Int. J. Radiation Oncology Biol. Phys., Vol. 66, No. 4, Supplement, pp. S128–S135, 2006

0360-3016/06/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2006.01.012

**SRS/SRT SUPPLEMENT**

# PROSPECTIVE STUDY ON STEREOTACTIC RADIOTHERAPY OF LIMITED-STAGE NON–SMALL-CELL LUNG CANCER

MORTEN HOYER, PH.D.,* HENRIK ROED, D.M.SC.,† ANDERS TRABERG HANSEN, B.S.,‡ LARS OHLHUIS,† JORGEN PETERSEN, B.S.,‡ HANNE NELLEMANN, M.D.,§ ANNE KIIL BERTHELSEN, M.D.,† CAI GRAU, D.M.SC.,* SVEND AAGE ENGELHOLM, D.M.SC.,† AND HANS VON DER MAASE, D.M.SC.*

Departments of *Oncology, ‡Medical Physics, and §Radiology, Aarhus University Hospital, Aarhus, Denmark; and †Department of Radiation Oncology, Copenhagen University Hospital, Copenhagen, Denmark

**Purpose: To test the effect of stereotactic body radiotherapy (SBRT) in the treatment of medically inoperable patients with limited-stage non–small-cell lung cancer (NSCLC) in a Phase II trial.**
**Methods and Materials: Forty patients with Stage I NSCLC were treated with SBRT with a central dose of 15 Gy × 3 within 5–8 days.**
**Results: Eight patients (20%) obtained a complete response, 15 (38%) had a partial response, and 12 (30%) had no change or could not be evaluated. Only 3 patients had a local recurrence, and the local control rate 2 years after SBRT was 85%. At 2 years, 54% were without local or distant progression, and overall survival was 47%. Within 6 months after treatment, one or more Grade ≥2 reactions were observed in 48% of the patients.**
**Conclusions: Stereotactic body radiotherapy in patients with limited-stage NSCLC resulted in a high probability of local control and a promising survival rate. The toxicity after SBRT of lung tumors was moderate. However, deterioration in performance status, respiratory insufficiency, and other side effects were observed.** 

**Non–small-cell lung cancer, Stereotactic radiotherapy, Phase II study.**

## INTRODUCTION

Surgery is preferred in the treatment of limited-stage non–small-cell lung cancer (NSCLC). However, a large proportion of patients with lung cancer have poor lung function caused by tobacco-induced chronic obstructive lung disease (COL). Because of COL, a number of patients with limited-stage NSCLC are not suitable for thoracotomy. So far, these patients have been offered conventional fractionated radiotherapy. Unfortunately, results after conventional radiotherapy are disappointing, with survival rates of 15–27% 5 years after treatment, depending on tumor size (1–4). Recently, stereotactic body radiotherapy (SBRT) was introduced in the treatment of solitary tumors, primarily in the lung and liver. Stereotactic body radiotherapy allows escalation of the radiation dose and might thereby be a tool to increase local control in small tumors. In SBRT, the gross tumor volume with a small margin is treated with one or a few large radiation fractions, most often by use of five to eight static beams.

In recent years, a number of reports on retrospective studies in SBRT on limited-stage NSCLC have been published (5–12). They all show high rates of tumor response, local control probability of 71–100%, and overall survival rates of 32–79%, with only very limited toxicity. Although these results are promising, they are hampered by a number of weaknesses. First of all, the patient materials are often inhomogeneous and poorly described. In some of the studies, a large proportion of patients are treated with SBRT because they refused surgery. Only few studies report the pretreatment lung function status, and some do not report whether the cancer diagnosis was verified by biopsy. In addition, most studies do not include follow-up visits at regular intervals, others do not report the results by actuarial methods, and generally the follow-up time is short. Data are retrospectively collected, which notoriously leads to the underestimation of toxicity. The studies might be difficult to compare and might not be representative of the patient group that is usually considered candidates for SBRT. To minimize these errors, it was decided to introduce SBRT of limited-stage NSCLC in Denmark as part of a joint, prospective, Phase II study between Aarhus and Copenhagen University Hospitals. The study was designed to focus primarily on tumor response, time to progression, and toxicity.

Reprint requests to: Morten Hoyer, M.D., Ph.D., Department of Oncology, Aarhus University Hospital, Building 5, Aarhus C 8000, Denmark. Tel: (+45) 89492529; Fax: (+45) 89492530; E-mail: hoyer@as.aaa.dk

This study was supported by a grant from the Kloppenborg X-knife Foundation.

Received July 28, 2005, and in revised form Oct 5, 2005. Accepted for publication Jan 4, 2006.

## METHODS AND MATERIALS

### *Patient selection*

Patients entered the study from January 2000 to September 2003 according to the following criteria: histologically proven NSCLC, International Union Against Cancer (UICC) Stage T1–2N0M0 (UICC 1997), tumor diameter <6 cm, patient unfit for surgery because of poor lung capacity or other severe comorbidity, and World Health Organization (WHO)/Eastern Cooperative Oncology Group performance status 0–2. Tumor and metastasis classification was based on CT scan and node classification by mediastinoscopy or by CT scan if mediastinoscopy was not performed. Only tumors with a distance of ≥10 mm from bronchi or esophagus were accepted.

The study was approved by the Ethics Committee of Aarhus County, informed consent was obtained from all patients, and the study was carried out in accordance with the Helsinki Declaration II.

### *Radiotherapy*

A detailed description of the principles of treatment has been given previously (13). In brief, the patients treated in Aarhus ($n$ = 32) were immobilized by the stereotactic body frame (SBF; Elekta, Stockholm, Sweden) with an external reference coordinate system visible on CT. The SBF has a diaphragm control that reduces respiratory movement (14). A maximum respiratory movement of the diaphragm of 10 mm during the respiratory cycle evaluated by fluoroscopy was allowed. Patients treated in Copenhagen ($n$ = 8) were immobilized by a custom-made vacuum pillow and skin marks. Computed tomography (CT) scans were performed for treatment planning in all 40 patients, and in 32 cases an additional CT scan was carried out to confirm the position of the isocenter at the day of the first treatment. Spiral CT scan was performed with a 5-mm slice thickness (8 mm/s) reconstructed with a 4-mm interslice distance. Treatment planning was carried out in Helax, TMS, or CadPlan Plus/Eclipse (Varian Medical Systems, Palo Alto, CA) (Fig. 1). The clinical target volume (CTV), defined as the lung tumor and surrounding spicular features and atelectasis, was delineated by both a radiotherapist and a radiologist. A margin around the CTV of at least 5 mm in the transverse and 10 mm in the craniocaudal direction was added to form the planning target volume. The CTV was encompassed by the 95% isodose, and the planning target volume by the 67% isodose surface. A planned dose of 45 Gy to the isocenter was delivered in three fractions within an overall treatment time of 5–8 days. Treatment was delivered without respiratory gating on a Siemens Primus (Siemens Medical Solutions, Concord, CA) or a Varian Clinac 2100/2300, most often by use of five to eight static coplanar or noncoplanar 6–8-MV beams formed by a multileaf collimator, with a leaf width of 5–10 mm at the isocenter. In Copenhagen, the position of the patient (vertebral spine) was checked by portal film or electronic portal imaging (PVI, Varian). In case of deviation, the isocenter was adjusted before treatment. All patients received prophylactic ondansetron (16 mg) during the treatment period.

### *Follow-up*

Patients were evaluated for toxicity at baseline, 2 weeks, and 2, 3, 6, 9, 12, 18, and 24 months after treatment according to the WHO performance status and toxicity grading system, and CT scans were performed at baseline and 3, 6, 9, 12, 18, and 24 months after treatment. Any increase in grade from baseline was considered toxicity related to the treatment. Tumor response was evaluated on CT scans, according to the WHO criteria.

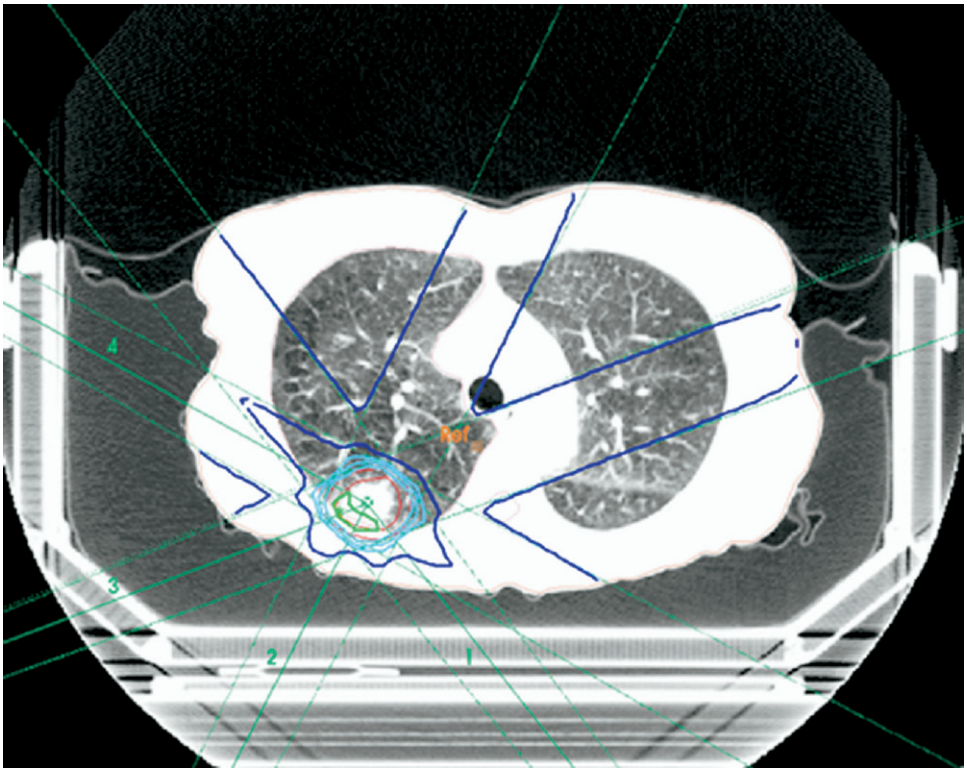


Fig. 1. Treatment plan for stereotactic body radiotherapy of a patient with non–small-cell lung cancer.