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CHAPTER 5

Toxicity after reirradiation of pulmonary tumours with stereotactic body radiotherapy

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ABSTRACT

Purpose

To assess toxicity and feasibility of reirradiation with stereotactic body radiotherapy (SBRT) after prior lung SBRT for primary lung cancer or lung metastases.

Patients and Materials

Twenty-nine patients reirradiated with SBRT on 32 lung lesions (11 central, 21 peripheral) were retrospectively reviewed. Median follow-up time was 12 months (range 1-97). The primary endpoint was toxicity, secondary endpoints were local control and overall survival time. Toxicity was scored according to the NCI-CTCAE version 3.

Results

Grade 3 to 4 toxicity was scored 14 times in eight patients. Three patients died because of massive bleeding (grade 5). Larger clinical target volumes (CTV) and central tumour localization were associated with more severe toxicity. There was no correlation between mean lung dose (MLD) and lung toxicity. Local control at 5 months after reirradiation was 52%, as assessed by CT-scan (*n*=12) or X-thorax (*n*=3). A larger CTV was associated with poorer local control. Kaplan-Meier estimated 1- and 2-year survival rates were 59% and 43%, respectively.

Conclusion

Reirradiation with SBRT is feasible although increased risk of toxicity was reported in centrally located tumours. Further research is warranted for more accurate selection of patients suitable for reirradiation with SBRT.

INTRODUCTION

Stereotactic body radiotherapy (SBRT) is a high precision treatment modality that delivers large biological equivalent radiation doses to tumours in extracranial sites [1-5]. In stage I non small cell lung cancer (NSCLC), SBRT results in excellent 3-year local control rates of more than 90% [6-10]. In case of tumour relapse, few alternative treatments are available for medically inoperable patients, such as radiofrequency ablation, and more recently microwave ablation [11]. Patients with metastasized disease generally receive chemotherapy. Reirradiation with conventional radiotherapy has been explored by multiple groups using several techniques, doses and fractionation schedules resulting in good palliation with acceptable toxicity [12-19]. Reirradiation with SBRT has the potential benefit of high dose delivery in a short overall treatment time and a reduced overlap with the previous treated volume. A recently published study of reirradiation with SBRT after prior conventional radiotherapy showed promising results with good local control and acceptable toxicity [20].

At the radiotherapy department of the Karolinska University Hospital, we have reirradiated both primary and metastasized lung tumours in patients using SBRT for a second time and in a few cases for a third time after local progression. Only a few cases of reirradiation with lung SBRT have been described in the literature. In this article we present the results of our experience. The primary endpoint was toxicity, secondary endpoints were local control and overall survival time.

MATERIALS AND METHODS

Patients

The records of all patients reirradiated with SBRT in the period 1994-2004, for stage II-III lung tumours or lung metastases, at the Radiotherapy Department of the Karolinska University Hospital were reviewed. Reirradiation was judged based on tumour localization and defined as more than 50% overlap of the Planning Target Volume (PTV) supported by three-dimensional measurements in all planes. In total, 34 patients with tumours of the lungs were identified of whom five patients were excluded due to lack of follow-up data. Patient, tumour and treatment characteristics are depicted in Table 1. Eighteen males and 11 females were reirradiated at a median age of 65 years (range 18-87) with a median interval of 14 months (range 5-54) between first SBRT and reirradiation. The median follow up from first day of reirradiation until the last clinical visit was 12 months (range 1-97). Five patients received reirradiation for local recurrence of primary lung cancer; four with NSCLC and one with small cell lung cancer (SCLC). One patient had a mediastinal recurrence of an oesophagus carcinoma and was included in the study, because of expected lung toxicity. The remaining 23 patients were reirradiated for lung metastases. The most common primary tumour was NSCLC, seen in 10 patients (34%) and colo-rectal cancer in 7 patients (24%) (Table 1).

Table 1. Patient, tumour and treatment characteristics

Gender, *n*	
Male	18
Female	11
Age at time of reirradiation (years)	65 (18-87), median (range)
Interval between first SBRT and reirradiation (months)	14 (5-54), median (range)
Follow up after reirradiation (months)	12 (1-97), median (range)
Primary tumour, *n*	
NSCLC	10
Colo-rectal carcinoma	7
Renal cell carcinoma	6
Sarcoma	3
SCLC	1
Oesophagus	1
Liver	1
Histology, *n*	
Adenocarcinoma	5 (17%)
Squamous cell carcinoma	4 (14%)
Clear cell carcinoma	3 (10%)
Sarcoma total	3 (10%)
SCLC	1 (3%)
Hepatocellular carcinoma	1 (3%)
Not confirmed with pathology report	12 (41%)
Localization primary tumour	
Central	11
Peripheral	21
Lobe	
right upper lobe	7
right middle lobe	5
right lower lobe	7
left upper lobe	4
left lower lobe	8
mediastinum	1
Chemotherapy, *n*	
yes	12 (41%)
no	17 (59%)
Lung resection, *n*	
lobectomy	1
bilobectomy	1
wedge resection	2
Mean EQD_2 to CTV, first treatment for $\alpha/\beta=10$ (*n*=32)	109 (49-163), median (range)
Mean EQD_2 to CTV, second treatment (*n*=32)	109 (79-163), median (range)
Mean EQD_2 to CTV, third treatment (*n*=3)	109 (99-112), median (range)
Mean EQD_2 to CTV, fourth treatment (*n*=1)	90

Table 1. Continued

Gender, *n*				
Peripheral EQD_2 to PTV, first treatment for α/β=3 (*n*=32)	104 (42-162), median (range)			
Peripheral EQD_2 to PTV, second treatment (*n*=32)	104 (70-162), median (range)			
Peripheral EQD_2 to PTV, third treatment (*n*=3)	104 (88-108), median (range)			
Peripheral EQD_2 to PTV, third treatment (*n*=1)	76			
PTV first treatment (cm^3) (*n* =32)	71 (7-150), median (range)			
PTV second treatment (*n* =32)	76 (16-355), median (range)			
PTV third treatment (*n* =3)	64 (60-278), median (range)			
PTV fourth treatment (*n* =1)	277			
Treatment schemes	First	Second	Third	Fourth
20 Gy x 1	-	1	-	-
15 Gy x 3	2	6	-	-
15 Gy x 2	12	10	1	-
11 Gy x 3	-	1	-	-
10 Gy x 4	7	4	1	-
10 Gy x 3	2	1	-	-
10 Gy x 2	2	-	-	-
8 Gy x 5	5	8	1	-
8 Gy x 4	1	1	-	-
7 Gy x 3	1	-	-	-
6 Gy x 7	-	-	-	1

n= number of patients, NSCLC=non small cell lung cancer, SCLC=small cell lung cancer, EQD_2=total equivalent dose in 2 Gy fractions, CTV= clinical target volume, PTV=planning target volume.

In these 29 patients, 32 tumours were reirradiated with SBRT; 11 tumours were centrally localized and 21 peripherally as defined by Timmerman *et al.* [21]. One patient received two and another patient had three reirradiations. Reirradiated tumours were most frequently located in the right upper lobe, right lower lobe or left lower lobe. Forty-one percent of the patients were treated with chemotherapy along the course of disease, but never concurrently with radiotherapy. Twenty-one patients (72%) were treated with SBRT for other lung metastases as well, of whom 14 patients (48%) for at least two more tumours (range 2-12).

Treatment planning

The methodology used for SBRT and treatment planning has been described in detail in previous reports [2,22-23]. The clinical target volume (CTV) included the gross tumour volume (GTV), with a margin of 1 to 2 mm including its diffuse growth at the borders. PTV was defined as the CTV with a margin of 5 to 10 mm in the transversal plane and 10 mm in the longitudinal direction. Tumour mobility was estimated using diaphragm movement with fluoroscopy. Abdominal compression was applied when diaphragm motion was greater than 10 mm. Several fractionation schemes were applied. The most frequently used regimens were 15 Gy x 2-3 and 10 Gy x 4 for the first SBRT and 15 Gy x 2-3 and 8 Gy x 5 for reirradiation (Table 1).

SBRT was delivered with 6 MV from a linear accelerator, after immobilizing the patient in a stereotactic bodyframe (Elekta AB, Stockholm, Sweden). All patients were planned with pencil beam algorithms with heterogeneity correction (Helax-TMS Nucletron, Helax AB, Uppsala, Sweden). A typical plan consisted of 5-10 coplanar multileaf collimated beams. Before the start of the first treatment, an additional CT-scan was performed to verify the reproducibility of the target in the stereotactic frame. Treatment was generally given every second day. Dose was prescribed at about the 67% isodose at the periphery of the PTV, resulting in a maximal tumour dose up to 150% of the prescribed dose.

The total equivalent dose in 2 Gy fractions (EQD_2) was calculated using the linear-quadratic model with an α/β ratio of 10 Gy for tumour response and an α/β ratio of 3 Gy for late lung toxicity. Repair between treatments was not accounted for. Mean lung dose (MLD) was calculated for both lungs as a paired organ excluding the CTV. Correlation of MLD and toxicity was investigated by summing up the MLD of the first SBRT and reirradiation, and if applicable other singular courses of SBRT delivered before the initial SBRT or between initial SBRT and reirradiation

Follow up and toxicity assessment

Generally, all patients were regularly followed up with a 3-4 monthly CT-scan or X-thorax. For patients still alive, the last follow up date was August 2010. Based on information in patient records, toxicity was retrospectively scored according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event version 3 (CTCAE v3). Time to toxicity was assessed from first reirradiation to first occurrence of grade 3-5 toxicity, to minimize the influence on toxicity of other singular courses of SBRT or a second reirradiation.

Statistical analysis

The Kaplan-Meier method was used to calculate overall survival and time to grade 3-5 toxicity with JMP (version 7 for windows, SAS Institute). Differences between high grade and low grade toxicity, and central and peripheral tumours, were analyzed with SPSS (version 17.0 for Windows).

RESULTS

Twenty-nine medically inoperable patients were analyzed with 32 reirradiated lung tumours of which 11 were centrally and 21 peripherally located. For each treatment plan the mean calculated CTV dose was on average 40% higher than the prescribed dose at the periphery of the PTV. To compensate for this a correction factor of 1.4 was used to calculate the mean biological equivalent tumour dose in 2 Gy fractions (EQD_2) with an α/β ratio of 10 Gy (Table 1). An overview of all scored toxicities is shown in Table 2 (for details per patient number

Table 2. All toxicity according to NCI-CTCAE v3.0 grouped according to localization

Central *n*=11						**Peripheral** *n*=18				
Grade1	Grade 2	Grade 3	Grade 4	Grade 5		Grade1	Grade 2	Grade 3	Grade 4	Grade 5
2	2	-	-	-	Atelectasis	1	3	-	-	-
1	1	3	-	-	Cough	2	6	-	-	-
1	1	1	-	-	Dyspnoea	-	5	3	-	-
-	1	1	-	-	Pneumonitis	-	2	-	-	-
-	-	1	-	-	Stenosis of airway	-	-	-	-	-
-	-	-	-	3	Bleeding	-	-	-	-	-
-	2	-	-	-	Pleural effusion	1	3	1	-	-
2	2	-	-	-	Pulmonary fibrosis	2	5	-	-	-
-	-	-	-	-	Fracture	1	-	-	-	-
-	1	-	-	-	Dermatitis	-	-	1	-	-
1	-	x	x	x	Hyperpigmentation	-	1	x	x	x
-	-	1	-	-	Pain	2	4	-	-	-
-	1	-	2	-	Other	-	1	-	-	-

n= number of patients, x= non existent. "Other" toxic events were mucus production (grade 2) in one patient. Another patient experienced two grade 4 events: a vena cava superior stenosis and a fistula between trachea and gastric tube.

please see the electronic supplement). After a median follow up of 12 months, eight patients experienced grade 3 to 4 toxicity at 14 occasions and three patients had grade 5 toxicity and died of massive haemorrhage. Median time from reirradiation to grade 3-5 toxicity was 4 months (range 1-39) with a steep increase up to 12 months and stabilization thereafter (Figure 1). Among these patients 50% had centrally located tumours. Two patients had remaining toxicity after their initial SBRT, that increased after reirradiation: pleural effusion from grade 1 to 2 in one patient (#6) and cough grade 1 to 3 in another patient (#14). In one patient (#21) dyspnoea grade 1 occurred after reirradiation and increased to grade 3 after the second reirradiation.

Toxicity related death occurred in three patients. A 69-year-old woman (#10) diagnosed with an inoperable stage IIB NSCLC of the left lower lobe received 30 Gy in 3 fractions (CTV=114 cm^3) and was reirradiated with 45 Gy in 3 fractions (CTV=77 cm^3) after an interval of 12 months. Toxicity was mild with grade 2 dermatitis as maximum toxicity. At eight months after reirradiation, the patient was diagnosed with a cT1N0 poorly differentiated squamous cell carcinoma of the epiglottis treated with curative 3D-conformal radiotherapy without overlap with the previous SBRTs. Three months later, she died due to severe acute haemoptysis. Autopsy was not performed, and reirradiation induced pulmonary bleeding could not be ruled out (toxicity grade 5).

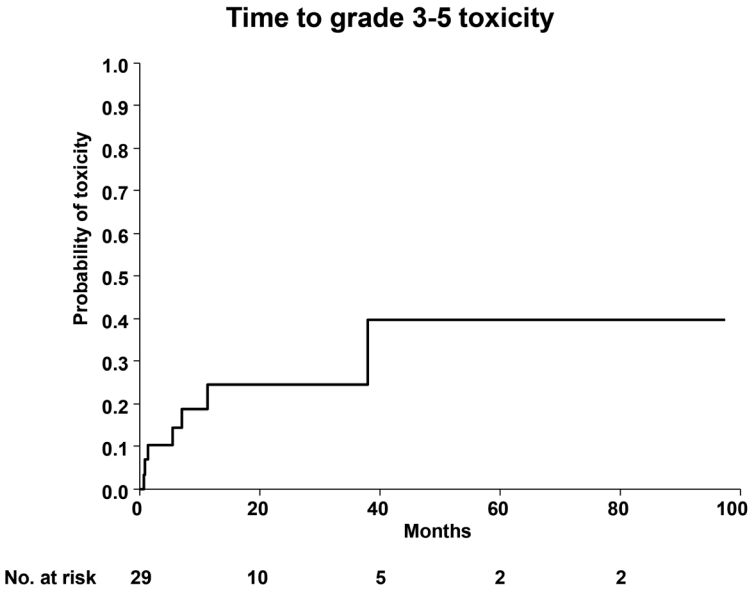

Figure 1. Kaplan-Meier time to first occurrence of grade 3-5 toxicity after reirradiation. Patients were censored for date of death, date of third irradiation or last follow up date.

A 65-year-old man (#22) was diagnosed with a left-sided renal cell carcinoma and underwent nephrectomy. Half a year later bilateral hilar metastases developed, which were both treated with 40 Gy in 4 fractions (CTV right hilus=12 cm^3). Three years later a recurrence near the right hilus was retreated with 40 Gy in 5 fractions (CTV=37 cm^3). Within three months after reirradiation several grade 3 toxicities developed: pneumonitis, cough, dyspnoea and pain. Nine months after reirradiation, a stenosis of the right and left lower lobe bronchus developed, followed by his death from severe acute haemoptysis one month later (toxicity grade 5). A CT-scan 3 weeks prior to his death, showed no evidence of disease. Autopsy revealed multiple infarctions in both lungs. There was no bleeding source and no residual tumour in neither the lungs nor in the mediastinum.

A 77-year-old man (#25), diagnosed with stage III NSCLC of the left hilus with encasement of the lobar bronchus and three mediastinal lymph nodes, was treated with 30 Gy given in 3 fractions plus a boost dose of 10 Gy to the hilus (total CTV=179 cm^3). After an interval of 13 months the hilar tumour was reirradiated with 33 Gy in 3 fractions (CTV=58 cm^3). Six weeks after reirradiation, the patient died due to massive bleeding in the upper pulmonary respiratory tract (toxicity grade 5).
An exceptional case was a 68-year-old man (#23) with a primary oesophagus carcinoma, treated with an oesophagectomy and gastric tube reconstruction. He developed a local recurrence at the carina one year after diagnosis and started with chemotherapy, where after

he received 40 Gy given in 5 fractions (CTV=13 cm^3). The tumour relapsed and was reirradiated 29 months later with 40 Gy in 5 fractions (CTV=6 cm^3). Ten months afterward, a fistula between the trachea and the gastric tube developed (toxicity grade 4). Thirteen months after reirradiation the tumour locally progressed again and treatment at the Karolinska University Hospital was refused. He was retreated twice more at another hospital with 40 Gy in 5 fractions (CTV=19 cm^3) and 42 Gy in 7 fractions (CTV=106 cm^3), with an interval of eight months. Seven months after the third reirradiation the patient developed a vena cava superior syndrome due to a severe radiation-induced fibrosis of the vena cava superior (toxicity grade 4). The patient died of a cardiac infarction during stent placement.

Comparison of patients with a maximum of grade 2 toxicity (*n*=12) versus grade 3-5 toxicity (*n*=9) revealed a median CTV of 7.5 cm^3 (range 1-461) versus 43 cm^3 (range 3-259) for the initial SBRT, and 17 cm^3 (range 5-49) versus 21 cm^3 (range 1-242) at reirradiation, respectively. Median dose and follow up were comparable, whereas the time between initial SBRT and reirradiation was a median of 19 months (range 8-54) in grade 2 toxicity patients and a median of 14.5 months (range 5-35) in the more severe toxicity group.

All grade 4-5 toxicity patients had central tumours. Comparing patients with central (*n*=8) and peripheral tumours (*n*=13) with grade ≥ 2 toxicity, the median CTV was 69 cm^3 (range 1-259) versus 8 cm^3 for initial SBRT, and 43 cm^3 (range 2-42) versus 14 cm^3 (range 1-28) at reirradiation (Table 3). In central tumours the median time between initial SBRT and reirradiation was almost twice as large, whereas the median follow up was only 10 months compared with 23 months for patients with peripheral tumours.
In total, eight patients with centrally located tumours experienced grade ≥ 2 toxicity (Table 4 electronic supplement). Of these patients, six received other singular courses of lung SBRT with a median of two treatments (range 2-4). Other SBRT courses were given at the time of initial SBRT in three patients (#13, #9, #22), in between initial SBRT and reirradiation in two patients (#13, #28) and at the time of reirradiation in 2 patients (#9, #28). Moreover, one patient received SBRT before initial SBRT (#14) and two patients after reirradiation (#14, #23). One patient received chemotherapy during the course of disease (#23). A patient that received 30 Gy in 2 fractions after prior SBRT with 30 Gy in 3 fractions (#14), developed grade 3 cough 1 month after reirradiation along with other minor grade 1 and 2 toxicities, and died one year later due to brain metastases. Patients #9, #13 and #28 all developed several grade 2 toxicities; cough dyspnoea, atelectasis, pulmonary effusion and fibrosis. One patient (#28) was treated three times in the same area and suffered from grade 2 atelectasis and pleural effusion after reirradiation. He died 29 days after the second reirradiation without any data on follow up.

No life-threatening toxicity was reported in the 13 patients reirradiated on peripheral tumours (Table 5 electronic supplement). Other SBRT courses were given before initial SBRT in one

patient (#5), at the time of initial SBRT in six patients (#2, #5, #6, #17, #20, #29), in between initial SBRT and reirradiation in three patients (#15, #17, #20), at the time of reirradiation in 6 patients (#4, #5, #11, #20, #21, #26) and after reirradiation in two patients (#11, #20). Eleven patients received other singular courses of lung SBRT with a median of two treatments (range 1-12). Five patients were treated with chemotherapy during the course of disease (#1, #2, #6, #17, #21). Interestingly, one of these patients (#18) received reirradiation on three lung metastases in both lungs, with a median PTV of 25 cm^3 (range 16-37), and singular SBRT on two other lung metastases. Treatment dose was 30 Gy in 2 fractions for all metastases. She survived for two years after retreatment until she succumbed to liver metastases. Another patient with a pulmonary metastasized osteosarcoma was reirradiated on two lung metastases and received 12 other singular courses of lung SBRT and four wedge resections (#20). He developed grade 3 dyspnoea and pleural effusion and five years after the first SBRT the disease rapidly progressed, and he died from bacterial pneumonia.

There were two patients with peripheral tumours that received three irradiations in the same area, as well as one other singular lung SBRT treatment. The maximum scored toxicity was grade 3 dyspnoea in one patient, having a poor baseline pulmonary function with an FEV1 of 0.38 litres (38%) (#15). The other patient developed grade 3 dermatitis with several grade 2 toxicities (#21). Both patients died 2 years after the last SBRT due to progression and unknown cause, respectively.

There was no statistical correlation between MLD and frequency of grade 3-5 lung toxicity (maximum grade of pneumonitis and/or fibrosis, and/or cough, and/or dyspnoea, and/or obstruction/stenosis and/or bleeding) after reirradiation, taking into account other singular courses of SBRT between initial SBRT and reirradiation. Moreover, there were no differences in MLD between patients with central and peripheral tumours.

Table 3. Subgroup analysis according to localization of patients with grade ≥ 2 toxicity

	SBRT	ΔT (months)	$EQD_{2,}$ mean to CTV (α/β=10)	$EQD_{2,}$ to PTV (α/β=3)	CTV (cm^3)	PTV (cm^3)	FU (months)	Potential FU (months)
Peripheral (*n*=13)	1		109 (56-163)	108 (78-162)	8 (1-259)	38 (15-461)		
	2	15 (5-54)	109 (84-163)	108 (52-162)	14 (1-28)	55 (16-160)	23 (4-97)	25 (6-97)
Central (*n*=8)	1		104 (84-163)	90 (88-162)	69 (3-461)	156 (21-750)		
	2	26 (9-48)	99 (98-163)	96 (78-162)	43 (2-242)	107 (31-242)	10 (1-46)	11 (1-46)

All values in median with range between brackets. n= number of patients, SBRT 1= first treatment, 2= reirradiation, ΔT= time between initial SBRT and reirradiation, CTV= clinical target volume, PTV= planning target volume, EQD_2=total equivalent dose in 2 Gy fractions, CTV mean dose in EQD_2=d*1.4*n (d*1.4)+10)/12 if α/β=10 (1.4 is a correction factor for the heterogeneous dose distribution) and dose prescribed to the periphery of the PTV in EQD_2=d*n((d+3)/5) if α/β=3, FU=follow up time from reirradiation, Potential FU= follow up time from reirradiation until death.

At 5 months follow up after reirradiation, local control was achieved in fifteen patients (52%), as assessed by CT-scan (*n*=12) or X-thorax (*n*=3), and eight patients locally progressed (28%). Five patients died with less than 5 months follow up and in one patient no conclusion could be drawn. The median CTV in the local control group at initial SBRT was 4 cm^3 (range 1-461) versus 126 cm^3 (range 1-259) in the progression group, and 16 cm^3 (range 4-193) versus 42 cm^3 (range 15-242) at reirradiation respectively. Dose and follow up time were comparable. Eleven patients received a higher dose (EQD_2) for reirradiation compared with initial SBRT, 13 patients received the same dose and five patients a lower dose. The regimen did not influence local control.

Kaplan-Meier estimated median overall survival time after reirradiation was 19.3 months (range 1-98) (Figure 2). The 1-, 2- and 3-year survival rates were 59%, 43% and 23%, respectively.

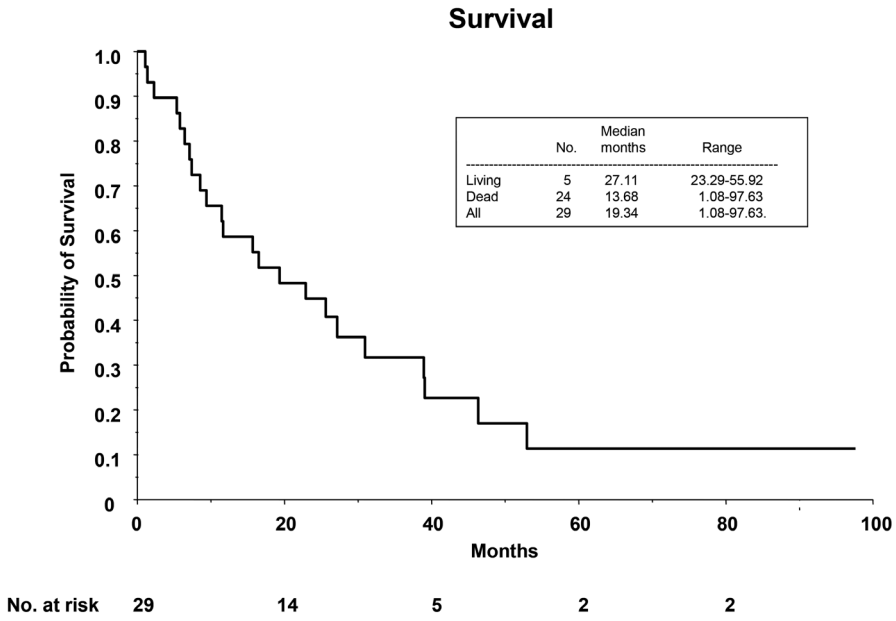

Figure 2. Kaplan-Meier overall survival

DISCUSSION

This study represents the largest group of patients reirradiated with SBRT for lung tumours described thus far. Toxicity was less than one might expect in this frail patient cohort with large treated volumes and extremely high accumulated doses. In a total of 29 patients grade 3-4 toxicity was scored 14 times in eight patients, and three patients experienced grade 5 toxicity. The most common toxicities were cough, pulmonary fibrosis, pleural effusion and pain. Overall, we found few side effects such as atelectasis and dyspnoea after high cumulative doses to the bronchi. Generally, the remaining toxicity after the first SBRT did not tend to increase after reirradiation. Although the number of cases in our study is limited, other courses of singular lung SBRT performed before or after the reirradiation, reirradiations of ≥ 2 tumours and second reirradiations were tolerated without severe toxicity. Comparing CTV's between patients experiencing grade 2 and grade 3-5, revealed a 6 times larger volume for the initial SBRT in the latter group. Together with a shorter interval between initial SBRT and reirradiation, this may explain the higher incidence of severe toxicity. The difference in CTV was more pronounced when comparing patients with central and peripheral tumours. Since the four patients with grade 4-5 toxicity all had central tumours, another causal factor may be tumour localization. Increased toxicity after one course of lung SBRT was reported by Timmerman *et al.* who predicted an eleven-fold increase of severe toxicity for centrally located tumours after 60-66 Gy [21]. This stands in contrast to other studies that reported acceptable toxicity, even in case of dose delivery in consecutive daily fractions [24], although the number of central tumours and the fraction dose was low [8,25-26]. In two studies only central tumours were treated with fraction doses of 2.5-10 Gy [27-28]. They reported significant toxicity and advised against multiple treatments to the same major bronchus. A recent study reported good results with risk adapted fractionation schedules in large stage I-II tumours (median PTV of 137 cm^3), of which thirteen out of eighteen patients had central tumours [29]. Acute radiation pneumonitis was best predicted by contralateral V5, whereas another group derived a dose-response relationship between risk of radiation pneumonitis and MLD, resembling the curve of conventional fractionated radiotherapy [30]. We could not demonstrate a correlation of MLD and grade 3-5 lung toxicity, taken into account other courses of SBRT.

Three patients in our patient cohort died from acute massive bleeding after reirradiation of central tumours. We could not find a correlation between maximum dose in the vessel wall or the 100% isodose line covering the complete circumference of an adjacent large mediastinal vessel with grade 3-5 toxicity (data not shown). Unfortunately, in the three patients with acute haemoptysis no direct dose-volume correlations could be calculated, since no bleeding source was found.

A late radiation-induced toxicity that has been demonstrated following SBRT, is bronchial stricture or stenosis occurring within 12-36 months following SBRT [21,28,31-32]. This complication can in some cases cause life-threatening pneumonia [21,32], which might have been the case in one patient, who was treated with two reirradiations and 12 other singular SBRTs and died from a bacterial pneumonia (#20). The autopsy report did not reveal any signs of bronchial stenosis, but a fungal component in the left lower lobe. However, due to extensive SBRTs it is very likely that stenosis and increased mucus production, together with disease progression, contributed to the pneumonia and fungal infection.

High doses of radiotherapy on small volumes of the bronchus might be well tolerated, as was demonstrated in a rodent model [33]. In this study no dose effect relation was found. In our study with involvement of large bronchial volumes within the PTV, the 14 months interval between first treatment and reirradiation might have allowed for tissue repair and acceptable tolerance in some cases. The RTOG 0813 phase I/II study is now open for accrual to asses the maximum tolerated dose in centrally located tumours.

What factors determine the increased toxicity after irradiation of central lung structures? From this study it may be concluded that a larger central volume irradiated with high dose will be an important factor. High dose covering large bronchi and vessels will not only affect the targeted tissue, but also the lung parenchyma distant to the radiation injury. The effects of microvascular atrophy in both bronchi and large vessels will increase local vascular permeability, hypoxia and inflammation resulting in oedema, inflammatory cell recruitment and increased levels of profibrotic cytokines [34]. Concomitant loss of bronchial epithelial transport and increase of mucus production in lung parenchyma distant to the injury, will likely result in an increased risk of pneumonia and reduced ventilation. Smaller volumes of central structures and avoidance of whole circumference high dose areas of various serial risk organs as bronchi and vessels seem to be better tolerated through salvage repair from nearby adjacent spared tissue [33].

This retrospective study has limitations. First, median follow up was relatively short, therefore we might have underestimated toxicity. Second, the diagnosis of local recurrence or a new lung metastasis was based on a growing tumour detected on CT-scan or chest X-ray, and in general, neither pathological confirmation nor PET-CT scans were done. In more than 50% of such patients, a mass-like consolidation may develop within 6 months after SBRT, associated with radiation-induced lung fibrosis [35-37]. Possibly, these consolidations were sometimes misinterpreted as recurrences. Third, patients receiving other courses of lung SBRT might have biased the interpretation of reirradiation toxicity. However, the most prominent factors determining toxicity of reirradiation in this study were CTV and central tumour localization.

Although interpretation of toxicity was hampered by confounding factors as other SBRT courses, chemotherapy, surgery or general disease progression, we showed promising results with regard to lung tissue tolerance. Reirradiation of the "same" lung volume seemed not to add to extra lung tissue damage, possibly since this tissue was already compromised. The increased use of modern techniques, such as four-dimensional computed tomography, image guided radiotherapy and intensity modulated radiotherapy, allow for smaller margins and treatment volumes [38-44]. Therefore we believe that radical reirradiation with SBRT should be considered in patients who have peripheral pulmonary tumours. However, prospective studies are needed to select patients most suitable for reirradiation. In the mean time, reirradiation of centrally localized tumours should only be performed with great concern of potential severe toxicity. Moreover, we believe that simply giving a sufficient dose in the first SBRT course would have avoided the risk of reirradiation for some patients in this study. This may even be even more the case in colorectal lung metastases, who seem to be more radioresistant [45].

Conclusion

Reirradiation with SBRT of pulmonary tumours is justified as a safe and effective procedure for a subpopulation of patients. However, reirradiation of central tumours should only be performed after careful considerations of potential severe toxicity. Prospective studies are needed to specify patient selection criteria and find dose-limiting constraints.

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APPENDIX

Table 4. Treatment characteristics per patient with central tumours and grade ≥ 2 toxicity: reirradiation and other singular lung SBRTs

Patient #	Fractionation scheme (Gy*fr#)	ΔTime (months)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median	PTV (cm^3)	Lung lobe	Max Tox	FU (months)	Other SBRT lung tumours	Fractionation scheme (Gy*fr#)	PTV (cm^3)	Time +/- first SBRT (months)
13	15x2		109	108	21	RML			RLL	15x2	24	0
									LLL	15x2	28	0
	15x2	48			82	RML	2	16	LLL	8x5	24	+48
									LLL	8x5	46	+48
9	8x5		99	88	750	RUL			RLL	8x5	54	0
									RLL	8x5	16	0
	8x5	9			119	RUL	2	46	RLL	10x3	47	+9
28	15x3		163	162	102	RML						
									Mediast	15x2	15	+10
	8x5	24	99	88	81	RML		16				
									LUL	15x2	35	+24
	8x5	39			64	RML	2	1				
14									Mediast	10x2	44	-6
	10x3		84	78	347	RML						
	15x2	27	109	108	242	RML	3	10				
									LUL	15x2	26	+35
23	8x5		99	88	42	Mediast						
	8x5	29			31	Mediast	4					
	8x5	42			67	Mediast						
	6x7	50	90	76	277	Mediast	4	16				
									Mediast	12x3	12	+50
10*	10x3		84	78	209	LLL			-			
	15x3	12	163	162	199	LLL	5	7	-			
22*	10x4		112	104	71	RLL						
									LLL	10x4	103	0
	8x5	35	99	88	95	RLL	5	10				
25*	10x3+10x1		84+28	104	198+121	LUL/ Mediast + hilus boost			-			
	11x3	13	98	92	152	LUL/ hilus	5	1	-			

* Death from toxicity. fr# =number of fractions, ΔTime = time between first treatment and reirradiation, CTV mean dose in EQD_2=d*1.4*n ((d*1.4)+10)/12 if α/β=10 (1.4 is a correction factor for the heterogeneous dose distribution) and dose prescribed to the periphery of the PTV in EQD_2=d*n((d+3)/5) if α/β=3, PTV= planning target volume, RUL=right upper lobe, RML=right middle lobe, RLL=right lower lobe, LUL=left upper lobe, LLL=left lower lobe, Mediast=Mediastinum. Max Tox= maximum toxicity scored according to CTCAE v3.0 after reirradiation, FU= follow up time from reirradiation.Time to (-) and from (+) first SBRT.

Table 5a. Treatment characteristics per patient with peripheral tumours and grade ≥ 2 toxicity: reirradiations

Patient #	Fractionation scheme (Gy*fr#)	ΔTime (months)	$EQD_{2,2}$ mean to CTV (α/β=10) median	$EQD_{2,2}$ to PTV (α/β=3) median	PTV (cm^3)	Lunglobe	MaxTox	FU (months)
1	15x3		163	162	36			
	15x3	9			55	LUL	2	8
2	15x3		163	162	21			
	15x3	22			54	LLL	2	23
3	10x4		112	104	97			
	10x4	33			71	RML	2	22
4	10x4		112	104	201			
	15x3	19	163	162	46	LLL	2	28
5	15x2		109	108	37			
	10x4	19	112	104	97	RLL	2	6
11	15x2		109	108	30			
	15x3	8	163	162	63	LLL	2	97
17	15x2		109	108	38			
	15x3	54	163	162	38	LUL	2	52
26	10x4		112	104	84			
	15x3	12	163	162	46	LLL	2	5
29	15x2		109	108	15			
	10x3	14	84	78	160	RUL	2	4
6	10x4		112	104	160			
	8x5	8	99	88	88	LLLdorsal	3	31
21	10x2		56	52	34			
	15x2	8	109	108	16			
	15x2	14			287	RLL	3	13
20*	15x2+15x2		109+109	108+108	46+33			
	15x2+15x2	5+16	109+109	108+108	24+27	RLL, LUL	3	39
15	8x5		99	88	461			
	8x5	16			70			
	10x4	31	112	104	60	RUL	3	23

* = patient with two reirradiated tumours. Other abbreviations defined in Table 4.

Table 5b. Treatment characteristics per patient with peripheral tumours and grade ≥ 2 toxicity: other singular lung SBRTs

Patient #	Fractionation scheme (Gy*fr#)	EQD_2 mean to CTV (α/β=10) median	EQD_2 to PTV (α/β=3) median	PTV (cm^3)	Localization	Time +/- first SBRT (months)
1	X	X	X	X	X	X
2	15x3	163	162	39	RUL	0
3	X	X	X	X	X	X
4	15x3	163	162	27	RLL	+19
5	10x2	56	52	22	RUL	-10
	15x3			44	RML	-10
	10x2			24	LLL	0
	15x2	109	108	28	LUL	+19
11	15x2	109	108	30	LLL	+8
	15x3	163	162	45	RLL	+86
	15x3			33	RLL	+86
17	15x2	109	108	186	RLL	0
	15x2			44	RLL	+4
26	15x2	109	108	14	LUL	+12
	15x2			40	FML	+12
	15x2			24	RLL	+12
29	15x2	109	108	38	LLL	0
	15x3	163	162	31	RLL	0
	15x3			199	LLL	0
6	10x4	112	104	74	LLL ventral	0
21	15x2	109	108	23	RML	+6
	10x2	56	52	22	LLL	+6
20	8x5	99	88	38	Mediastinum	0
	10x4	112	104	41	Mediastinum	+6
	10x4			19	LLL	+6
	10x4			28	RLL	+6
	15x2	109	108	27	LUL	+11
	15x2			32	LLL	+11
	15x2			19	LLL	+16
	15x2			40	LLL	+16
	15x3	163	162	28	LLL	+35
	15x3			78	RLL	+35
	15x3			124	RLL	+50
	15x3			40	RLL	+50
15	8x5	99	88	32	LLL	+11

X= no other singular SBRT. Other abbreviations defined in Table 4.

Overview. Toxicity and treatment per patient

#1 ♂

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	EQD_2 mean to CTV (α/β=10) median	EQD_2 to PTV (α/β=3) median	PTV (cm^3)	Treated other sites	Dose (Gy*fr#)	PTV (cm^3)	CTx
2007/12/17		Peripheral	LUL	15x3	163	162	36				
2008/15/13								Segm 7	16x2	26	
2008/09/16	9	Peripheral	LUL	15x3	163	162	55				+

ΔTime = time between first SBRT and reirradiation. Central or peripheral tumour localization was defined according to the RTOG criteria. RUL=right upper lobe, RML=right middle lobe, RLL=right lower lobe, LUL=left upper lobe, LLL= left lower lobe. Dose: Gy=Gray per fraction, fr# =number of fractions, CTV mean dose in EQD_2=d*1.4*n ((d*1.4)+10)/12 if α/β=10 (1.4 is a correction factor for the heterogeneous dose distribution) and dose prescribed to the periphery of the PTV in EQD_2=d*n((d+3)/5) if α/β=3, PTV = planning target volume, Segm = Liversegment, CTx = chemotherapy yes/no = +/-

Toxicity according to CTCAE v3.0:
- Pain grade 1 (G1)
- Pulmonary fibrosis G2

#2 ♂

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	EQD_2 mean to CTV (α/β=10) median	EQD_2 to PTV (α/β=3) median	PTV (cm^3)	Treated other sites	Dose (Gy*fr#)	PTV (cm^3)	CTx
2006/09/15		Peripheral	LLL	15x3	163	162	21				
2006/09/15								RUL	15x3	39	
2008/07/08	22	Peripheral	LLL	15x3	163	162	54				+

Toxicity:
- Atelectasis G2
- Cough G2
- Pulmonary fibrosis G2

#3 ♂

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median				PTV (cm^3)	CTx
2005/08/15		Peripheral	RML	10x4	112	104				97	
2008/05/23	33	Peripheral	RML	10x4	112	104				71	-

Patient history: 2000 lobectomie RUL

Toxicity:
- Cough G2
- Dyspnoea G2
- Pneumonitis/pulmonary infiltrates G2
- Pulmonary fibrosis G2
- Other: Mucus production G2

#4 ♂

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median	PTV (cm^3)	Treated other sites	Dose (Gy*fr#)	PTV (cm^3)	CTx
2005/09/05		Peripheral	LLL	10x4	112	104	201				
2007/04/20	19	Peripheral	LLL	15x3	163	162	46				
2007/04/20								RLL	15x3	27	-

Toxicity:
- Atelectasis G2
- Cough G2
- Pleural effusion G2
- Pulmonary fibrosis G2

#5 ♂

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median	PTV (cm^3)	Treated other sites	Dose (Gy*fr#)	PTV (cm^3)	CTx
1999/12/10								RUL	10x2	22	
1999/12/10								RML	15x3	44	
2000/04/10								Adrenal gland	10x3	161	
2000/09/25								LLL	10x2	24	
2000/09/25		Peripheral	RLL	15x2	109	108	37				
2002/02/08	19	Peripheral	RLL	10x4	112	104	97(35+62)				
2002/02/08								LUL	15x2	28	-

Toxicity:
- Cough G1
- Pneumonitis/pulmonary infiltrates G2

#6♂

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median	PTV (cm^3)	Treated other sites	Dose (Gy*fr#)	PTV (cm^3)	CTx
2002/11/27								LLLvent	10x4	74	
2002/11/27		Peripheral	LLLdors	10x4	112	104	160				
2003/07/31	8	Peripheral	LLLdors	8x5	99	88	88				+

Patient history: May 2000 diagnosis of an oesophagusCA treated with 3D conformal radiotherapy 2 Gy x 20.
Toxicity:
- Pain G1
- Atelectasis G2
- Pleural effusion G2
- Pulmonary fibrosis G2
- Dyspnoea G3

#7

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median	PTV (cm^3)				CTx
2004/04/13		Peripheral	LLL	8x5	99	88	320				
2005/06/16	14	Peripheral	LLL	10x4	112	104	162				+

Toxicity:
- Atelectasis G1

#8 ♀

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median	PTV (cm^3)				CTx
2000/08/16		Central	RUL	8x5	99	88	254				
2004/03/24	43	Central	RUL	8x5	99	88	135				-

Toxicity:
- Cough G1

#9

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median	PTV (cm^3)	Treated other sites	Dose (Gy*fr#)	PTV (cm^3)	CTx
1999/12/22								RLL	8x5	54	
1999/12/22								RLL	8x5	16	
1999/12/22		Central	RUL	8x5	99	88	750				
2000/09/12	9	Central	RUL	8x5	99	88	119				
2000/09/12								RLL	10x3	47	-

Toxicity:
- Atelectasis G2
- Pleural effusion G2
- Pulmonary fibrosis G2

#10 ♀

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median	PTV (cm^3)				CTx
1997/06/09		Central	LLL	10x3	84	78	209				
1998/06/08	12	Central	LLL	15x3	163	162	199				-

Patient history: February 1999 supraglottic laryngeal carcinoma T1N0M0 treated with 3D conformal radiotherapy.

Toxicity:
- Dyspnoea G1
- Pulmonary fibrosis G1
- Dermatitis G2
- Bleeding G5

#11 ♂

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median	PTV (cm^3)	Treated other sites	Dose (Gy*fr#)	PTV (cm^3)	CTx
1998/03/27		Periphery	LLL	15x2	109	108	30				
1998/11/11	8	Periphery	LLL	15x3	163	162	63				
1998/11/11								LLL	15x2	30	
2006/01/12								RLL	15x3	45	
2006/01/12								RLL	15x3	33	-

Toxicity:
- Cough G2

#12 ♂

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median	PTV (cm^3)	Treated other sites	Dose (Gy*fr#)	PTV (cm^3)	CTx
2001/08/15								LUL	10x2	13	
2001/08/15								RUL	10x2	16	
2001/08/15		Peripheral	RLL	10x2	56	52	7				
2002/05/17								Segm2,3	15x3	136	
2002/11/01								RUL	20x1	12	
2002/11/01	15	Peripheral	RLL	20x1	89	92	64				+

Toxicity:
- Cough G1
- Pleural effusion G1

#13 ♀

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median	PTV (cm^3)	Treated other sites	Dose (Gy*fr#)	PTV (cm^3)	CTx
1999/12/23								RLL	15x2	24	
1999/12/23		Central	RML	15x2	109	108	21				
1999/12/23								LLL	15x2	28	
2003/12/12								LLL	8x5	24	
2003/12/12								LLL	8x5	46	
2003/12/12	48	Central	RML	15x2	109	108	82				-

Toxicity:
- Cough G2
- Dyspnoea G2

#14 ♂

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median	PTV (cm^3)	Treated other sites	(Gy*fr#)	PTV (cm^3)	CTx
1994/05/11		Central	RML	10x3	84	78	347(322+25)				
1994/11/10								Mediast	10x2	44	
1996/08/09	27	Central	RML	15x2	109	108	242				
1997/04/01								LUL	15x2	26	-

Toxicity:
- Atelectasis G1
- Hyperpigmentation G1
- Pneumonitis/pulmonary infiltrates G2
- Other: Mucus production G2
- Cough G3

#15 ♀

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median	PTV (cm^3)	Treated other sites	Dose (Gy*fr#)	PTV (cm^3)	CTx
2001/12/19		Peripheral	RUL	8x5	99	88	461				
2002/11/13								LLL	8x5	32	
2003/04/30	16	Peripheral	RUL	8x5	99	88	70(25+15+30)				
2004/07/02	31	Peripheral	RUL	10x4	112	104	60				-

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Patient history: March 2006 palliative radiotherapy 4 Gy x 1 and 5 Gy x 4 on metastatic disease of the supraclavicular fossa

Toxicity:
- Pain G2
- Dyspnoea G3

#16 ♂

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median	PTV (cm^3)	Treated other sites	Dose (Gy*fr#)	PTV (cm^3)	CTx
2000/03/10								LLL	15x2	33	
2000/03/10		Peripheral	RML	10x4	112	104	125(26+99)				
2003/01/09	34	Peripheral	RML	10x4	112	104	84				+

No toxicity reported

#17 ♀

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median	PTV (cm^3)	Treated other sites	Dose (Gy*fr#)	PTV (cm^3)	CTx
2001/06/15								RLL	15x2	186	
2001/06/15		Peripheral	LUL	15x2	109	108	38(19+19)				
2002/10/18								RLL	15x2	44	
2005/12/29	54	Peripheral	LUL	15x3	163	162	38				+

Patient history: 1993 bilobectomy (probably RUL+RML), pathology showed no malignancy. This resulted in Dyspnea G1 at baseline with FEV1=27%.

Toxicity:
- Fracture G1
- Dyspnoea G2

#18 ♀

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median	PTV (cm^3)	Treated other sites	Dose (Gy*fr#)	PTV (cm^3)	CTx
2002/02/21								Segm6	10x4	203	
2003/11/27		Peripheral	RULdors	15x2	109	108	16				
2003/11/27		Peripheral	RULvent	15x2	109	108	20				
2003/11/27		Peripheral	LLL	15x2	109	108	21				
2003/11/27								RLL	15x2	31	
2004/05/19	6	Peripheral	RULdors	15x2	109	108	28				
2004/05/19	6	Peripheral	RULvent	15x2	109	108	30				
2004/05/19	6	Peripheral	LLL	15x2	109	108	37				
2004/05/19								LLLdors	15x2	32	+

Toxicity:
- Pulmonary fibrosis G1

#19 ♀

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median	PTV (cm^3)	Treated other sites	Dose (Gy*fr#)	PTV (cm^3)	CTx
2003/02/20								LUL	12x4	46	
2003/02/20		Peripheral	RLL	15x2	109	108	16				
2003/02/20								LUL	12x4	7	
2003/10/28								LLL	15x2	6	
2003/10/28								LUL	15x2	21	
2003/10/28								LLL	15x2	22	
2003/10/28	8	Peripheral	RLL	15x2	109	108	81				+

No toxicity reported

#20 ♂

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median	PTV (cm^3)	Treated other sites	Dose (Gy*fr#)	PTV (cm^3)	CTx
2002/11/29		Periphery	LUL	15x2	109	108	33				
2002/11/29								Mediast	8x5	38	
2003/06/02								Mediast	10x4	41	
2003/06/02								LLL	10x4	19	
2003/06/02								RLL	10x4	28	
2003/10/22		Periphery	RLL	15x2	109	108	46				
2003/10/22								LUL	15x2	27	
2003/10/22								LLL	15x2	32	
2004/03/16	16	Periphery	LUL	15x2	109	108	27				
2004/03/16								LLL	15x2	19	
2004/03/16								LLL	15x2	40	
2004/03/16	5	Periphery	RLL	15x2	109	108	42				
2005/10/21								LLL	15x3	28	
2005/10/21								RLL	15x3	78	
2007/02/08								RLL	15x3	124	
2007/02/08								RLL	15x3	40	-

Patient history: Wedge resections in 2002, 2003, 2004 and 2006. In May 2007 palliative radiotherapy 5 Gy x 5 Th5-12.

Toxicity:
- Pulmonary fibrosis G1
- Pain G2
- Dyspnoea G3
- Pleural effusion G3

21 ♀

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median	PTV (cm^3)	Treated other sites	Dose (Gy*fr#)	PTV (cm^3)	CTx
1999/10/11		Peripheral	RLL	10x2	56	52	34				
2000/06/27								RML	15x2	23	
2000/06/27	8	Peripheral	RLL	15x2	109	108	16				
2000/06/27								LLL	10x2	22	
2000/12/15	14	Peripheral	RLL	15x2	109	108	287				+

Patient history: 1999 several wedge resections of the right lung. Patient had a lot of other not sarcoma related surgery.

Toxicity (only pulmonary fibrosis occurred after first reirradiation, all others after the second reirradiation, so the 3rd treatment of the RLL):

- Pulmonary fibrosis G1
- Cough G2
- Dyspnoea G2
- Pleural effusion G2
- Hyperpigmentation G2
- Pain G2
- Dermatitis G3

#22 ♂

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median	PTV (cm^3)	Treated other sites	Dose (Gy*fr#)	PTV (cm^3)	CTx
2000/09/01		Central	RLL	10x4	112	104	71				
2000/09/01								LLL	10x4	103(35+68)	
2001/10/11								Adrenal gland	8x3	27	
2003/08/21	35	Central	RLL	8x5	99	88	95				-

Toxicity:

- Atelectasis G1
- Pulmonary fibrosis G2
- Cough G3
- Dyspnoea G3
- Pneumonitis/pulmonary infiltrates G3
- Obstruction/stenosis of airway G3
- Pain G3
- Bleeding G5

#23 ♂

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median	PTV (cm^3)	Treated other sites	Dose (Gy*fr#)	PTV (cm^3)	CTx
2001/08/01		Central	Mediast	8x5	99	88	42				
2004/01/15	29	Central	Mediast	8x5	99	88	31				
2005/01/24	42	Central	Mediast	8x5	99	88	67				
2005/10/03	50	Central	Mediast	6x7	99	76	277				
2005/10/03								Mediast	12x3	12	+

Toxicity:
- Pulmonary fibrosis G1
- Obstruction/stenos is of vena cava superior G4
- Other: Fistula between trachea and gastric tube G4

#24 ♂

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median	PTV (cm^3)	CTx
1999/10/29		Central	RUL	7x3	49	42	151(52+54+22+23)	
2000/05/04	7	Central	RUL	8x5	99	88	133	-

Patient history: April 2000 occipital bone metastases palliative radiotherapy 3 Gy x 10.

No toxicity reported

#25 ♂

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median	PTV (cm^3)	Treated other sites	Dose (Gy)	PTV (cm^3)	CTx
1997/03/13		Central	LUL/ mediastinum	10x3	84		198				
1997/03/13		Central	hilus boost	10x1	28	104 (10x4)	121				
1998/04/23	13	Central	LUL/ hilus	11x3	98	92	152				-

Toxicity:
- Cough G3
- Bleeding G5

#26 ♂

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median	PTV (cm^3)	Treated other sites	Dose (Gy*fr#)	PTV (cm^3)	CTx
1999/02/22		Peripheral	LLL	10x4	112	104	84				
2000/02/21								LUL	15x2	14	
2000/02/21								RML	15x2	40	
2000/02/21								RLL	15x2	24	
2000/02/21	12	Peripheral	LLL	15x3	163	162	46				-

Toxicity:
- Cough G2
- Dyspnoea G2

#27 ♂

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median	PTV (cm^3)				CTx
1997/11/04		Central	RLL	8x4	79	70	446				
1998/07/17	8	Central	RLL	8x4	79	70	355				+

No toxicity reported, but only 33 days of follow up due to death. Cause: central nervous system metastases of primary SCLC.

#28 ♀

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	$EQD_{2,}$ mean to CTV (α/β=10) median	$EQD_{2,}$ to PTV (α/β=3) median	PTV (cm^3)	Treated other sites	Dose (Gy*fr#)	PTV (cm^3)	CTx
1999/01/28		Central	RML	15x3	163	162	102				
1999/12/08								Mediast	15x2	15	
2001/01/18	24	Central	RML	8x5	99	88	81				
2001/01/18								LUL	15x2	35	
2002/04/11	39	Central	RML	8x5	99	88	64				-

Toxicity:
- Atelectasis G2
- Pleural effusion G2

Remark: there was no information about toxicity after second reirradiation. The side effects mentioned are the ones that were reported after the first reirradiation.

#29 ♂

Date of treatment	ΔTime (months)	Tumour localization	Lung lobe	Dose (Gy*fr#)	EQD_2 mean to CTV (α/β=10) median	EQD_2 to PTV (α/β=3) median	PTV (cm^3)	Treated other sites	Dose (Gy*fr#)	PTV (cm^3)	CTx
1997/11/26		Peripheral	RUL	15x2	109	108	15				
1997/11/26								LLL	15x2	38	
1997/11/26								RLL	15x3	31	
1997/11/26								LLL	15x3	199	
1999/01/18	14	Peripheral	RUL+mediast	10x3	84	78	160(109+51)				-

Patient history: April 1999 3 Gy x 10 palliative radiotherapy C7-Th11.

Toxicity:
- Pain G2