractions (EQD_2) was calculated from the dose at the edge of the PTV using the linear quadratic formula with α/β of 10 Gy for tumour/early responding tissue and α/β of 3 Gy was assumed for late effects. The EQD_2 was adjusted for overall treatment time ($EQD_{2,T}$) to take into account accelerated repopulation after 21 days [27], but knowing that these estimations may be less appropriate with fraction sizes over 10 Gy [28].

$$EQD_{2,T} = D \cdot \frac{d + \alpha/\beta}{2 + \alpha/\beta} - MAX(0, T - T_{ref}) \cdot D_{prolif}$$

where the second term is zero for $T \leqslant T_{ref}$ and equal to D_{prolif} ($D_{prolif} = 0.6$) multiplied by the number of days beyond T_{ref} for $T > T_{ref}$. To compare SBRT with accelerated high-dose conformal radiotherapy, patients from the CALGB 39904 study and the MAASTRO NCT00573040 trial were included [12,13]. From the latter only patients with stage I disease were included in this analysis and the overall survival for this group was updated. To compare the different schedules the therapeutic ratio was calculated by dividing the $EQD_{2,T}$ for tumour by the EQD_2 for late effects.

Statistics

Considering that a small sample size of a subset of patients will increase the uncertainty of the estimated treatment effect, the data were weighted by the number of patients included in a subset of patients. Results (FFLP, EQD_2 for tumour and late effects, therapeutic ratio) are expressed as median ± standard deviation (SD) and range. A linear regression analysis was performed to analyse the dose–effect relation. The data were analysed in SPSS version 17.0 (SPSS Inc., Chicago, IL).

Results

Of the 54 studies considered, 15 studies (1076 patients) met our inclusion criteria of having a follow-up of at least 30 months, and reporting data on both 3-year freedom from local progression and dose prescription [7,29–42] (Table 1).

The prescribed total doses ranged from 30 to 72.5 Gy in 3–11 fractions. All patients had stage I disease (66% T1 and 34% T2 tumours).

Results were separated for different schedules if more than one schedule was used within a study and were weighted by the number of patients included in a subset of a study. The two accelerated, fractionated trials [12,13] delivered a mean dose of 70 Gy in 24 fractions (CALGB) and 75.6 Gy in 42 fractions (MAASTRO). Reported incidences of severe side effects were similar in all series, being less than 10%.

The median FFLP for all SBRT schedules was 88.0 ± 10.4% (range 49–100%), with a median $EQD_{2,T}$ for tumour of 76.9 ± 17.4 Gy (50–126 Gy) and for late effects of 119.2 ± 35.4 Gy (72.6–226.8 Gy). For the subset of SBRT study arms with an $EQD_{2,T}$ for tumour >60 Gy (24 studies, including 955 patients) the median FFLP was 90.6 ± 9.5% and for the accelerated schedules 87.6 ± 6.0% (Table 2).

As depicted in Fig. 1, there was no correlation between the FFLP and the $EQD_{2,T}$. A regression analysis showed no significant relation between FFLP and the $EQD_{2,T}$ for all studies ($r^2 = 0.050$; $p = 0.23$) and for all studies with an $EQD_{2,T}$ for tumour >60 Gy ($r^2 = 0.042$; $p = 0.32$) (Fig. 1). Among the included fractionation schedules, none was superior to the other. Supplementary regression analyses were performed to address the possibility that the main regression analysis was affected by heterogeneity among studies. None of the studies showed a significant dose–response relationship for FFLP when analysed separately (data not shown). Also, a regression analysis stratified by study showed no significant relationship between FFLP and dose (data not shown).

Discussion

For patients with clinical stage I and II non-small cell lung cancer, surgery remains the first treatment of choice. However, for patients not fit for surgery or those who refuse surgery, SBRT/SABR is a good alternative [2–8]. Moreover, SBRT/SABR is a cost-effective alternative with stable global quality of life during the first year after treatment [43,44]. However, conventional radiotherapy schedules are often used in centrally located tumours due to possibly increased toxicity with hypo-fractionation in these cases [9]. Alternatively "risk-adaptive strategies" for SBRT can be employed [20–23]. Haasbeek et al. describe e.g. a fractionation scheme of 8 fractions of 7.5 Gy for patients with a tumour with a hilar location or tumours adjacent to the pericardium or mediastinal structures [23]. As the reported dose at the edge of the PTV may have been overestimated in many SBRT series [8,25], the

Table 1
Study characteristics. TD = total dose, fd = fraction dose, FFLP = freedom from local progression, $EQD_{2,T}$ = equivalent dose in 2 Gy fractions corrected for overall treatment time.

	Publication	Total number of pt	Number of pts	TD	Number of fr	fd at edge PTV	FFLP	$EQD_{2,T}$-edge PTV	$EQD_{2,T}$-late	Therapeutic ratio
SBRT										
1	Baumann (2006)	138	80	45	3	15.00	0.86	93.75	162.00	1.73
			13	40	4	10.00	0.77	66.07	104.00	1.57
			33	30	3	10.00	0.94	48.80	78.00	1.60
2	Baumann (2009)	57	57	45	3	15.00	0.92	91.35	162.00	1.77
3	Kopek (2009)	88	62	45	3	10.05	0.88	46.78	78.69	1.68
			28	68	3	15.08	0.91	90.30	163.49	1.81
4	Koto (2007)	31	20	45	3	13.50	0.75	73.91	133.65	1.81
			11	60	8	6.75	0.64	69.38	105.30	1.52
5	Nagata (2005)	45	45	48	4	10.53	0.98	64.81	113.88	1.76
6	Nyman (2006)	45	45	45	3	15.00	0.80	85.35	162.00	1.90
7	Onishi (2007)	257	55	48	4	10.80	0.97	65.28	119.23	1.83
			54	73	10	6.53	0.73	79.65	124.30	1.56
			44	60	8	6.75	0.91	64.58	105.30	1.63
			24	63	5	11.25	1.00	88.21	160.31	1.82
			19	50	5	9.00	0.84	59.25	108.00	1.82
			16	40	4	9.00	0.49	44.40	86.40	1.95
			10	48	8	5.40	0.55	42.24	72.58	1.72
8	Salazar (2008)	102	45	40	4	10.00	1.00	52.27	104.00	1.99
			15	40	4	10.00	0.93	51.67	104.00	2.01
9	Takeda (2009)	63	63	50	5	10.00	0.95	67.13	130.00	1.94
10	Chen (2008)	26	10	66	11	5.70	0.90	62.83	109.10	1.74
			15	64	8	7.60	0.92	69.37	128.90	1.86
			1	48	6	7.60	1.00	46.48	96.67	2.08
11	Ricardi (20100	62	62	45	3	15.00	0.88	72.15	162.00	2.25
12	Matsuo (2011)	101	101	48	4	10.53	0.87	47.41	113.88	2.40
13	Videtic (2010)	28	28	50	5	9.50	0.94	51.39	118.75	2.31
14	Nagata (2010)	65	65	48	4	10.53	0.69	45.01	113.88	2.53
15	Timmerman (2010)	55	55	60	3	18.00	0.98	97.80	226.80	2.32
Accelerated fractionated RT										
1	van Baardwijk (2010)	47	47	72	40	1.71	0.84	61.95	64.43	1.04
2	Bogart (2010)	39	39	70	40	2.89	0.92	117.47	136.04	1.16

Table 2
Results for all studies, SBRT studies, fractionated, accelerated studies and studies with an $EQD_{2,T}$ > 60 Gy. FFLP = freedom from local progression, $EQD_{2,T}$ = equivalent dose in 2 Gy fractions corrected for overall treatment time. Results are expressed as median ± standard deviation (range).

	Number of study subsets	Total number of pt	FFLP Median ± SD		$EQD_{2,T}$-tumour Median ± SD		$EQD_{2,T}$-late effects Median ± SD		Therapeutic ratio Median ± SD	
			(in %)	(range)	(in Gy)	(range)	(in Gy)	(range)		(range)
All studies	30	1160	88.0 ± 10.4	(49–100)	76.6 ± 18.5	(50.0–126.0)	119.2 ± 36.5	(64.4–226.8)	1.8 ± 0.3	(1.5–2.5)
All studies with an EQD_2 > 60 Gy	26	1039	90.4 ± 9.2	(63.6–100)	82.8 ± 16.2	(61.9–126.0)	124.3 ± 31.0	(64.4–226.8)	1.8 ± 0.3	(1.5–2.5)
All SBRT studies	28	1074	90.6 ± 9.5	(63.6–100)	76.9 ± 17.4	(50.0–126.0)	119.2 ± 35.4	(72.6–226.8)	1.8 ± 0.3	(1.5–2.5)
All SBRT studies with an EQD_2 > 60 Gy	24	953	88.0 ± 10.4	(49–100)	82.9 ± 14.7	(66.7–126.0)	124.3 ± 32.1	(96.7–226.8)	1.9 ± 0.3	(1.5–2.5)
All fractionated, accelerated studies	2	86	87.6 ± 6.0	(83.8–92.3)	86.9 ± 39.1	(61.9–117.5)	96.6 ± 50.4	(64.4–136.0)	1.7 ± 0.2	(1.5–1.8)

corresponding dose–response curves may overestimate the radiation dose that is needed to eradicate early stage NSCLC. Should this be the case, SBRT could be given at lower doses, thus improving the therapeutic ratio further and allowing safe treatment also of central small tumours with a few fractions.

For this reason, in this systematic review, we have re-calculated the dose to the edge of the PTV in SBRT series with a long follow-up and used our results to compare them to recent series that delivered accelerated radiotherapy with fraction sizes of around 2 Gy. Ideally, individual dose distributions should have been available to calculate the EUD and the influence of over- and under-dosage at different points in the PTV, but this information was not available. We therefore chose the dose at the margin (“edge”) of the PTV where the dose is the lowest and the underdosage due to the use of older dose calculation algorithms is the highest. In many patients, the maximum dose in the PTV may have been 30% higher than at the edge [25]. The LQ model was employed to estimate the $EQD_{2,T}$, acknowledging that these tumour $EQD_{2,T}$ using large doses per fraction are uncertain. Our estimates show that when ICRU 50 guidelines [45] are used, i.e. a minimum dose of 95% in the PTV, local tumour control rates of over 90% could be obtained with $EQD_{2,T}$ doses of about 65 Gy at the prescription point, irrespective whether SBRT or accelerated high dose 3D conformal radiotherapy (3D-RT) was given. This is of importance, since SBRT dose distributions are highly inhomogeneous compared with 3D-conformal radiotherapy. The increased equivalent uniform dose delivered using SBRT did not result in higher local tumour control. In this reasoning, we assume that the radiosensitivity is uniformly distributed through the tumour, which may not be the case [46,47]. Moreover, it would be of interest to know what is the most related

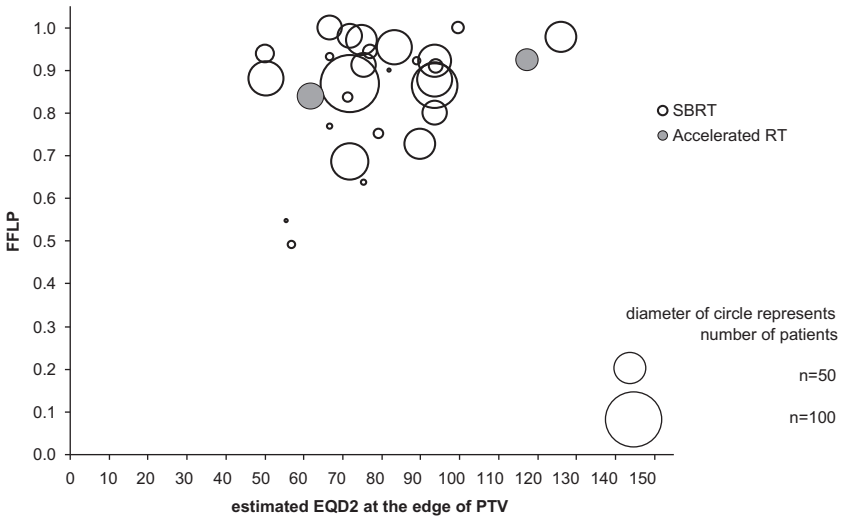

Fig. 1. EQD_2 versus FFLP for SBRT studies (○) and fractionated, accelerated studies (◉). FFLP = freedom from local progression, EQD_2 = equivalent dose in 2 Gy fractions. The diameter of the circle represents the number of patients included in the specific study.

to the tumour control probability: the dose at the edge of the PTV or the uniform dose. As unavoidable steep dose-gradients occur at the edge of the PTV, reliable information could come from prospective studies.

With local tumour control rates being already over 90%, it is possible that the remaining local failure might be due to biological (e.g. hypoxia) or technical factors such as a geographical miss. In fact, all published series deliver doses that lead to very high local tumour control rates and thus are located at the upper but shallow part of the dose–response curve. The finding that $EQD_{2,T}$ doses of 65 Gy might suffice to eradicate NSCLC tumours with diameters up to 3 cm opens nevertheless the door to investigate lower doses in this disease in a prospective clinical trial. Indeed, in centrally located tumours, three fractions of 18 Gy resulted to too high an incidence of severe side effects [9]. At present, there is not sufficient data to justify the use of gentler schedules such as 60 Gy in 8 fractions when the PTV includes major parts of the main bronchi or the oesophagus. The $EQD_{2,T}$ for the tumour ($\alpha/\beta = 10$ Gy) would be 81.3 Gy and for late responding tissues ($\alpha/\beta = 3$ Gy) it would be 115.4 Gy, exceeding tolerance levels [48,49]. Therefore, from a theoretical point of view, a dose of 55 Gy given in 11 fractions of 5 Gy covering 95% of the PTV, would be worth investigating. The $EQD_{2,T}$ for the tumour would be 64 Gy and for late responding tissues it would be 81 Gy, just within tolerance levels.

Obviously, our study has some drawbacks. First, the real doses and dose distributions were estimated from the publication and only in a minority we did have insight in what was actually given. Second, techniques and dose calculations differ between studies, which might influence the dose estimation at the edge of the target volume [50,51]. We have tried to account for this, but our results remain only estimations. Third, the linear quadratic model was used. There is heterogeneity in the α/β values for tumours and organs at risk (OARs) and the value of the model is uncertain for doses per fraction above 10 Gy. Fourth, the definition of FFLP might differ between studies: some authors only included local failure at the site of the primary tumours others if a recurrence developed in the same lobe. Moreover, the method of follow-up (regular imaging or not) might influence the number of recurrences. Fifth, many dose–response curves for NSCLC are derived from historical data of which many also suffer from inaccurate dose calculation algorithms. Our point estimates that are placed on these dose–response curves should thus be interpreted with caution.

In conclusion, published results in the literature do not support the hypothesis of a positive dose–response relationship for tumour control within the applied dose range. It might thus be possible to reduce the dose to a level that still achieves tumour control rates in excess of 90% in stage I NSCLC. This opens the possibility to embark on clinical trials for central lesions with hypo-fractionated radiotherapy at lower doses than are currently used.

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