Effectiveness of Stereotactic Body Radiotherapy in the Treatment of Inoperable Early-stage Lung Cancer

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Abstract. *Background: Non-small cell lung cancer (NSCLC) is the leading cause of cancer death worldwide. Stereotactic body irradiation offers a non-invasive treatment modality for patients with early stage NSCLC who are not amenable to surgery or other invasive approaches because of their poor medical condition. Patients and Methods: Forty-three inoperable patients with NSCLC were treated with SBRT at our institution. A mean total dose of 30.5 Gy in 1-4 fractions was applied. The median follow-up duration was 14 months (range 6-36 months). Results: The actuarial survival at two years was 53%: two patients died from cancer progression whereas a further 8 patients died from comorbidities. Acute toxicity was practically absent, with 7 (16.3%) patients suffering from grade 1 symptoms and two from (4.6%) grade II effects. At the time of this report, only 1 patient had grade II and 6 patients (13.9%) grade I chronic symptoms. Conclusion: Our results compare favourably with recently published studies and confirm that stereotactic radiotherapy has the potential to produce high local control rates with a low risk of lung toxicity in patients not amenable to curative resection. The low grade of side-effects is encouraging for shortening the treatment using a greater dose per fraction.*

Lung cancer is the most commonly occurring cancer and the most common cancer-related cause of death among men and women (1, 2). It has a poorer prognosis than breast, prostate and colon cancer, with an overall relative 5-year survival rate no higher than 5% to 15% (3). Several attempts have been made to improve outcome, in particular in the detection of initial stage of the tumor, increasing the possibility of cure.

Currently the standard management of early stage non-small cell lung cancer (NSCLC) is surgical resection, with a 5-year survival rate ranging from 60% to 70% in stage IA and about 50% in stage IB (4-6). The surgical procedure consists of lobectomy or pneumonectomy with lymphadenectomy, allowing a radical treatment of the tumor. Other limited resections do not produce the same results in terms of local recurrences and distant metastases (7).

Unfortunately in certain instances, surgical resection cannot be performed due to the patient being unable to endure the procedure. This is mainly related to reduced respiratory function or older age, but also to cardiac disease and several other comorbidities; other patients refuse surgery for personal reasons. For these patients, conventionally fractionated radiotherapy with doses of 45-66 Gy in 1.8-2 Gy fractions used to be the best treatment of choice. However, results following these conventional schedules are disappointing, with survival rates of 15%-27% 5 years after treatment (8-11), probably because these relatively large RT fields represent a crucial issue for patients with such a poor pulmonary reserve. Thus it is becoming more and more important to define optimal radiotherapeutic regimens for these patients.

It is well-known that hypofractionated radiation therapy may overcome repopulation in rapidly proliferating tumors such as NSCLC. Nowadays the development of innovative treatment techniques to ensure a very high level of dose-sparing to crucial normal tissue is making the use of hypofractionated radiotherapy more realistic, although a careful evaluation of acute and late toxicity is still essential. The escalation of the radiation dose can be achieved easily with stereotactic body radiotherapy (SBRT), where the gross tumor volume with a small margin is treated with one or a few large radiation fractions, mostly by the use of dynamic arcs. In the past three years there have been several studies evaluating the role of SBRT for the treatment of Stage I

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NSCLC in patients who are otherwise inoperable, with 2- to 3-year overall survival ranging from 32% to 83% (12).

Here we report our experience with SBRT and the results in terms of local control and the disease-free period.

Patients and Methods

Patient selection. From January 2004 to January 2006, patients with NSCLC Stage T1–2-N0M0 judged medically inoperable by a multidisciplinary team of thoracic surgeons and pulmonologists entered the SBRT study.

Patients were excluded from SBRT if the tumor diameter exceeded 5.5 cm or if there was central growth with tumor extension close (<2 cm) to the trachea, main bronchus or oesophagus. Patients who had prior chemotherapy were excluded.

Since histological confirmation was often difficult to obtain due to the poor patient condition, CT scans combined with positive PET (SUV ≥5) were considered sufficient for treatment acceptance. PET confirmed no lymph node involvement. All patients provided an informed consent.

Radiotherapy. The fractionation schedule applied in this study was 32 Gy in 4 fractions; thereafter this radiotherapy regimen was modified according to the lung function parameters, size and location of the tumor (Table I). The clinical target volume was the gross tumor volume seen with the CT scan.

For every patient, a personalized immobilization system with a vacuum lock and/or a thermoplastic mask was used. A virtual simulation procedure and 3D line stereotatic body frame localization system were used to check the simulation procedure accuracy. No significant differences within parameters were observed. The target contouring was performed taking into account internal organ motion. In particular, a total 1 cm in lateral and antero-posterior direction margins were used while a 1.5 cm margin in cranio-caudal direction from the gross tumor volume to the irradiated tumor volume was used. A setup made of four or more dynamic arcs was chosen with a 3Dline micro Multi Leaf Collimator device (3Dline Medical Systems, Milan, Italy) and the Ergo TPS software (3Dline Medical Systems, Milan, Italy). The dose conformation was evaluated slice-by-slice and using a dose volume histogram between competitor plans.

Follow-up. The clinical follow-up was conducted 45 days and every 3 months after treatment using CT scans according to the WHO criteria (13). Spirometry was performed every 6 months from treatment.

Tumor response was defined as follows: 1: Complete remission (CR): no sign of tumor in CT scan and/or PET; 2: Partial remission /reduction of at least 50% (PR>50%) or of less than 50% in tumor volume (PR<50%) in CT scan and/or reduced uptake in PET; 3: Stability (ST): no change in tumor volume in CT scan and/or reduced uptake in PET; 4: Local progression (LC): increase of tumor volume of more than 25% in volume in CT scan and/or increased uptake in PET; 5: Distant progression/metastasis (M) in locoregional lymph nodes or in distant sites proven by CT scan and/or PET.

Toxicity to normal tissues was defined according to RTOG/EORTC criteria (14) during treatment up to 3 months (acute toxicity) after radiotherapy and after 3 months (late toxicity), with grading from 0 to 4 (Tables II and III).

Table I. *Stereotactic body radiation therapy schedules used.*

Number of lesions	Total dose (D)	Number of fractions	Dose per fraction (d)	BED (a/b=3)	BED (a/b=10)
41	32 Gy	4	8 Gy	117.3	57.6
1	28 Gy	4	7 Gy	93.3	47.6
1	20 Gy	2	10 Gy	86.6	40

BED: biological effective dose.

Statistics. The Kaplan-Meier method was used for survival evaluations. Log-rank statistics were used to test for differences in survival between groups; a p-value <0.05 was considered statistically significant The follow-up duration was defined as the time from the date of completion of SBRT to the last date of follow-up for surviving patients or to the date of death.

Results

Patients. Forty-three patients, 9 female and 34 male, with a mean age of 75.3 years (range 52-90 years), were treated in our Institution with SBRT. Patient and tumor characteristics are summarized in Table IV. Twenty-four patients were judged inoperable due to being affected by chronic obstructive pulmonary disease (mean FEV1: 1.07 L) whereas the remainder were excluded on the basis of age and/or cardiovascular disease. All patients were in ECOG performance status ≤2. Twenty-nine patients (67.4%) had stage IA and the remaining 14 had stage IB lung cancer. The diagnosis revealed 9 patients with adenocarcinoma, 12 with squamous cell carcinoma, 5 with bronchioalveolar carcinoma, 14 with NSCLC, 1 with mixed neoplasia and 2 had no confirmed diagnosis. In the latter group, the indication was made on the basis of a combination of CT and PET scan (SUV max >5). The average size of the lesions was 30.2 mm (median 30 mm, range 15-55 mm) (Figure 1) and the average percentage tumor volume compared to omolateral lung volume was 7% (median 5.2%; range 0.8-21.1%).

Tumor response. The follow-up at the time of analysis was a median of 14 months (range 6-36 months) and no patient was lost to follow-up. Actuarial survival at 1 year was 93%±5% and at 2 years was 53%±11%: 2 patients died 8 and 16 months respectively after treatment for distant disease progression, while a further 8 patients died from causes other than lung cancer. The follow-up showed that the proportion of progression-free patients after the 1st year was 70%, whereas after the 2nd year it was 40% (Figure 2).

There was no significant difference in the response rate between patients with stage I and those with stage II disease (p=0.865). In addition, no significant differences were seen between the overall survival curves of our patients grouped for gender (p=0.158), for tumor diameter (p=0.39) or for

Table II. *Radiation Therapy Oncology Group - Acute Radiation Morbidity Scoring Criteria – Lung.*

Grade				
0	1	2	3	4
No change	Mild symptoms of dry cough or dyspnea on exertion	Persistent cough requiring narcotic, antitussive agents; dyspnea with minimal effort but not at rest	Severe cough unresponsive to narcotic antitussive agents or dyspnea at rest; clinical or radiologic evidence of acute pneumonitis; intermittent oxygen or steroids may be required	Severe respiratory insufficiency; continuous oxygen or assisted ventilation
34 patients	7 patients	2 patients	None	None

Table III. *Radiation Therapy Oncology Group - Late Radiation Morbidity Scoring Criteria – Lung.*

Grade					
0	1	2	3	4	5
None	Asymptomatic or mild symptoms (dry cough). Slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough). Low grade fever. Patchy radiographic appearances.	Severe symptomatic fibrosis or pneumonitis Dense radiographic changes.	Severe respiratory insufficiency/ continuous O_2/ assisted ventilation.	Death directly related to radiation late effects
36 patients	6 patients	1 patient	None	None	None

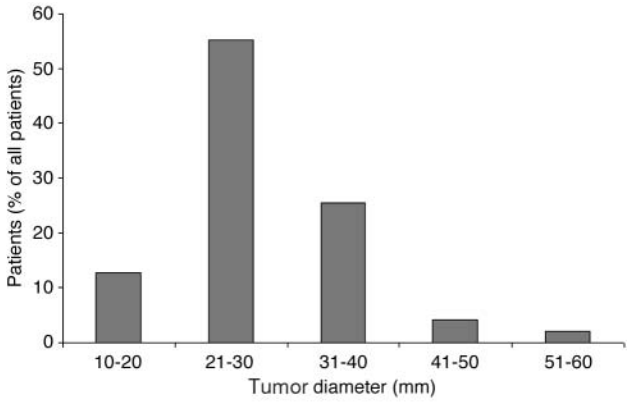

Figure 1. *Tumor diameter (mm) distribution among patients treated with stereotactic body radiotherapy.*

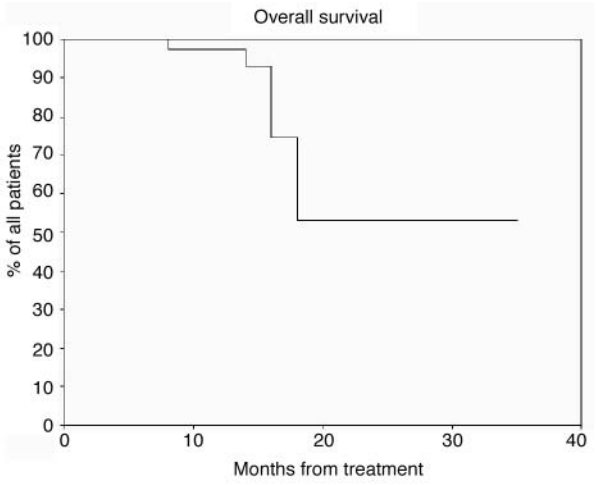

Figure 2. *Overall and progression-free survival curves at 6-36 months (median 14 months) after treatment in 43 patients treated with stereotactic body radiotherapy.*

the percentage of the volume irradiated (ITV) with respect to the omolateral lung volume. Although it was not possible to find any correlation with the patients' age ($p=0.065$) there was a trend to a negative outcome for elderly patients with a cut-off at 75 years of age (Table V).

Normal tissue toxicity. The acute toxicity was very mild since only 9 patients (20.9%) showed grade I or grade II early toxicity according to RTOG. Concerning late toxicity, the results were even better: 6 patients had grade I symptoms and no clinically significant chronic lung fibrosis or esophageal damage was found in any of the patients (Tables II and III).

Table IV. *Patient and tumor characteristics.*

Age (years)	
Average	75.3
Median	75.5
Range	52-90
Male/female	34/9 (79%/21%)
Pretreatment FEV1	
Mean	1.07L (44%)
Range	0.86L-1.40L (36%-53%)
Performance status (ECOG)	
0	29 (20.9%)
1	9 (67.4%)
2	5 (11.6%)
3	0
4	0
Histology	
ADN	9 (20.9%)
Squamous cell carcinoma	12 (27.9%)
BA	5 (11.6%)
NSCLC	14 (32.6%)
Mixed	1 (2.4%)
No diagnosis	2 (4.6%)
T-stage	
IA	29 (67.4%)
IB	14 (32.5%)
Tumor diameter	
Mean	30.1 mm
Range	1.5-5.5 mm
GTV (cm^3)	
Mean	29.3
Range	17.2
Tumor localization	
Right upper lobe	18 (39.1%)
lower lobe	8 (17.3%)
hilum	2 (4.3%)
Left upper lobe	11 (23.8%)
lower lobe	4 (8.7%)
hilum	3 (6.8 %)

NSCLC: non-small cell lung cancer; ADN: adenocarcinoma; BA: bronchioalveolar carcinoma; PET: position emission tomography; CT: computed tomography.

Table V. *Prognostic factors related to disease progression survival.*

Factor	Group 1	Group 2	*p*
Tumour diameter	<30 mm (n=19)	≥30 mm (n=28)	0.39
Age (y)	<75 (n=22)	>75 (n=21)	0.06
Gender	Female (n=9)	Male (n=34)	0.16
Tumour stage	T1 (n=29)	T2 (n=14)	0.86

Discussion

The number of patients with early stage NSCLC is going to rise due to the increase in screening programs for lung cancer. The treatment of choice for early stage NSCLC is surgery with an overall survival rate after 5 years of 60-70% (4-6). Unfortunately, a large proportion of patients with lung cancer are not amenable to surgery because of co-morbidities. For this subgroup of patients radiotherapy remains the only reasonable treatment but data from conventional fractionated radiotherapy (45-60 Gy in 1.8-2 Gy-fractions) are not encouraging so far with survival rates at 5 years of only 10%-30% (8-11, 15).

Dose escalation studies have recorded improved local control with increasing dose (16) for inoperable NSCLC patients. Nowadays the clinical application of modern radiotherapy technology can ensure accurate targeting with minimized delivery of doses to normal tissues. In particular, SBRT offers a very effective treatment option for rapidly proliferating tumors such as NSCLC where the shortening of the overall treatment time with respect to standard fractionation might increase the tumor control probability (TCP). Moreover, this short regimen, requiring half of the number of hospital visits, is very convenient for sick/elderly patients since it is not invasive and thus does not require either anaesthesia or hospitalization and reduces costs. In addition, the reduction of the treatment time prevents interruptions due to either technical inconveniences or to high-grade toxicity.

Historically, radiation fields for inoperable NSCLC have involved the tumor as well as ipsilateral hilar and mediastinal lymph nodes. However, patients, particularly those with a poor pulmonary reserve, may have difficulties with these relatively large RT fields (17) and previous studies indicated that elective regional nodal irradiation is not required to achieve good disease control (18). Nevertheless, it is important to exclude mediastinal lymph node metastases with PET and CT. Another favourable point for this regimen comes from the radiobiological observation that the decrease of overall treatment time to less than one week compared to more than 6 weeks for conventional protocols prevents repopulation of tumor cells during radiotherapy increasing local control rates.

Published data from other centres, and in particular the results from a huge Japanese cohort reported by Onishi *et al.* (19), indicated a biological effective dose (BED) ≥100 Gy as optimal to achieve good tumor control with mild normal tissue toxicity. The BED value calculated using the linear quadratic model with an α/β of 10 Gy for the protocol used in the present study is 117.3 Gy (Table I).

Our results, with 53% as overall survival at 2 years, compare favourably with published data from other series for SBRT where 2- to 3-year survival ranges from 32% to 83% (20-23). Indeed, considering overall survival data, one has to be aware of the fact that these are patients with high age, co-morbid diseases and thus poor in general physical condition. At two years from SBRT, most patients from our cohort (18%) died from causes other than lung cancer,

such as exacerbation of severe chronic obstructive lung disease or heart failure.

One of the major concerns with the use of a hypofractionated radiation regimen is toxicity. In our experience, acute symptoms were minimal and to date even the late toxicity in our cohort was negligible since no patient suffered from severe effects. Thus SBRT might be considered a safe curative treatment for inoperable NCSLC patients.

In conclusion, our experience gives further support to the application of SBRT as an effective treatment option with high local control rates and low toxicity for inoperable patients with early stage lung cancer. Additionally, the very low toxicity observed in these studies encourages us to optimize the fractionation schedule for inoperable NSCLC by increasing the dose per fraction.

References

1 Little AG, Gay EG, Gaspar LE and Stewart AK: National survey of non-small cell lung cancer in the United States: Epidemiology, pathology and patterns of care. Lung Cancer *57*: 253-260, 2007.

2 Howe HL, Wu X, Ries LA, Cokkinides V, Ahmed F, Jemal A, Miller B, Williams M, Ward E, Wingo PA, Ramirez A and Edwards BK: Annual report to the nation on the status of cancer, 1975-2003, featuring cancer among U.S. Hispanic/Latino populations. Cancer *107*: 1711-1742, 2006.

3 Gregor A, Thomson CS, Brewster DH, Stroner PL, Davidson J, Fergusson RJ, Milroy R, Scottish Cancer Trials Lung Group and Scottish Cancer Therapy Network: Management and survival of patients with lung cancer in Scotland diagnosed in 1995: results of a national population based study. Thorax *56*: 212-217, 2001.

4 Mountain CF: A new international staging system for lung cancer. Chest *89*: 225S-233S, 1986.

5 Naruke T, Goya T, Tsuchiya R and Suemasu K: Prognosis and survival in resected lung carcinoma based on the new international staging system. J Thorac Cardiovasc Surg *96*: 440-447, 1988.

6 Adebonojo SA, Bowser AN, Moritz DM and Corcoran PC: Impact of revised stage classification of lung cancer on survival. Chest *115*: 1507-1513, 1999.

7 Chang MY and Sugarbaker DL: Surgery for early stage non-small cell lung cancer. Semin Surg Oncol *21*: 74-84, 2003.

8 Coy P and Kenelly GM: The role of curative radiotherapy in the treatment of lung cancer. Cancer *45*: 698, 1980.

9 Armstrong JG and Minsky BD: Radiation therapy for medically inoperable stage and 11 non-small cell lung cancer. Cancer Treat Rev *16*: 247, 1989.

10 Haffty BG, Goldberg NB, Gerstley J, Fischer DB and Peschel RE: Results of radical radiation therapy in clinical stage I, technically operable non-small cell lung cancer. Int J Radiat Oncol Biol Phys *15*: 69-73, 1988.

11 Dosoretz DE, Katin MJ, Blitzer PH, Rubenstein JH, Salenius S, Rashid M, Dosani RA, Mestas G, Siegel AD and Chadha TT: Radiation therapy in the management of medically inoperable carcinoma of the lung: results and implications for future treatment strategies. Int J Radiat Oncol Biol Phys *24*: 3-9, 1992.

12 Beitler JJ, Badine EA, el-Sayah D, Makara D, Friscia P, Silverman P and Terjanian T: Stereotactic body radiation therapy for nonmetastatic lung cancer: an analysis of 75 patients treated over 5 years. Int J Rad Oncol Biol Phys *65*: 100-106, 2006.

13 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC and Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst *92*: 205-216, 2000.

14 Trotti A, Byhardt R, Stetz J, Gwede C, Corn B, Fu K, Gunderson L, McCormick B, Morrisintegral M, Rich T, Shipley W and Curran W: Common toxicity criteria: version 2.0. an improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. Int J Radiat Oncol Biol Phys *47*: 13-47, 2000.

15 Kaskowitz L, Graham MV, Emami B, Halverson KJ and Rush C: Radiation therapy alone for stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys *27*: 517-523, 1993.

16 McGarry RC, Papiez L, Williams M, Whitford T and Timmerman RD: Stereotactic body radiation therapy of early-stage non-small-cell lung carcinoma: Phase I study. Int J Radiat Oncol Biol Phys *63*: 1010-1015, 2005.

17 Curran WJ Jr, Moldofsky PJ and Solin LJ: Analysis of the influence of elective nodal irradiation on postirradiation pulmonary function. Cancer *65*: 2488-2493, 1990.

18 Krol AD, Aussems P, Noordijk EM, Hermans J and Leer JW: Local irradiation alone for peripheral stage I lung cancer: could we omit the elective regional nodal irradiation? Int J Radiat Oncol Biol Phys *40*: 149-154, 1998.

19 Onishi H, Araki T and Shirato H: Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: Clinical outcome in 245 patients in a Japanese multiinstitutional study. Cancer *101*: 1623-1631, 2004.

20 Uematsu M, Shioda A, Suda A, Fukui T, Ozeki Y, Hama Y, Wong JR and Kusano S: Computed tomographyguided frameless stereotactic radiotherapy for Stage I non-small-cell lung cancer: a 5-year experience. Int J Radiat Oncol Biol Phys *51*: 666-670, 2001.

21 Nagata Y, Takayama K, Matsuo Y, Norihisa Y, Mizowaki T, Sakamoto T, Sakamoto M, Mitsumori M, Shibuya K, Araki N, Yano S and Hiraoka M: Clinical outcomes of a Phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. Int J Radiat Oncol Biol Phys *63*: 1427-1431, 2005.

22 Hoyer M, Roed H, Hansen AT, Ohlhuis L, Jorgen P, Nellemann H, Berthelsen AK, Grau C, Engelholm S and von der Maase H: Prospective study on stereotactic radiotherapy of limited stage non-small-cell lung cancer. Int J Radiat Oncol Biol Phys *63*: S396, 2005.

23 Wulf J, Haedinger U, Oppitz U, Thiele W, Mueller G and Flentje M: Stereotactic radiotherapy for primary lung cancer and pulmonary metastases: A noninvasive treatment approach in medically inoperable patients. Int J Radiat Oncol Biol Phys *60*: 186-196, 2004.

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