Outcomes and Prognostic Factors for Recurrence After High-Dose Proton Beam Therapy for Centrally and Peripherally Located Stage I Non–Small-Cell Lung Cancer

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Abstract

This study was conducted to determine disease control rates and prognostic factors after high-dose proton beam therapy (PBT) for centrally and peripherally located stage I non–small-cell lung cancer (NSCLC). Eighty tumors were treated. The 3-year overall survival and local control rate were 76.7% and 81.8%. Radiation dose was shown to be the more significant prognostic factor for tumor control than tumor diameter and others.

Introduction: This study was conducted to determine disease control rates and prognostic factors associated with recurrence of centrally and peripherally located stage I NSCLC treated using high-dose PBT. **Patients and Methods:** Seventy-four patients with 80 centrally or peripherally located stage I NSCLCs were treated with PBT. A protocol using 72.6 Gy (RBE) in 22 fractions was used for centrally located tumors, and 66 Gy (RBE) in 10 or 12 fractions was used for peripherally located tumors. Data were collected and control rates and prognostic factors for recurrence were evaluated retrospectively. **Results:** The median follow-up period was 31.0 months. The overall survival, disease-specific survival, and progression-free survival rates were 76.7%, 83.0%, and 58.6% at 3 years, respectively. Disease recurrence was noted in 30 patients and local recurrence of 11 tumors occurred. The 3-year local control rate was 86.2% for stage IA tumors and 67.0% for stage IB tumors. Radiation dose was identified as a significant prognostic factor for disease recurrence and local recurrence. Tumor diameter and age were only significantly associated with disease recurrence. The 3-year local control rate was 63.9% for centrally located tumors irradiated with 72.6 Gy (RBE) and 88.4% for peripherally located tumors irradiated with 66 Gy (RBE). **Conclusion:** Radiation dose was shown to be the most significant prognostic factor for tumor control in stage I NSCLC treated using high-dose PBT. Tumor diameter was not significant for local control. Further evaluation of PBT for centrally located tumors is warranted.

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Keywords: Outcome, Prognostic factor for tumor control, Proton beam therapy, Stage I lung cancer, Radiation dose

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Introduction

For stage I non–small-cell lung cancer (NSCLC), surgical resection is typically performed, yielding a 60% to 80% survival rate.[1] Stereotactic body radiotherapy (SBRT) has previously been used for patients with medically inoperable stage I NSCLC and more recently for operable tumors. For stage I NSCLC patients treated with SBRT consisting of photons and protons, the 3-year overall survival (OS) rate was reported to be 57% to 86%[2-7] and the 3-year local control rate was reported to be 74% to 95%.[2,4-6,8,9]

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Treatment outcomes for SBRT have been reported to not differ between tumors that are diagnosed pathologically and those diagnosed solely based on clinically data,[10,11] and this procedure has been shown to be a safe and radical treatment for operable stage I NSCLC.[12,13]

In addition to peripherally located tumors, use of SBRT has also recently been reported for centrally located tumors.[14,15] However, the protocol for performing SBRT for centrally located tumors remains controversial. High-dose proton beam therapy (PBT) has been used to treat peripherally and centrally located tumors in our hospital. The purpose of this study was to determine the disease control rate and prognostic factors associated with recurrence of centrally and peripherally located stage I NSCLC treated using high-dose PBT.

Patients and Methods

Patients and Tumor Characteristics

From February 1997 to September 2011, 74 patients with stage I NSCLC received PBT at our hospital and were followed for at least 6 months after PBT until August 2012. These patients were evaluated retrospectively. The median age at the time of treatment was 75 years (range, 51-86 years). Patients fell into the following Eastern Cooperative Oncology Group performance status (PS) groups: PS = 0 (n = 44), PS = 1 (n = 21), PS = 2 (n = 8), and PS = 3 (n =1). Sixteen patients (21.6%) had cardiovascular disease, 33 (44.6%) had respiratory disease, and 32 (43.2%) had other cancers.

Of these patients, 80 centrally or peripherally located stage I NSCLCs, based on the tumor, node, metastases (TNM) classification defined by the 7th International Union Against Cancer, were identified and treated. Overall, 68 patients (92%) had a single tumor, and 6 (8%) had 2 tumor masses. Sixty-four tumors (80%) were histologically confirmed, and the remaining 16 (20%) were diagnosed using tumor markers, computed tomography (CT), and positron emission tomography (PET). Centrally located tumors were defined as tumors irradiated in parts of the mediastinum or located more central than the lobar bronchus, which definition did not absolutely equal T2a criteria. Overall, 21 tumors (26%) were centrally located and 59 (74%) were peripherally located. The median tumor diameter was 22 mm (range, 10-48 mm). Characteristics of these 80 tumors are summarized in Table 1.

Table 1 Tumor Characteristics

Characteristic	Value
Total Number of Tumors	80
Clinical Stage	
Stage IA	59 (74%)
Stage IB	21 (26%)
Histology	
Adenocarcinoma	32 (40%)
Squamous cell carcinoma	26 (33%)
Non–small-cell carcinoma	6 (8%)
Unproven	16 (20%)
Tumor Location	
Centrally located tumor	21 (26%)
Peripherally located tumor	59 (74%)
Tumor Site	
S1-3 and S6	51 (64%)
S4-5 and S7-10	29 (36%)

Abbreviation: S = lung segment.

Proton Beam Therapy

At our hospital, the following 2 treatment protocols are commonly used, depending on tumor location: 72.6 Gy (RBE) in 22 fractions and 66 Gy (RBE) in 10 or 12 fractions.[2,16] The 72.6 Gy (RBE) protocol was used for centrally located tumors, and the 66 Gy (RBE) protocol was used for peripherally located tumors. The photon equivalent dose was defined as the physical dose (Gy) × the relative biological effectiveness (RBE) of the proton beam, which was assigned a value of 1.1 in this study.[17] The biologically effective dose (BED) of 72.6 Gy (RBE) in 22 fractions calculated with an α/β ratio of 10 Gy was 97 Gy_{10} (RBE), and the dose of 66 Gy (RBE) in 10 or 12 fractions was 110 Gy_{10} (RBE) or 102 Gy_{10} (RBE).

The clinical target volume (CTV) encompassed the gross tumor volume with a 5- to 8-mm margin in all directions.[2,16] An additional 5-mm margin was included in the caudal axes to compensate for uncertainty due to respiration-induced organ motion. Two or 3 beams were used, and an additional margin of 5 to 10 mm was added to cover the entire CTV by enlarging the multileaf collimator and adjusting the range shifter. Proton beams of 155 to 250 MeV were generated using a synchrotron accelerator, and were delivered during the expiratory phase under a respiration-gated system.[18]

Follow-up and Evaluations

Follow-up examinations, including measurement of tumor marker levels and imaging, were performed periodically at intervals of 3 to 6 months. Acute and late treatment-related complications were assessed using the National Cancer Institute Common Toxicity Criteria for Adverse Events (v.4.0) and the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) late radiation morbidity scoring scheme. Recurrence, survival, and general condition of patients after PBT were also evaluated. Recurrences were holistically identified according to detection of clinical changes in levels of tumor markers and imaging results such as CT and PET.[19]

Statistical Analysis

Data were collected and analyzed retrospectively. Survival and local control rates were estimated using the Kaplan-Meier method. To analyze prognostic factors for recurrence, Cox regression analysis was used to evaluate difference in age at time of treatment, sex (men vs. women), PS (0-1 vs. 2-4), cardiovascular disease, respiratory disease, T factor (T1 vs. T2a), histology, tumor diameter, lung segment of tumor site (lung segment 1-3 and segment 6 vs. segment 4-5 and segment 7-10), and tumor location (centrally vs. peripherally located tumors) which is same meaning of radiation dose difference (72.6 Gy [RBE] vs. 66 Gy [RBE]). Data analysis was performed using the Ekuseru-Toukei software package (version 2010; Social Survey Research Information Co, Ltd); values of $P < .05$ were considered significant.