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FULL PAPER

Stereotactic body radiation therapy for a new lung cancer arising after pneumonectomy: dosimetric evaluation and pulmonary toxicity

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Objective: To evaluate the tolerance of stereotactic body radiation therapy (SBRT) for the treatment of secondary lung tumours in patients who underwent previous pneumonectomy.

Methods: 12 patients were retrospectively analysed. The median maximum tumour diameter was 2.1 cm (1–4.5 cm). The median planning target volume was 20.7 cm^3 (2.4–101.2 cm^3). Five patients were treated with a single fraction of 26 Gy and seven patients with fractionated schemes (3 × 10 Gy, 4 × 10 Gy, 4 × 12 Gy). Lung toxicity, correlated with volume (*V*) of lung receiving >5, >10 and >20 Gy, local control and survival rate were assessed. Median follow-up was 28 months.

Results: None of the patients experienced pulmonary toxicity > grade 2 at the median dosimetric lung parameters of V_5, V_{10} and V_{20} of 23.1% (range 10.7–56.7%), 7.3% (2.2–27.2%) and 2.7% (0.7–10.9%), respectively. No patients required oxygen or had deterioration of the performance status during follow-up if not as a result of clinical progression of disease. The local control probability at 2 years was 64.5%, and the overall survival at 2 years was 80%.

Conclusion: SBRT appears to be a safe and effective modality for treating patients with a second lung tumour after pneumonectomy.

Advances in knowledge: Our results and similar literature results show that when keeping V_5, V_{10} V_{20} <50%, <20% and <7%, respectively, the risk of significant lung toxicity is acceptable. Our experience also shows that biologically effective dose 10 >100 Gy, necessary for high local control rate, can be reached while complying with the dose constraints for most patients.

INTRODUCTION

Surgery is widely considered to be the standard therapy for operable patients with early-stage non-small-cell lung cancer (NSCLC). Surgical resection offers a reasonable chance of cure with 5-year survival rate for Stage I and Stage II ranging from 60% to 80% and 40% to 50%, respectively.[1,2] Nevertheless, also in this favourable group of patients, the risk of recurrence or of a new lung cancer is high. Approximately 20% (range 16–28%) of patients with Stage I disease and 50% (range 43–66%) of those with Stage II present recurrence.[3–9] Moreover, the incidence of a new primary lung cancer (NPLC) has been estimated to be about 2% per patient-years.[7,10,11] Most recurrences are distant metastases, and in these patients, the prognosis is very poor with a median survival of few months from the date of recurrence detection. However, some isolated chest recurrence[4,5,10] or NPLC[7,10,12–14] can be managed aggressively with a reasonable chance of cure. Some authors report that about 50% (range 38–73%) of NPLC can undergo resection[7,10,11,14] with a long-term survival in most series ranging between 18% and 50%.[10–13]

Despite these encouraging results, a significant proportion of patients cannot undergo surgery owing to the inadequate respiratory reserve or poor general condition. Johnson,[11] in his review, reported that 25% of patients with potentially resectable NPLC cannot tolerate further lung resection.

Surgery is even more arduous if the previous resection was pneumonectomy which usually has a significant negative impact on pulmonary reserve. Very few patients undergo additional resection after pneumonectomy,[15–28] and morbidity is not negligible.[20,23] Even a limited resection on the contralateral lung has a negative impact on pulmonary function.[20,23,26]

In recent years, a growing body of evidence suggested that stereotactic body radiation therapy (SBRT) is an effective treatment for patients with medically inoperable peripheral Stage I NSCLC.[29–32] Local control rates of ≥90% are reported in several studies[33–36] with an acceptable incidence of high-grade toxicity. Even in patients with severely impaired pulmonary function, SBRT has shown to be safe and to preserve quality of life.[37–40] This indicates that SBRT could have major advantages in selected patients with isolated chest recurrence or NPLC after a previous pneumonectomy. To date, there is very limited clinical experience published on this topic.[41–43] The purpose of this study was to evaluate the tolerance, and more specifically lung toxicity, in 12 patients treated with SBRT.

METHODS AND MATERIALS

Patients

Since 2007, 12 patients were treated with SBRT for a new tumour in the contralateral lung after previous pneumonectomy for a NSCLC (6 patients with squamous cell carcinoma and 6 patients with adenocarcinoma). Four patients were female and eight were male. The median patient age was 55.5 years (range 36–73 years) at the time of pneumonectomy and 59 years (range 38–82 years) at the time of SBRT. The median interval from pneumonectomy to new tumour was 34 months (range 14–127 months). Tumour characteristics at the time of pneumonectomy and at the time of SBRT are summarized in Table 1. No patient had pathological confirmation of disease because all tumours were located peripherally and, thus, were inaccessible to bronchoscopy. No transthoracic biopsies were attempted because it was considered to be too dangerous owing to the risk of developing a fatal pneumothorax in these single-lung patients. The diagnosis of new lung tumour (recurrent or second primary) was made by a multidisciplinary disease management team and in all patients based on a new ^{18}F-fludeoxyglucose-positron emission tomography (FDG-PET) positive lesion with CT characteristics of malignancy. In this high-risk population, the likelihood of treating a benign lesion with such a presentation is considered <5%.[44–46] All patients were deemed ineligible to undergo repeat surgery because of poor pulmonary reserve. Nine lesions, according to criteria proposed by Martini et al,[3] were scored as metachronous primary Stage I tumour, and three lesions as solitary metastasis because the disease-free interval between cancers was <2 years. The World Health Organisation performance score was one in five patients, two in six patients and three in one patient. The median age-adjusted Charlson score was four (range 0–6). Three patients had previous adjuvant thoracic radiation therapy.

Treatment

Simulation and treatment planning procedures can be briefly described as follows: patients were positioned in a vacuum-formed cradle immobilization device and underwent a thin-slice (1 mm) four-dimensional treatment planning CT scan (Philips Brilliance Big Bore™; Philips Healthcare, Eindhoven, Netherlands), without intravenous contrast medium injection, to characterize tumour motion for target delineation. An internal target volume was derived by delineating the visible gross tumour volume, in lung CT window (level −500 HU, width 1500 HU), reconstructed from four to six respiratory phases. The clinical target volume was defined as equal to the internal target volume. The PTV was obtained by adding a 4- to 5-mm margin in all directions to the CTV. The median PTV was 20.6 cm^3 (range 2.3–101.2 cm^3). In three patients, 7–10 days before the planning CT scan, four gold fiducial markers, under CT guidance, were transcutaneously inserted near the spinal process of vertebrae at appropriately selected levels.

Treatment planning was performed with the Multiplan® Treatment Planning System v. 2.1.0 (Accuray Inc., Sunnyvale, CA). A ray tracing algorithm for dose calculation, with heterogeneity correction, was used for 10 patients and a Monte Carlo dose calculation algorithm was used for 2 patients. Prescriptions were specified at the 75–85% isodose line so that 95% of the prescribed dose covered the PTV. Treatment plans resulted in a median of 117 non-co-planar beams (84–197) using one or two circular collimators.

Treatment was delivered using the CyberKnife® Robotic Radiosurgery System (Accuray Inc., Sunnyvale, CA).[47] All patients were treated with treatment delivery software defined as Fiducial Marker Tracking (three patients) or Xsight® (Accuray Inc.) Spine Tracking (nine patients).[47] This modality of treatment compares in real-time orthogonal X-ray views of gold fiducial markers placed near the spinal process of vertebrae at appropriately selected levels or vertebral skeletal structures located in the nearest area of tumour with digitally reconstructed radiographs that are derived from the treatment planning CT. The difference between the fiducial marker array and skeletal structures' position was reported in three translational and there rotational co-ordinates and corrected for. During treatment, tracking images were obtained for verification every three beams and the patient repositioned if necessary. Each treatment lasted on average 60 min (45–90 min) and was performed as an outpatient procedure. Five patients were treated with a single fraction of 25–26 Gy and seven patients with fractionated schemes (two patients with three fractions of 10 Gy, three patients with four fractions of 10 Gy, one patient with three fractions of 15 Gy and one patient with four fractions of 12 Gy). All radiation schedules were recalculated and expressed as biologically effective dose (BED) assuming α/β ratio of 10 Gy (BED 10) for tumour tissue and 3 Gy (BED 3) for normal tissue.[48] The total dose expressed in BED, as reported in Table 1, allows different dose schedules to be compared.

Radiation doses to the lung parenchyma were reanalysed in order to evaluate a possible correlation with toxicity. The parameters evaluated were the percentage of lung volume that received ≥5 Gy (V_5), ≥7 Gy (V_7), ≥13 Gy (V_{13}), ≥17 Gy (V_{17}) and ≥20 Gy (V_{20}). The subtraction of the PTV was not performed when calculating V_5–V_{20}.

Toxicity assessment, follow-up and statistics

Toxicity was assessed according to the Common Terminology Criteria of Adverse Events v. 4.0. All patients were followed with clinical visit and CT every 3 months during the first year and every 6 months thereafter. FDG-PET scans were obtained only if clinically indicated. The median follow-up was 28 months, and no patients were lost to follow-up.

Table 1. Tumour characteristics, treatment descriptions and follow-up

Patient number	Previous pneumonectomy TNM stage	Initial treatment	New lesion (Ø cm)[a]	Fractions × Gy	BED Gy 10[b]	BED Gy 3[c]	PTV (cm^3)[d]	Local failure	Follow-up
1	T2 N0	P	1	1 × 25 Gy	87.5	233	2.3	20 months	Dead owing to local progression and distant metastases at 32 months
2	T3 N0	P	4.5	3 × 10 Gy	60	130	101.2	10 months	Dead owing to local progression at 25 months
3	T2 N2, T1 N0	Lobectomy, completion P	1.8	1 × 25 Gy	87.5	233	6.4	No	Death owing to regional and distant metastases at 32 months
4	T3 N0	P	3	1 × 25 Gy	87.5	233	24.4	no	Dead owing to distant metastases at 27 months
5	T2 N1	P and post-operative RT	2.2	3 × 10 Gy	60	130	20.5	no	Dead owing to intercurrent disease at 10 months
6	T2 N0	P	1.8	1 × 26 Gy	93	251	7.8	19 months	Dead owing to local progression at 34 months
7	T2 N2	P and post-operative RT	1.8	1 × 25 Gy	87.5	233	20.4	No	Alive without disease at 33 months
8	T2 N0	P	2.8	3 × 15 Gy	112	270	24.6	No	Alive without disease at 31 months
9	T2 N0	P	2.1	4 × 10 Gy	80	173	25.1	No	Alive without disease at 26 months
10	T4 N0	P	3	4 × 10 Gy	80	173	20.9	No	Dead owing to distant metastases at 11 months
11	T2 N2	P and post-operative RT	3.3	4 × 10 Gy	80	173	24.1	No	Alive without disease at 11 months
12	T1 N0, T2 N1	P (synchronous tumour)	2.1	4 × 12 Gy	105.6	240	17.2	No	Alive without disease at 10 months

P, pneumonectomy; PTV, planning target volume; RT, radiotherapy.
[a](Ø cm), greatest tumour dimension.
[b]BED Gy 10, biologically effective dose with assumed α/β ratio of 10 for tumour tissue.
[c]BED Gy 3, biologically effective dose with assumed α/β ratio of 3 for normal tissue.
[d]PTV consists of the tumour volume including all respiratory movements plus a 3- to 5-mm safety margin for RT planning.

Descriptive statistic, *i.e.* proportions, median, mean and range values were used to describe the patient cohort, treatment parameters and observed toxic events. Overall survival, cancer-specific survival, disease-free survival and local control probability were evaluated using Kaplan–Meier analysis. All time intervals were calculated from the last day of the stereotactic radiotherapy. Analyses were performed using SPSS® v. 15.0.0 (IBM Corporation, Armonk, NY; formerly SPSS Inc., Chicago, IL) and Microsoft Office Excel® 2007 (Microsoft Corp., Redmond, WA).

RESULTS

Local control

Clinical outcomes of patients are summarized in Table 1. All patients completed treatment as planned. The first site of recurrence was: local in three patients (number 1, 2 and 6) at 20, 10 and 19 months post-treatment, respectively; regional in one patient (number 3) at 4 months; and distant in two patients (number 4 and 10) at 16 and 3 months, respectively. Of the three patients who developed local recurrence two patients (number 1 and 6) were treated with palliative chemotherapy and one patient (number 2) underwent the second course of stereotactic radiotherapy (single fraction of 10 Gy). Patient number 3 and 10 who had, respectively, mediastinal lymph node failure and distant metastases were treated with chemotherapy. Patient number 4 who developed brain metastases was treated with radiotherapy (stereotactic radiotherapy initially and whole brain irradiation thereafter). The actuarial local control probability at 2 years was 64.5%.

Overall and disease-free survival

Six patients died of disease progression at 11, 25, 27, 32, 32 and 34 months (local: two patients; local and distant: one patient; regional and distant: one patient; and distant: two patients). One patient died of intercurrent disease at 10 months. Five patients are alive and without evidence of disease at 33, 31, 26, 11 and 10 months. The actuarial 2-year disease-free survival, overall and disease-specific survival were 36.1%, 80% and 88.9%, respectively.

Toxicity

None of the patients experienced acute or late thoracic toxicity of grade ≥3 at the median lung parameters of V_5, V_{10} and V_{20} of 23.1% (range 10.7–56.7%), 7.3% (range 2.2–27.2%) and 2.7% (range 0.7–10.9%), respectively. Early side effects were limited to mild fatigue in four patients (Grade 1 in three patients and Grade 2 in one patient) and chest pain in one patient (Grade 1). One patient (number 4) developed symptomatic grade 2 radiation pneumonitis which responded to a short course of steroids. Grade 1 pulmonary fibrosis occurred in four patients (number 4, 5, 7 and 10). Two of those patients received previous radiotherapy to the chest (number 5 and 7). Of the other two patients, one patient (number 4) received a moderately higher lung dose than the rest of the cohort and was suffering from severe diabetes. This may have contributed to her pulmonary toxicity.

No patient required oxygen or had deterioration of performance status during follow-up if not as a result of clinical progression of disease. Pulmonary function tests were not performed during follow-up. The dosimetric analysis of the treatment plans is summarized in Table 2. No correlations between target volume, lung dose and complication rate were possible because of the low rate of adverse effects.

DISCUSSION

Patients successfully treated for their initial NSCLC have a non-negligible risk of developing NPLC or isolated chest recurrence[3–9] that potentially can be managed aggressively by surgery with a reasonable chance of cure.[4,5,7,10,12–14] The long-term survival after the second resection is reported in the range of 18–50% in most series,[10–13] and the surgical mortality rate is reported as "acceptable" and ranging between 0% and 5.8%.[5,12,13] However, optimal management of these patients is affected by a number of factors including the patients' pulmonary reserve, associated medical comorbidity and clinical stage of the second lung cancer. Johnson,[11] in his review, stated that 25% of patients, following a successful resection of their NSCLC, could not undergo surgery for their new lung cancer because of inadequate pulmonary reserve.

Additional resection is even more difficult if previous surgery was pneumonectomy which usually has a significant negative impact on pulmonary reserve. Available data on surgical treatment of the second tumours after pneumonectomy are limited to small series[15–25] or case reports.[26–28] In Table 3, we report data of main series on surgical treatments after pneumonectomy published after 1985. The results appear to demonstrate that limited lung resection is a worthwhile procedure in appropriately selected patients since it carries a relatively low operative risk and allows acceptable long-term control of disease and survival. However, the percentage of patients with a potentially resectable tumour that can tolerate additional resection is not well known. Grodzki et al[23] reported that only 18% of patients with a new lung cancer in the remaining lung after pneumonectomy assessed at Thoracic Surgery Department of Pomerian Medical University, Poland, meet their inclusion criteria for a further pulmonary resection. Donington et al[20] reported that only 3% of patients who had pneumonectomy for lung cancer at Mayo Clinic went on to subsequent resection during a 21-year period but does not report how many patients came back with a metachronous lung cancer and were turned down. Patients reported in surgical series are most likely a selected group that represents only a small proportion of patients with a potentially resectable tumour. The morbidity of surgical treatment in single-lung patients is also not negligible. Donington et al[20] reported that 25% of patients need home oxygen after lung resection. Grodzki et al[23] observed a significant negative impact on pulmonary reserve and a deterioration of the performance status on 56% of patients.

Available data on non-surgical treatment of the second tumour after pneumonectomy are even more limited (Table 4).[41–43,49–53] Sofocleous et al[49] described outcomes and complications of percutaneous thermal ablation in a cohort of 12 patients with a single lung. In these 12 patients, 17 ablations were performed for 13 tumours (9 primary and 4 metastatic) and 4 subsequent local recurrence. The median tumour size was 2.2 cm (1.1–4 cm). The authors observed three deaths (25%) related to treatment, and six patients (50%) required chest tube placement for pneumothorax. 5 (45%) of the 11 evaluable patients showed local tumour progression during follow-up. Hess et al,[50] in their

Table 2. Dosimetric parameters

Patient number	V_5 [a]	V_7 [a]	V_{10} [a]	V_{13} [a]	V_{15} [a]	V_{17} [a]	V_{20} [a]	V_{25} [a]	V_{30} [a]	Dose calculation algorithm
1	11.4	7	4.2	3.1	2.5	2.1	1.6	1	0.1	rt
2	56.7	38.4	27.2	18.8	16.1	12.1	9.8	5.8	1.2	rt
3	14.2	9.4	6.8	5.1	4.2	3.1	2.2	1.1	0.03	rt
4	39.2	26	15.9	11.3	8.8	6.9	4.5	3	0.2	rt
5	16.1	9.1	4.6	3.4	2.9	2.5	1.9	1.1	0.4	rt
6	10.7	5.1	2.2	1.3	1.1	0.9	0.7	0.3	0.03	rt
7	21.1	13.3	7.3	5.3	4.4	3.7	2.7	1.2	0.01	rt
8	23.1	15.7	9.4	6.6	5.4	4.9	3.7	2.8	2.03	rt
9	43	31.4	20	12.9	10	8.2	6.1	3.7	2.1	rt
10	23.1	13.1	7.2	5	3.9	3.1	2.1	1.2	0.7	rt
11	37	29	20	17.1	14.7	13.3	10.9	7.4	5.5	mc
12	26.5	18.1	11.5	8.1	6.6	5.8	4.5	3.3	2.3	mc

mc, Monte Carlo dose calculation algorithm; rt, Ray Tracing dose calculation algorithm.
[a]Vx, the percentage of lung that received a total radiation dose ≥x Gy.

series of 15 patients (16 ablations, 1 patient had 2 ablations), did not report any procedure-related death. Six patients (37%) developed pneumothorax that required chest tube placement and one patient developed lung infection that required prolonged hospitalization. Only one patient showed local progression of the treated lesion, but the follow-up was very short (only seven patients followed at 1 year and three patients at 2 years). Very few data are available on radiation therapy for a new lung tumour arising after pneumonectomy. Results of high-dose conventional radiation therapy are reported by Lagerwaard et al,[51] in a small series of eight patients. Three patients were treated with 50 Gy in 20 fractions followed by endobronchial brachytherapy, one patient with 66 Gy in 33 fractions and four patients with 70 Gy in 28–35 fractions. Of the six valuable patients, two died for local progression, two for distant metastasis and two were alive and without disease at 12 and 18 months. No patient developed grade ≥3 lung toxicity. The limited literature on conventional radiotherapy in these patients may reflect the fear of inducing serious or fatal radiation pneumonitis.

In recent years, SBRT has become a valid treatment alternative in patients with medically inoperable Stage I lung cancer.[29–32] This technique allows excellent local control to be obtained,[33–36] and significant toxicity is uncommon even in patients with severely compromised pulmonary function [predicted percentage forced expiratory volume in 1 second (FEV1) inferior to 40%].[37–40] Indeed, a non-negligible proportion of patients treated with SBRT have worst pulmonary function test results compared with patients treated in the surgical series. The median percentage of FEV1 reported by Terzi et al,[21] Donington et al,[20] and Grodzki et al[23] were 59%, 48% and 63%, respectively. Haasbeek et al[41] described the outcome of 15 patients, with a new lung cancer arising post-pneumonectomy and treated with SBRT. All patients were treated with BED >100 Gy (18–20 Gy × 3 in eight patients, 12 Gy × 5 in four patients and 7.5 Gy × 8 in three patients). At a median follow-up of 16.5 months (range 4–55 months), no patient had local progression, and the disease-free survival and overall survival rates were 91% and 80.8%, respectively. The authors described two episodes of late Grade 3 toxicity (one patient who previously underwent radiation therapy of the mediastinum-developed radiation pneumonitis and a patient who had pre-treatment FEV1 of only 17% of the predicted value required continuous oxygen administration after SBRT). No treatment-related deaths were described. These results have recently been upgraded by Senthi et al,[42] who reported clinical outcomes of 27 patients treated with SBRT (20 patients), hypofractionated radiotherapy (6 patients) or conventional radiotherapy (1 patient). Only one patient had local progression, with a 3-year probability of local relapse and overall survival of 8% and 63%, respectively. Unlike the study by Haasbeek[41], the authors did not report lung toxicity of grade ≥3 in 20 patients treated with SBRT, all with BED ≥100 Gy. Nevertheless, they reported three cases of radiation pneumonitis grade ≥3 (including one that likely contributed to the death of the patient) in patients treated with hypofractionated radiotherapy (60 Gy in 12 fractions). Thompson et al[43] reported the clinical outcome of 13 patients with previous pneumonectomy and treated with SBRT. All but three patients were treated with BED >100 Gy. At a median follow-up of 24 months, the authors did not report local failure, and 3-year overall survival was 36%. Two patients (15.3%) experienced at least Grade 3 lung toxicity including one that likely contributed to the death of the patient.

Our study has many limitations that need to be highlighted. First is the heterogeneity of irradiation schedules. This is mainly due to two reasons: the change in 2009 of our irradiation regimens with the adoption, to the light of the most significant international experiences,[34,54,55] of fractionated prescription instead of the use of schedule in single fraction of 25–26 Gy and the cautious approach owing to the possibility of significant lung

Table 3. Published data of surgical treatment after pneumonectomy

Reference	Number of patients	Median follow-up (months)	Perioperative mortality (number of patients)	Local recurrence (number of patients)	OS, 2 years (months)	OS, 3 years (months)	OS, 5 years (months)	Comment
Kittle et al[15]	15	18	1	3	52[a]	35[a]	35[a]	
Levasseur et al[16]	9	nr	3	nr	17[a]			Only one patient followed at 2 years
Westermann et al[17]	8	16.5	1	2	62[a]	62[a]		Only one patient followed at 2 years
Massard et al[18,b]	4	17	0	0	–	–	–	Two patients alive at 5 and 67 months and two patients dead at 4 and 29 months
Spaggiari et al[19]	13	nr	0	8		46		
Donington et al[20]	24	37	2	nr		61	40	
Terzi et al[21]	14	11.5	0	3		50	37	
Spaggiari et al[22,b]	6	nr	0	nr		53		
Grodzki et al[23]	18	nr	0	nr	61		44	
Vázquez-Pellilo et al[24]	4	33.5	0	0	–	–	–	Two patients alive at 12 and 15 months and two patients dead at 52 and 183 months
Ramírez Gil et al[25,b]	9	20	0	nr	39[a]	19[a]		

nr, not reported; OS, overall survival.
[a]Estimated data.
[b]Letter to editor, only series with at least four patients were included.

Table 4. Published data of non-surgical treatment after pneumonectomy

Reference	Type of treatment	Number of patients	Median follow-up (months)	Treatment-related deaths (number of patients)	Local recurrence (number of patients)	OS, 1 year	OS, 2 years	OS, 3 years	Comment
Sofocleus et al[49]	Thermal ablation	12	23	3	5	89%	59%	30%	
Hess et al[50]	Radiofrequency ablation	15	17.6	0	1		71.4%		Only three patients followed at 2 years
Lagerwaard et al[51]	Conventional radiotherapy	8	18	0	2	82%[a]			No patients followed at 2 years
Senthi et al[42]	SBRT, hypofractionated and conventional radiotherapy	27	39	1[b]	1			63%	In 20 patients treated with SBRT, no lung toxicity ≥ grade 3 was reported
Thompson et al[43]	SBRT	13	24	1[b]	0	69%	61%	36%	
Current study	Stereotactic radiation therapy	12	25	0	3	80%	80%		

OS, overall survival; SBRT, stereotactic body radiation therapy.
[a]Estimated data.
[b]Probable relationship, only series with at least four patients were included.

toxicity. The dose prescription was primarily chosen on the basis of expected tolerance of critical structures and we placed particular attention in maintaining the value of V_{20} <5–7%, when possible. Another limitation, closely related to the previous one, is the total dose used. Although the optimal dose and fractionation schedule for lung cancer SBRT is unknown,[56,57] many authors found improved treatment efficacy for biologically effective doses >100 Gy;[36,54,58–62] however, we treated only two patients with this dose. It should also be stressed that in our experience, the dose was prescribed using the equivalent path-length algorithm in 10 of 12 patients. Several studies[63–65] show that an equivalent path-length (EPL)-based algorithm overestimates the dose delivered to pulmonary targets by 20% on average, compared with dose distributions calculated with more accurate algorithms (Monte Carlo or collapsed cone). This may explain why in the present study the actuarial local control probability at 2 years was only 65.5%. This appear significantly lower than that reported by Senthi et al[42] and Thompson et al[43] and similar to that described by Lagerwaard et al[51] with conventional radiotherapy or by Westermann et al,[17] Spaggiari et al[19] and Terzi et al[21] with surgery or by Sofocleous et al[49] with radiofrequency ablation.

Another limitation of our study is the lack of histological verification in all patients. Obtaining a pre-treatment pathological diagnosis in patients presenting with peripheral lung nodules, suspicious for lung cancer can be challenging, especially for patients with a single lung, as these lesions are often beyond the reach of conventional bronchoscopy. Although the incidence of complication of a diagnostic transthoracic biopsy may be acceptable in fit patients, the risk of clinically relevant or even life-threatening pneumothorax is significant, and even unacceptable, in patients with both emphysema and single lung. However, the risk of inadvertently treating benign disease in patients at high clinical risk of developing lung cancer with a new lesion on CT scans with characteristics of malignancy and a FDG-PET positive lesion is very low (<5%).[44–46] According with recent analysis,[35] we believe that the treatment of frail patients is justified also in the absence of histological diagnosis, if all of the above characteristics are fulfilled and that high-risk diagnostic procedures should be avoided.

We calculated the dose distribution to the remaining single lung for correlation with the observed toxicity, but this analysis was not possible in our series because of the low rate of complication. The only clinically evident lung toxicity was a grade 2 pneumonitis that responded readily to a short course of steroids. The lung dosimetric parameters of this patient (number 4) are reported in Table 2. Haasbeek et al,[41] in their analysis, reported two episodes of Grade 3 lung toxicity. None of the 11 patients with V_{20} <10% (mean value 4.9%, range 1.9–8.2%, values only slightly higher than those of our experience) experienced lung toxicity in contrast with 2 of 4 (50%) treated with higher dose (V_{20} value of 10.7% and 10.2%, respectively). These data were not yet confirmed in a recent revaluation. Senthi et al[42] did not report any significant lung toxicity in 20 patients treated with SBRT and BED >100 Gy. The median V_5, V_{10}, V_{20} and mean lung dose (MLD) were 26.8%, 14.9%, 5.3% and 5.2 Gy, respectively. The authors however reported significant toxicity in a small cohort of patients treated for central tumour with a hypofractionated schedule (5 Gy until 60 Gy, BED 90 Gy).

Three out of four patients treated with this scheme had grade ≥3 toxicity (two patients with grade 3 and one patient with grade 5). In this group of patients, the mean dose parameters were significantly higher than in patients treated with SBRT (V_5 39.1%, V_{10} 30.5%, V_{20} 16%, MLD 10.4 Gy), but similar to those of three patients treated with less aggressive hypofractionated radiotherapy who did not develop lung toxicity. In the experience of Thompson et al,[43] it appears difficult to correlate lung dose–volume histogram (DVH) parameters and the two episodes of toxicity reported. One patient had in fact received higher lung dose (V_5 43%, V_{10} 25%, V_{20} 11%, MLD 8.2 Gy) than the rest of the patients who did not experience toxicity (mean V_5 28%, V_{10} 17%, V_{20} 7%, MLD 5.5 Gy); however, the other patient presented very low lung DVH parameters (V_5 21%, V_{10} 12%, V_{20} 6%, MLD 4.6 Gy).

In other experiences, the patients with single lung were treated with conventionally fractionated radiation schedules and therefore the comparison of outcome in terms of radiation toxicity should be evaluated with caution. Models that predict the incidence of radiation pneumonitis have never been validated for hypofractionated SBRT.[66] Lagerwaard et al,[51] in their series of six patients (two patients were reported as in treatment), did not report grade ≥3 lung toxicity. The mean V_{20} was 24.6% and the MLD was 15.1 Gy. Significant and even fatal toxicity was instead reported with adjuvant radiotherapy after pneumonectomy for mesothelioma.[67–72] The available data of those experiences suggest that perhaps what ultimately determines the risk of pulmonary toxicity is the combination not only of volume of lung exposed to relatively high dose (V_{20}) superimposed on extensive exposure to low-radiation doses (V_5 and V_{10}), but also the amount of lung spared completely from irradiation. The latter may be particularly important when using intensity-modulated radiation therapy with multiple non-co-planar beams. It is worth noting that the importance of the lung volume that receives a dose of 5 Gy has recently been highlighted also in patients treated with SBRT. Ong et al,[73] in a small cohort of patients (18) with large Stage I–II tumours (PTV > 80 cm^3), found that lung V_5 is strongly correlated with the risk of pulmonary toxicity. The risk of severe lung toxicity seems nevertheless low when the dosimetric parameters of V_5, V_{10}, V_{20} and MLD are kept under 60–75%,[69,70] 20–30%,[68,71] 7–8%[68,69,72] and 8.5–9.5 Gy,[68–70] respectively. Only one case of fatal pneumonitis occurred when V_{20} was <6.9 Gy,[68] but in this patient, other dosimetric parameters were high (V_5, V_{10} and MLD equal to 95%, 27% and 8.9 Gy, respectively). Given the overall paucity of data, those parameters should be considered with caution, and it should also be stressed that data from the studies of mesothelioma may not be comparable to studies of NSCLC treatments. However, while being aware of all limitations of the data presented above, it seems reasonable to assume that in some of our patients, we could have used higher doses of radiation maintaining the risk of lung toxicity reasonably low. We recalculated dosimetric lung parameters by prescribing a dose of 51 Gy in 3 fractions (BED 10 = 137.7 Gy) for Patients 5, 7 and 10. All constraints mentioned above were respected (V_5 31.3%, 49.3%, 33.46%, V_{10} 13.5%, 22.4%, 16%, and V_{20} 4.4%, 6.9%, 3.95%, respectively).

CONCLUSION

Our experience shows that SBRT is possible, effective and safe in patients with the second lung cancer after previous pneumonectomy. Despite the paucity and heterogeneity of our data and similar experiences reported in the literature[41–43,51,67–72] related to lung dosimetric parameters (different fractionation schemes and different diseases), it seems reasonable to assume that keeping V_5, V_{10} and V_{20} <50%, <20% and <7%, respectively, and MLD <8 Gy, the risk of significant lung toxicity would be low even in patients with severely compromised pulmonary function. Despite the prognosis likely remaining unfavourable owing to the high risk of distant metastasis or death for intercurrent disease, an analysis of dose–volume histograms shows that biologically equivalent doses >100 Gy, necessary for high local control rate, can be reached while complying with dose constrains for most patients.

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