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Curative radiotherapy for a second primary lung cancer arising after pneumonectomy — techniques and results ☆

Frank J. Lagerwaard, Peter W.J. Voet, Jan P. van Meerbeeck, Sjaak A. Burgers, Suresh Senan*

University Hospital Rotterdam, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands

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Abstract

Background and purpose: Only limited data exist on the outcome of curative radiotherapy in patients who develop a second primary lung tumour after pneumonectomy. The treatment of eight such patients is described.

Materials and methods: The case records of patients who underwent curative radiotherapy for stage I non-small cell lung cancer after a previous pneumonectomy were reviewed. Treatment was delivered using 3D external radiotherapy to a dose of 50–70 Gy, in once-daily fractions of 2–2.5 Gy. An endobronchial brachytherapy boost was used in three patients. Original treatments were re-planned in an attempt to minimize the volume of irradiated lung.

Results: A complete remission was achieved in five (of six) evaluable patients, but two patients subsequently developed a local relapse. All patients survived for a minimum of 1 year after treatment. Only one patient developed significant (grade 2) radiation pneumonitis. When treatments were re-planned to optimize beam arrangements, and when customized blocks were used, the mean lung volume receiving $\geq$20 Gy (calculated for 70 Gy) decreased from 24.6 $\pm$ 4.1 (range, 18–31%) to 17.3 $\pm$ 5.1% (range, 12–26%). Similarly, the radiation conformity index improved from 0.44 $\pm$ 0.11 to 0.61 $\pm$ 0.06.

Conclusions: Involved-field radiotherapy can be curative in patients who develop a new lung tumour after pneumonectomy. Recent advances in defining target volumes, treatment planning and delivery are likely to improve upon these results.

Keywords: Lung cancer; Second primary; Conformal radiotherapy; Pneumonectomy

1. Introduction

Patients who are successfully treated for non-small cell lung cancer (NSCLC) have a 2–5% annual risk for developing a second primary lung cancer [2,12,21]. The criteria for differentiating second primary lung tumours from metastatic disease have been described by Martini et al. [11]. These include a separate histology and, when a similar histology is found, a disease-free interval of 2 years between cancers, or an origin from carcinoma in situ, or a second cancer in a different lobe or lung, without extrapulmonary metastases or carcinoma in the lymphatics common to both lesions. If patients have undergone a pneumonectomy for their initial tumour and when lung function does not permit further surgery, the risk of toxicity is often considered a contraindication for curative radiotherapy (RT). In recent years, small series have been described of patients who have undergone limited surgical resections after an earlier pneumonectomy [9,13,16,17,22]. However, as surgical resection on the remaining lung can be associated with considerable morbidity and mortality, only conservative resections are recommended [16].

The reluctance to perform curative RT in this situation may explain the limited literature available on this topic. However, RT can be a useful alternative for patients with stage I NSCLC in whom surgery is contraindicated. We describe our experience in eight patients who developed a second primary lung tumour after pneumonectomy, and who were treated with curative intent using either external-beam radiotherapy (EBRT) alone, or in combination with endobronchial brachytherapy. The treatment plans of all eight patients were re-analyzed.

2. Materials and methods

The medical records of all patients with stage I NSCLC who were treated with curative EBRT since the introduction of 3D conformal radiotherapy (3D-CRT) at our institution in

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* Corresponding author.

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Table 1
Patient and tumour characteristics

	Sex	Age	Initial stage	Initial histology	Interval to new primary (years)	Stage – new primary[a]	Location – new primary[b]	Histology – new primary
1	M	63	T1N0M0	Squamous	12	T2	RUL	Adeno
			T1N0M0	Adeno	6.5			
2	M	72	T1N1M0	Squamous	3	T1	RUL	Unknown
3	M	60	T2N1M0	Squamous	2	T1	LUL	Squamous
4	M	55	T1N1M0	Adeno	2	T1	RUL	Unknown
5	M	65	T2N0M0	Squamous	1	T1	RUL	Unknown
6	M	69	Unknown	Unknown	27	T2	LUL	Adeno (FDG +)
7	F	56	T1N1M0	Squamous	8	T1	LUL	Unknown (FDG +)
8	M	56	T1N1M0	Squamous	12	T1	RUL	Squamous (FDG +)

[a] All patients had N0M0 disease.
[b] RUL, right upper lobe; LUL, left upper lobe; FDG, Fluorodeoxyglucose.

1992 were analyzed. Eight patients who underwent curative RT for stage I NSCLC after a previous pneumonectomy were identified. The clinical details are summarized in Table 1. All lesions were located in the upper lobes. The lesions in all but one patient fulfilled the criteria for metachronous primary tumours [11]. The treated lesion was the second tumour in seven patients, and the third primary lung cancer in another patient. All patients were staged using at least a bronchoscopy and computed tomography (CT) scan of the chest and abdomen. Radionuclide bone scans and ultrasound investigation of the liver were performed if indicated. Pulmonary function tests were performed before the start of treatment, and in four patients, at 6–12 months after RT. Fluorodeoxyglucose (FDG) scans using a coincidence mode, dual-head gamma camera were performed for the last three patients.

The original treatment consisted of 3D-CRT (50–70 Gy in 2–2.5 Gy/fraction) using two or three co-planar photon beams (Table 2). At our institution, the planning target volume (PTV) for upper lobe lesions is derived by adding a symmetric margin of 10 mm to the contoured gross tumour volume (GTV). Brachytherapy was used as a boost in three patients with endobronchial tumour extension. In cases of the latter, one or two fractions of 5–8 Gy were prescribed to the bronchial wall as previously described [14]. Elective irradiation of hilar/mediastinal nodes is not performed for stage I NSCLC at our centre. In a patient with a poorly defined tumour located in an area of extensive fibrosis, the treatment portals were reduced after 46 Gy. All fields were irradiated using the multileaf collimator of the MM-50 Scanditronix Microtron (leaf width, 1.25 cm/0.5 inch) and all treatment plans fulfilled the ICRU-50 criteria.

Follow-up data on response, survival and toxicity were obtained from the case records. Response after EBRT was evaluated in accordance with the recommendations of Green et al. [6], and survival was measured from the initiation of treatment. Acute radiation pneumonitis was classified according to the Southwest Oncology Group (SWOG) toxicity criteria which define: grade I (mild) toxicity when radiographic (chest X-ray or CT scan) changes appear and clinical symptoms exist, but do not require steroids; grade 2 (moderate) toxicity when steroids are required; grade 3 (severe) toxicity when oxygen is needed; grade 4 (life-threatening) toxicity when assisted ventilation is necessary; and grade 5 toxicity when radiation pneumonitis is fatal.

In order to evaluate the feasibility of high-dose EBRT alone in such patients, a dosimetric analysis was performed to study the consequences of treating all patients to a total dose of 70 Gy, using the original treatment plan. The original plans were then compared with the results obtained with optimized beam configuration and customized blocking. The following parameters were evaluated: mean lung dose, the volume of lung tissue receiving a dose of $\geq$20 Gy after the PTV has been subtracted, i.e. V_{20} [5], and the

Table 2
Treatment and outcome[a]

Pt	FEV_1 (% predicted)	Treatment	Response	Outcome
1	1.84 (50)	EBRT 70 Gy/35 fx	CR	Dead due to distant metastasis at 12 months, no local failure
2	1.56 (48)	EBRT 66 Gy/33 fx	CR	Dead due to metastatic rectal cancer at 19 months, no local failure
3	1.81 (61)	EBRT 50 Gy/20 fx; EB 2 × 8 Gy	CR	Alive without disease at 12 months
4	2.31 (57)	EBRT 70 Gy/35 fx	CR	Dead due to local progression after 22 months
5	1.26 (39)	EBRT 70 Gy/28 fx	CR	Alive without disease at 18 months.
6	0.92 (28)	EBRT 50 Gy/20 fx; EB 1 × 5 Gy	PR	Dead due to local progression and distant metastases after 19 months
7	1.63 (60)	EBRT 70 Gy/28 fx	–	Undergoing treatment
8	0.86 (26)	EBRT 50 Gy/20 fx; EB 2 × 7.5 Gy	–	Undergoing treatment

[a] FEV_1, forced expiratory volume in 1 s; EB, endobronchial brachytherapy; fx, fractions; CR, complete remission; PR, partial remission.

radiation conformity index, which is the PTV divided by the volume receiving 95% of the prescribed dose.

3. Results

3.1. Clinical results

Six patients have been followed-up for more than 1 year and two are currently undergoing treatment. Radiological follow-up showed complete responses in five out of six evaluable patients and a partial remission in one patient. Two patients (patients 4 and 6) developed a local recurrence at 18 and 12 months post-treatment, respectively. Four patients died at 12, 19, 19 and 22 months, and two patients are alive without evidence of disease at 12 and 18 months after treatment (Table 2). One patient (patient 5) developed symptomatic grade 2 radiation pneumonitis which responded to a course of steroids. A patient (patient 6) with a prior history of cardiac disease developed cardiac ischemia during his second therapeutic bronchoscopy procedure, and did not receive the planned second brachytherapy fraction.

Pulmonary function tests were not routinely performed during follow-up, but post-treatment tests were available for four patients at 3 (patient 6) and 12 months (patients 3, 4 and 5). Patient 6 had similar forced expiratory volume in 1 s (FEV_1) values before, and at 3 months post-treatment. At 1 year after treatment, decreases in the FEV_1 to 94, 90 and 76% of the pre-treatment values were observed for patients 3, 4 and 5, respectively.

3.2. Dosimetric analysis

The dosimetric analysis of the original and optimized treatment plans is summarized in Table 3. The mean V_{20} of the original treatment plans (calculated for 70 Gy) was 24.6 ± 4.1% (range, 18–31%). Although the original treatment had been planned by dedicated dosimetrists, improvements in beam arrangement were achieved for all patients (see example in Fig. 1).

Beam optimization alone resulted in a reduction of the mean V_{20} to 19.6 ± 5.1% (range, 14–27%). When planned using customized blocks, instead of the multileaf collimators which were routinely used, the V_{20} was further reduced to 17.3 ± 5.1% (range, 12–26%). Similarly, this optimization reduced the mean lung dose from 15.1 ± 2.6 to 12.0 ± 3.3 Gy, and improved the radiation conformity index from 0.44 ± 0.11 to 0.61 ± 0.06.

4. Discussion

Following treatment for primary lung cancer, criteria have been proposed in order to distinguish second primary lung carcinomas from recurrences [11]. Advances in molecular genetic analysis can also enable a new tumour to be distinguished from a recurrence [15], but none of our patients were analyzed in this manner. A lobectomy is the treatment of choice for peripheral stage I NSCLC, as more conservative resections such as wedge resections result in a significantly higher rate of local recurrence, i.e. 7 versus 17% [10]. Spaggiari et al. [16] reviewed the published literature on surgery on the remaining lung following a pneumonectomy, and described 16 cases of their own. In contrast to the 15% incidence of postoperative mortality reported in the literature, Spaggiari et al. encountered low morbidity and mortality when performing limited resections, such as wedge resection or segmentectomy. However, limited surgery was associated with a 46% incidence of local recurrence in these patients.

Surgery may not be an option for second lung primaries due to the size, location, or cardio-respiratory status. It has been suggested that diagnoses of N2/3 disease in the initial primary tumour or proximal bronchial involvement of the second primary, which could indicate the need for more than a segmentectomy, are contraindications to surgery [16]. The same authors required the following cardio-respiratory criteria as prerequisites for surgery: a preoperative FEV_1 of greater than 40% and an estimated postoperative FEV_1

Table 3
Comparison of treatment planning parameters for original and optimized plans[a,b]

Pt	Planning parameters	Original treatment	Optimized treatment
1	V20 (%)	27	12
	Mean lung dose (Gy)	15.5	8.9
	Conformity index	0.36	0.56
2	V20 (%)	24	16
	Mean lung dose (Gy)	11.8	9.2
	Conformity index	0.38	0.57
3	V20 (%)	21	12
	Mean lung dose (Gy)	13.1	8.6
	Conformity index	0.28	0.62
4	V20 (%)	31	23
	Mean lung dose (Gy)	20.2	16.9
	Conformity index	0.53	0.63
5	V20 (%)	23	19
	Mean lung dose (Gy)	15.7	13.9
	Conformity index	0.43[c]	0.63[c]
		0.56[d]	0.71[d]
6	V20 (%)	25	16
	Mean lung dose (Gy)	13.9	10.5
	Conformity index	0.34	0.56
7	V20 (%)	18	14
	Mean lung dose (Gy)	13.8	12.3
	Conformity index	0.50	0.57
8	V20 (%)	28	26
	Mean lung dose (Gy)	17.1	15.9
	Conformity index	0.58	0.67
Mean	V20 (%)	24.6 ± 4.1	17.3 ± 5.1
	Mean lung dose (Gy)	15.1 ± 2.6	12.0 ± 3.3
	Conformity index	0.44 ± 0.11	0.61 ± 0.06

[a] All treatment plans were calculated for 70 Gy.
[b] Conformity index = PTV/V95.
[c] Large fields.
[d] Small fields.

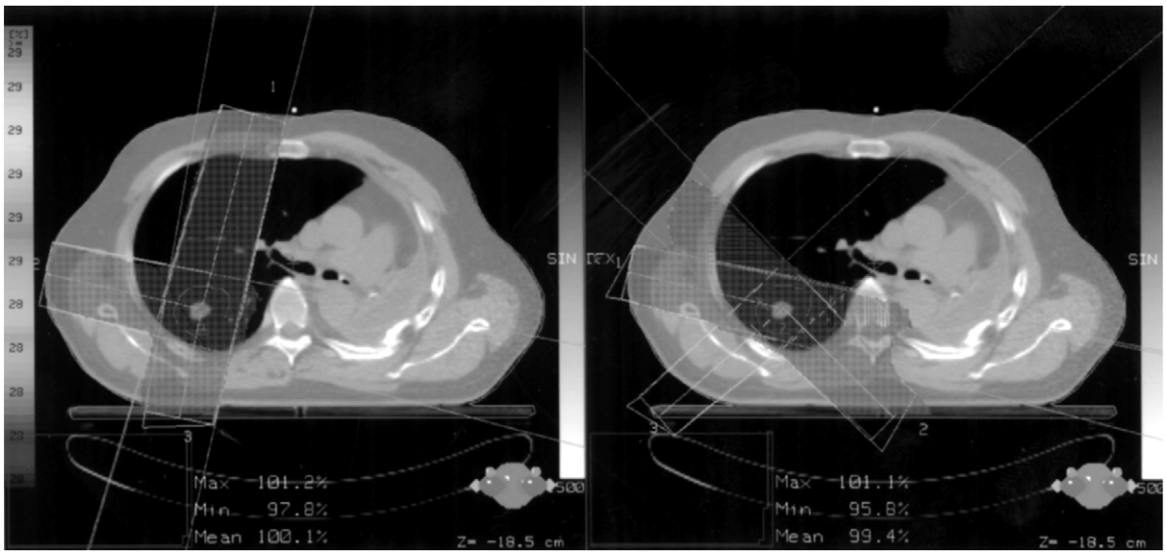

Fig. 1. Figures showing the shaded lung volume which receives 20 Gy (V_{20}). With optimization of the beams (right), the V_{20} is limited to the region of the tumour.

of above 30% of the predicted value, perfusion defect(s) which are limited to the area of the planned lung resection, and absence of echocardiographic signs of pulmonary hypertension. Relatively few patients are likely to fulfil all of the above criteria after pneumonectomy.

High-dose 3D-CRT would appear to be an attractive alternative for these patients as the survival is relatively poor after limited surgery. The limited literature on curative RT for these patients may reflect the fear of inducing serious or fatal radiation pneumonitis. Our experience shows that high-dose RT, either using EBRT as a single modality, or a combination of EBRT and brachytherapy can lead to prolonged local control with only minor toxicity, in patients who would otherwise be considered untreatable. However, the low incidence of radiation pneumonitis in our patients may be due to tumour location (all patients had upper lobe lesions), and partly the result of our policy of omitting elective irradiation of hilar and/or mediastinal nodes. The incidence of radiation pneumonitis is higher for lesions located in the lower than in the upper lobes of the lung in both animal models [19] and patients [5,23]. Isolated nodal relapse is uncommon in patients with stage I tumours who are treated using 'involved-field' RT [8]. Furthermore, FDG scans can improve the non-invasive staging of regional nodal disease in stage I NSCLC [3,4], and also exclude distant metastases, which would otherwise have remained undetected [7].

The incidence of radiation pneumonitis correlates with V_{20}, and grade 2 (or higher) pneumonitis was not observed in patients whose V_{20} was 22% or lower [5]. Furthermore, even modest gains in dosimetry may be important in patients who have marginal lung function, as an annual decline in FEV_1 of 0.05 l has been reported in patients with chronic obstructive airway disease [18]. With improved treatment planning, a reduction in mean V_{20} values from 24.6 to 17.3% was achieved in our patients. In particular, improvements were obtained when the beams were directed through the pneumonectomy cavity in tumours which were located adjacent to the mediastinum. The use of customized blocking instead of multileaf collimation allowed for a further (mean) reduction of 3% in the V_{20}. Recent advancements in radiation treatment delivery, such as the implementation of set-up-correction protocols at the treatment unit, can reduce the margins needed to derive the PTV from the CTV, thereby further lowering the V_{20} [1]. In order to minimize the risk of geometric errors arising from tumour movements which are not captured on rapid spiral planning CT scans, we recently implemented a technique of slow CT scanning (CT revolution time, 4 s/slice) for patients with stage I NSCLC [20]. These studies have shown that slow CT scans generate larger, and more reproducible, target volumes than were captured using spiral CT scans. However, slow CT scans were only used for planning the treatment of patient 8.

5. Conclusions

Our experience shows that curative RT is possible in patients who present with a new stage I NSCLC after earlier pneumonectomy. However, patients should first undergo careful screening in order to justify involved-field RT. The application of advanced planning and delivery techniques, with optimized beam arrangement and customized shielding, can further improve upon these results.

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