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Stereotactic Body Radiation Therapy Is Effective and Safe in Patients with Early-Stage Non-Small Cell Lung Cancer with Low Performance Status and Severe Comorbidity

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Key Words
Early-stage non-small cell lung cancer · Stereotactic body radiation therapy · Low performance status · Severe comorbidity

Abstract
Background: The purpose of this study was to assess stereotactic body radiation therapy (SBRT) results and toxicity for stage I non-small cell lung cancer patients with low performance status and severe comorbidity.
Patients and Methods: From September 2008 to April 2010, 36 patients with 38 lesions were treated with hypofractionated SBRT. All except one were medically inoperable, had low performance status and/or severe cardiovascular and/or cardiopulmonary comorbidity. The patients were immobilized in an Elekta stereotactic body frame to improve setup accuracy, and four-dimensional CT scans were used for target delineation. Fractions of 15 Gy were prescribed to cover the planning target volume, giving a total dose of 45 Gy, with 1 fraction every second day. Cone beam CT was applied at each fraction to correct for setup errors. The patients were followed with toxicity evaluation and radiographic follow-up.
Results: Median follow-up time was 13.8 months (0–21 months). The local tumor control after 12 months was 100%. Four patients developed regional relapse about 12 months after SBRT. The 1-year disease-free survival was 83%. The median tumor shrinkage at 1 year was 22 mm. Three patients experienced systemic relapse after 13 months. One patient developed grade 3 chest pain toxicity and 16 patients reported temporary grade 1 chest pain toxicity. Two patients reported temporary increased dyspnea. No patient experienced a reduction of the performance status after SBRT.

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Conclusion: SBRT is an effective and safe treatment modality for elderly patients with early-stage non-small cell lung cancer, having low performance status and severe comorbidity. It is possible to achieve high local control rates with good tolerance.

Introduction

The treatment of choice for patients with early-stage non-small cell lung cancer (NSCLC) is surgical resection [1]. The outcome after lobectomy for early-stage NSCLC shows satisfying local control rates between 45 and 95% and 5-year survival rates of 50–80% [2]. The eligibility criteria for lung surgery include good performance status, adequate expected lung function after surgery and limited medical comorbidity. For medically inoperable patients, conventionally fractionated radiotherapy has traditionally been offered. The probability of local tumor control and survival increases with higher doses [3], but even at dose levels of 70 Gy, 30–66% isolated local failure has been observed, with a higher rate of distant metastases in patients failing to achieve local control [4, 5]. In addition, conventional three-dimensional conformal radiotherapy can cause serious side effects, including radiation-induced pneumonitis which is reported in 14–30% of patients [6, 7]. Due to the fact that many patients with NSCLC have smoking-related marginal lung function and cardiovascular diseases, these side effects become clinically highly relevant.

Stereotactic body radiation therapy (SBRT) is a treatment modality which allows delivery of higher doses to the tumor without increasing doses to the surrounding tissue, compared to conventional radiation therapy. Hence, the therapeutic ratio is increased, which is especially relevant for patients with severe cardiopulmonary comorbidity. This approach for early-stage NSCLC in medically inoperable patients or patients refusing surgery has been used and evaluated in several studies [8]. SBRT is proposed as the treatment-of-choice for patients with medically inoperable stage I NSCLC [9], yet no randomized studies have proven its superiority over conventionally fractionated therapy.

In this study, we retrospectively reviewed our results in patients with early-stage NSCLC and accompanying low performance status and severe comorbidity, treated with SBRT.

Patients and Methods

Patients

This is a retrospective study including patients treated with SBRT in our institution, as well as 6 patients participating in the Nordic Stereotactic Precision and Conventional Radiotherapy Evaluation (SPACE) study. The eligibility criteria for SBRT included: (1) pathologically confirmed NSCLC, or PET positive pulmonary lesion with evidence of growth evaluated by at least 2 consecutive CT scans, (2) stage I (T1N0M0 or T2N0M0) or metachronous cancer, (3) tumor size <60 mm in the longest diameter, (4) tumors located >20 mm from the main bronchus or the mediastinal structures, (5) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–4, and (6) medically unfit for surgery or refusal of surgery by the patient.

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The pretreatment evaluation included complete history and physical examination, baseline assessment of respiratory function, chest X-ray and computed tomography (CT) of the chest. PET/CT scan was mandatory in the absence of a histological diagnosis.

Radiation Therapy

All patients were immobilized using a stereotactic body frame (SBF) (Elekta AB, Stockholm, Sweden). Respiration-related mobility was controlled by fluoroscopy and if tumor movement was more than 10 mm in the longitudinal direction, diaphragm control was applied to the SBF to reduce respiratory movements. Four-dimensional (4D) CT scans (GE Healthcare, Bucks, UK) were used to visualize the time dependence of the geometrical positions of the target volumes and organs at risk. The 4D CT only covered the area around the patient's tumor, while a full regular CT scan was applied for dose planning. Based on the time-dependent information of the 4D CT, a maximum-intensity projection CT image series was created and the gross tumor volume (GTV), also accounting for tumor movements, was outlined based on these images (center –300; width 1,000). The GTV was expanded by 5 mm in all directions to create the clinical target volume, which includes microscopic disease. Finally, setup margins of 5 mm in all directions were added to create the planning target volume (PTV).

SBRT dose planning was performed by using collapsed cone algorithm based on the results obtained by Lax et al. [10]. The dose was prescribed to the minimum of the PTV, with a total dose of 45 Gy in 3 fractions, and the 100% isodose line covered the PTV resulting in a homogenous dose distribution. The treatment was given every second day. Due to patient conditions and doses to risk organs, some patients received dose plans deviating from what is described. Heart, esophagus (defined as 5 cm above and below the target), spinal cord (defined as 6 mm above and below the target), the nearest rib to the high-dose area and the remaining lung volume (total lung minus PTV) were defined as organs at risk.

The patients were treated using an Elekta Synergy (Elekta AB) linear accelerator, and X-ray volume imaging/cone beam CT was used at each fraction to correct for setup errors. Treatment times were approximately 40 min per fraction, including immobilization, positioning, imaging and repositioning. No significant intrafractional displacement of the target volume was observed as determined by X-ray volume imaging.

Follow-Up

Response assessment and toxicity evaluation were performed at 6, 12 and 24 weeks after SBRT, and then in 6 months intervals. The follow-up included physical examination and chest CT at each visit, and PET/CT twice a year. The initial tumor response was evaluated by chest CT according to the RECIST criteria. Metabolic response was measured by PET/CT. Toxicity was scored by the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 3.0. Performance status, dyspnea, coughing, esophagitis, chest pain, radiation pneumonitis, emesis, fever, skin erythema, and fatigue were registered.

Statistical Methods

Local failure was defined as progressive CT scan abnormalities and/or incremental increases in standardized uptake values (SUVs) on PET imaging. Overall survival was defined as time from treatment start until death or last patient contact. The survival probabilities were calculated using the Kaplan-Meier method. The Fisher exact test was used to evaluate statistical differences between patient groups. A p value <0.05 was considered statistically significant.

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Results

Patient Characteristics

Between September 2008 and April 2010, 36 patients with 38 primary lung cancer lesions were treated with SBRT in our institute. The characteristics of the patients are summarized in **table 1**.

The patient's median age was 74 years (range, 54–85 years). Twenty-six patients (72%) were classified as ECOG PS ≥2 at the point of treatment.

The majority of the patients had a heavy smoking history with a median of 34.4 pack years (range, 0–61 pack years).

Thirty-two patients (82%) had a diagnosis of severe cardiovascular comorbidity, such as previous cardiac infarction, coronary heart disease, severe peripheral vascular disease, history of stroke or intracranial hemorrhage or aneurysm. Thirty-two patients (88%) had chronic lung disease with a significantly reduced lung function. The median FEV1 of all patients was 1.4 liter (range, 0.4–4.5 liter), and the FEV1/forced vital capacity ratio was 45.5% (range, 27–91%). Twenty-two patients (61%) had a diagnosis of Global Initiative for Obstructive Lung Disease (GOLD) grade 3 or worse chronic obstructive pulmonary disease. Three patients were dependent on continuous oxygen therapy, and 28 patients (77%) had dyspnea grade 3–4.

All 38 cases were discussed at a multidisciplinary tumor board and all but one were found to be technically operable. All patients, except one who refused surgery, were declared medically inoperable.

Histological evaluation was performed in 28 lesions (73%; table 1). In 10 cases (26%), no histological diagnosis was available due to an unacceptable high risk for pulmonary failure related to pneumothorax following thoracocentesis. The 2 lesions identified in 2 patients were histologically verified as 2 primary tumors.

All patients without histological diagnosis showed an increasing lung mass on serial follow-up chest CT scans, along with high FDG uptake (SUV >3.2) on PET/CT prior to treatment.

The median pretreatment tumor size was 27 mm (range, 11–59 mm) and 18 tumors (47%) were >30 mm. In 31 cases (81.5%), we had pretreatment PET/CT, and the median SUV was 5.9 (range, 0.9–22.6) in the tumor.

Radiation Treatment Parameters

Thirty-six tumors (95%) were treated with 45 Gy in 3 fractions. One patient received 30 Gy in 3 fractions, limited by the spinal cord dose. Another patient developed a bacterial pneumonia, and further treatment had to be aborted after 2 fractions of 15 Gy. Two patients were treated with SBRT for bilateral metachronous lung carcinomas, and 1 patient received SBRT for lung cancer on one side and conventional radiotherapy with 66 Gy delivered in 2-Gy fractions on the other side, due to hilar localization of this tumor.

Diaphragmal control by abdominal compression was used in 12 treated tumors (31%). Median craniocaudal respiratory motion of the tumor at CT simulation was 5.1 mm (range, 1–13 mm).

The median GTV volume was 7.26 cm^3 (range, 0.6–57 cm^3) with a corresponding PTV volume of 50.6 cm^3 (range, 11.1–171 cm^3). The median and maximum doses to PTV were 129.4% (range, 118.8–147.1%) and 152.3% (range, 147–189%), respectively. A conformity index ($V_{100\%}/V_{PTV}$) of <1.4 was intended in all cases.

The median dose exposure to the heart was 0.27 Gy (range, 0.07–6.5 Gy). The maximum dose to the esophagus and the spinal cord was median 10.7 Gy (range, 0.8–40 Gy) and 8.4 Gy (range, 0.8–20.8 Gy), respectively. The part of the total lung volume minus PTV receiving 10 Gy or more (V10) was median 11.7% (range, 5.4–33.2%). The median dose per fraction to 2 cm^3 of the ribs was 12.1 Gy (range, 0.2–24.3 Gy).

Local Tumor Control and Survival

The follow-up data included clinical and radiographic results from 36 patients treated for 38 pulmonary lesions. All results are summarized in **table 2**. The median follow-up time was 13.8 months (range, 0–21 months). At the time of analysis, all except 1 patient were alive. The local control rate was 100% after 1.5 years. The disease-free survival was 89% (24/27) and 83% (20/24), at 6 and 12 months, respectively. Four patients (11%) developed metastasis in the mediastinal lymph nodes at an average of 1.5 years after SBRT. In 3 patients, we diagnosed distant failure: 2 patients had developed liver metastasis 15 months after SBRT, and 1 patient developed brain metastasis and died 6 months after SBRT. The median tumor shrinkage after 6 and 12 months was 17 mm (range, 5–38 mm) and 22 mm (4–59 mm), respectively. The reduction of the metabolic activity measured by SUV in PET/CT 12 months after SBRT was 7.95 (range, 1.2–22.6).

Toxicity

None of the patients reported aggravation of coughing, esophagitis, emesis, fever or fatigue, and we did not observe any case of radiation-induced rib fracture.

The observed performance status of the patients was stable throughout the observation period, except the variations following exacerbating chronic obstructive pulmonary disease.

Follow-up CT's detected pneumonitis grade 1 in 34 cases (89%) according to CTC3.0, 1 patient with grade 2 pneumonitis, initiating 6 weeks after SBRT, and 1 patient experiencing a period with grade 3 pneumonitis. Only 2 patients (5%) reported temporary increased dyspnea. Three patients reported subjective respiratory improvement after SBRT.

Sixteen patients (44%) reported temporary chest pain, related to the radiation field. All patients except one classified the pain as grade 1, and after 1 year only 3 patients (8%) had chest discomfort once in a while. There was no significant association between chest pain and given dose to the ribs ($p = 0.683$). One patient presented with thoracic pain, dyspnea, chest wall edema with a distinct bulge and severe erythema over the right chest wall,

already 4 weeks after SBRT. The CT scan showed significant tumor reduction, consolidating lung parenchyma and atelectasis due to stricture of a segment bronchus and a pronounced thoracic edema. The solid swelling over the right chest wall was histologically confirmed as inflammatory tissue without evidence of atypical cells. After 3 months of treatment with corticosteroids, NSAID, and morphine, the clinical and radiological alterations reversed and medication could be reduced.

Discussion

This study shows promising results after SBRT for early-stage NSCLC with a local control rate of 100% after 18 months and a 1-year disease-free survival of 83% in a cohort of elderly patients with a high degree of comorbidities. It has been previously shown that SBRT in early-stage NSCLC results in excellent local control rates that are equal to surgery with a minimal toxicity [11, 12]. Surgery alone may result in a 5-year survival of 60–80% in stage I and about 30–40% in stage II [13]. Kelsey et al. published an extensive series of 975 patients operated for stage I NSCLC [14]. They reported a 5-year local recurrence rate of 23%, with a median time to recurrence of 14 months. The 5-year risk of treatment failure was 42%, including local and/or distant relapses [14]. SBRTs for stage I NSCLC with doses between 18 and 75 Gy have shown a 2-year survival between 64 and 79% and local control rates between 80 and 100% [15–17].

Three-dimensional conformal radiotherapy with doses up to 70 Gy is less effective than surgery and many patients experience local recurrence [18, 19].

Both dose escalation and reduction of treatment time have great impact on survival as shown in the CHART trial [15, 20]. SBRT allows both increasing the total biological dose dramatically and reducing overall treatment time. In our study, the total dose was delivered in only 5 days. If we calculate the biologic effect of 45 Gy (periphery dose) delivered in 3 fractions, converted into standard fractions of 2 Gy (EQD_2) and taking α/β values of 10 for tumor and 3 for normal tissue effects, the result is equivalent to total doses of 94 and 162 Gy, respectively. However, the use of the LQ model in such extremely hypofractionated treatment schedules is questionable.

In our material, the median age was 74 years at the time of treatment. Moreover, over 70% of our patients had a poor performance status (ECOG PS ≥2), which may reflect the future patient population. Haasbeek et al. have recently published data on a group of elderly patients with early-stage NSCLC and excessive cardiopulmonary comorbidity, treated with SBRT with a local control rate of 89% after 3 years and a 1- and 3-year survival rate of 86 and 45%, respectively [21].

Radiological changes in the lung parenchyma, suggesting acute pneumonitis or fibrosis are commonly seen after SBRT, but usually without clinical relevance [22]. In our material, only 4 patients had no clinical or radiographic sign of radiation-induced pneumonitis and after 1 year, 66% of our patients still had typical radiographic patterns visible on their chest CT scans, mostly asymptomatic. The radiological changes were transient, and decreased over time. Only 2 patients experienced increased dyspnea after SBRT. Even the patients dependent on continuous oxygen therapy tolerated the treatment excellently. Unfortunately, we do not have data from spirometric tests after treatment in

all patients. Studies measuring pulmonary function before and after treatment with SBRT have not shown permanent declines in measured functions [8].

Extrapulmonary toxicity in SBRT is a potential problem, and high-dose contribution to mediastinal organs such as esophagus, large airways and large vessels should be avoided. Skin erythema, fractures of the ribs, vertebral body, and chest wall inflammation with acute or chronic chest pain are side effects that may appear in high-dose areas. For chronic chest pain and rib fracture after SBRT, a dose response correlation and a dose volume relationship are well documented [23]. Uematsu et al. reported 2 patients developing bone fractures in the rib and vertebra within the 80%-isodose prescription line [17]. Pettersson et al. found 13 rib fractures in 33 patients after SBRT with 45 Gy in 3 fractions [24]. The authors suggest that the risk of radiation-induced rib fracture following SBRT is related to the dose to 2 cm^3 of the rib. In our population, we saw no correlation between dose to the ribs and chest pain incidence. Another group identified the volume of the chest wall, receiving >30 Gy as a predictor for acute and chronic chest wall pain and rib fracture [25]. In our material, 1 patient with doses exceeding the recommended values developed transient thoracic pain, chest wall edema and severe skin erythema in the radiation field 4 weeks after SBRT. The minimum distance from the lesion to the chest wall was just 25 mm, resulting in a high dose to this region. However, chronic chest pain after thoracic surgery is a common problem for up to 10% of patients and the response to treatment is poor [26].

Even if we lack results from randomized clinical trials comparing SBRT with surgery or three-dimensional conformal radiotherapy, the non-invasive character of the procedure, the short treatment time with few fractions, the possibility of outpatient treatment and nearly no restriction for the patients with medical problems in addition to high local control rates and mild toxicity, makes SBRT a highly attractive treatment approach [23]. Combination of rising life expectancy, more sophisticated and available diagnostics, increasing incidence of lung cancer and advances in management of cardiopulmonary diseases will result in a growing group of patients with early-stage NSCLC, not accessible for surgery.

Conclusion

SBRT with 45 Gy in 3 fractions is a safe and effective treatment for patients with early-stage NSCLC with low performance status and severe comorbidity. The local control rate and disease-free survival after 1 year was 100 and 83%, respectively. Toxicity, even for elderly patients with severe comorbidity is acceptable.

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Table 1. Patient characteristics of 36 patients treated with SBRT for 38 lesions

Gender, n	
Male	13
Female	23
Age at treatment, years	
Median	74
Range	54–85
ECOG PS, n	
0	3
1	9
2	18
3	8
Tumor histology, n	
Adenocarcinoma	17
Squamous cell carcinoma	10
Large cell carcinoma	1
No histology	10
Tumor diameter, mm	
Median	26
Range	11–59
Pretreatment PET, SUV	
Median	6.8
Range	0.9–22.6
FEV1 pretreatment, liter	
Median	1.4
Range	0.4–4.5
Cardiovascular comorbidity, n	32

Table 2. Treatment results of 36 patients treated with SBRT for 38 lesions

Follow-up, months	
Median	13.8
Range	0–21
Local control	38 (100%)
Disease-free survival after 1 year	83%
Tumor shrinkage after 1 year, mm	
Median	22
Range	4–59
Recurrence, n	
In-field	0
Regional lymph nodes	4 (10.5%)
Distant	3 (8%)
Radiation pneumonitis, n	
Radiographic	34 (89.5%)
Clinical	2 (5%)
Chest pain	16 (44%)
Dyspnea	2 (5%)

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