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Clinical Investigation: Thoracic Cancer

Image Guided Hypofractionated 3-Dimensional Radiation Therapy in Patients With Inoperable Advanced Stage Non-Small Cell Lung Cancer

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Summary

Hypofractionated radiation therapy can potentially improve local control with a higher biological effect and shorter overall treatment time. The present open-label prospective study reports outcomes and feasibility for 30 patients with inoperable, advanced stage non-small cell lung cancer who received hypofractionated radiation therapy. Our data support the finding that hypofractionated radiation therapy offers good disease control, increasing the biologically equivalent dose to the tumor volume and obtaining acceptable toxicity rates when 3-dimensional conformal radiation therapy and image guided radiation therapy techniques are used.

Purpose: Hypofractionated radiation therapy (HypoRT) can potentially improve local control with a higher biological effect and shorter overall treatment time. Response, local control, toxicity rates, and survival rates were evaluated in patients affected by inoperable advanced stage non-small cell lung cancer (NSCLC) who received HypoRT.

Methods and Materials: Thirty patients with advanced NSCLC were enrolled; 27% had stage IIIA, 50% had stage IIIB, and 23% had stage IV disease. All patients underwent HypoRT with a prescribed total dose of 60 Gy in 20 fractions of 3 Gy each. Radiation treatment was delivered using an image guided radiation therapy technique to verify correct position. Toxicities were graded according to Radiation Therapy Oncology Group morbidity score. Survival rates were estimated using the Kaplan-Meier method.

Results: The median follow-up was 13 months (range, 4-56 months). All patients completed radiation therapy and received the total dose of 60 Gy to the primary tumor and positive lymph nodes. The overall response rate after radiation therapy was 83% (3 patients with complete response and 22 patients with partial response). The 2-year overall survival and progression-free survival rates were 38.1% and 36%, respectively. Locoregional recurrence/persistence occurred in 11 (37%) patients. Distant metastasis occurred in 17 (57%) patients. Acute toxicities occurred consisting of grade 1 to 2 hematological toxicity in 5 patients (17%) and grade 3 in 1 patient; grade 1 to 2 esophagitis in 12 patients (40%) and grade 3 in 1 patient; and grade 1 to 2 pneumonitis in 6 patients (20%) and grade 3 in 2 patients (7%). Thirty-three percent of patients developed grade 1 to 2 late toxicities. Only 3 patients developed grade 3 late adverse effects: esophagitis in 1 patient and pneumonitis in 2 patients.

Conclusions: Hypofractionated curative radiation therapy is a feasible and well-tolerated treatment for patients with locally advanced NSCLC. Randomized studies are needed to compare HypoRT to conventional treatment. © 2013 Elsevier Inc.

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Introduction

Lung cancer is the most commonly diagnosed cancer worldwide and the leading cause of cancer-related death (1). Approximately 80% of the patients have non-small cell lung cancer (NSCLC), and most of them present with advanced stage at diagnosis (2). The prognosis is poor, with a 5-year overall survival (OS) rate from 5% to 10% for NSCLC patients (3). High-dose conventional radiation therapy (60-70 Gy in 30-35 daily fractions of 2 Gy/each fraction) and concurrent chemotherapy with platinum-based regimen is the standard evidence-based treatment for locally advanced inoperable NSCLC (4, 5). Median survival time is approximately 16 to 17 months after concurrent treatment, so intensification of regional effect has been attempted to improve local control and survival rates (6).

Hypofractionated regimens consist of fewer fractions with higher doses per fraction. Large fractions may improve disease control, obtaining a higher biological effect and a shorter overall treatment time. Hypofractionated radiation therapy (HypoRT) is based on the concept that the repopulation of tumor cells increases between the third and the fourth week of treatment (7). Thus, larger dose fractions can be an alternative treatment in order to increase local control for the population of patients not eligible for the concurrent approach (8). Limits remain due to the intensification of severe adverse effects, particularly in esophagitis and pneumonitis.

Currently, only a few studies have investigated efficacy and tolerance of hypofractionated radiation schedules in locally advanced NSCLC. These studies demonstrated good local control with acceptable acute and late toxicity rates after HypoRT based on 3-dimensional conformal radiation therapy (3D-CRT) modern planning system that facilitates development of safe regimens (9, 10).

Our rationale was to obtain a shorter overall radiation therapy treatment time and to deliver higher dose to the target volume (primary tumor and clinically positive lymph nodes) by using 3D-CRT planning system for a safe hypofractionated regimen. This was a prospective open-label study including a series of 30 patients affected by inoperable advanced stage NSCLC, who received HypoRT. Response, local control, toxicity rates and survivals were evaluated.

Methods and Materials

Patients' characteristics

Thirty patients with advanced stage NSCLC were enrolled to undergo HypoRT at our Institute from 2009 to 2011. A performance status $\geq$2 (Eastern Cooperative Oncology Group criteria) was required for all patients. Also, all patients had histologically confirmed NSCLC and unresectable advanced stage (III/IV) according to American Joint Committee on Cancer (AJCC) 2002 staging system criteria. Stage IV patients presented with $\leq$2 metastatic sites and stable disease. They were included when local control was judged to be important for quality of life, tumor-related symptoms, and prognosis. There were no restrictions on previous chemotherapy regimens. Exclusion criteria were malignant pleural or pericardial effusion. The study included 4 females (13%) and 26 males (87%). The mean age was 70 years (range, 49-87 years). Patient characteristics are summarized in Table 1.

Pretreatment evaluation included clinical examination, complete blood count, chest x-ray, total body computed tomography (CT), bronchoscopy with histological examination, lung function tests, bone scan, and ^{18}F-labeled fluorodeoxyglucose-positron emission tomography/CT ([^{18}F]FDG-PET).

Treatment

All patients underwent CT pretreatment planning (slice thickness of 2.5 mm) in the supine position, using a wing-board system for immobilization. Planning CT images were matched with diagnostic CT with contrast medium and with PET using point-to-point matching to increase target volume (Gross Tumor Volume=GTV, Clinical Target Volume=CTV) delineation. GTV1 included the pulmonary lesion; GTV2 include clinically positive lymph nodes with a short axis diameter $\geq$1 cm and/or positive nodes at PET. GTV1 and GTV 2 were expanded by 4 to 5 mm in all directions to create CTVs. A margin of 5 mm was added to CTV1 and CTV2 in all directions to generate planning target volumes (PTVs). All patients were treated with 3D-CRT using multiple coplanar and noncoplanar fields. Image guidance was performed with kilovoltage on-board cone beam CT that was matched to the planning CT prior to each treatment. The patient's position was adjusted with an initial automatic bone alignment, followed by a soft tissue alignment. Radiation therapy was delivered by a linear accelerator using 6-MV photon beams. The radiation treatment regimen consisted of 60 Gy in 20 fractions of 3 Gy each 5 times per week for 4 weeks. The biological effective dose (BED) for the present fractionated schedule was estimated by using the time-adjusted formula described by Mehta et al (11), where BED = $nd\,(1 + d/$

Table 1 Patient characteristics (n=30)

Characteristic	No (%)
Age (y)	
Mean	69.7
Range	49-87
Sex	
Male	26 (87)
Female	4 (13)
T stage	
T1	1 (4)
T2	10 (33)
T3	9 (30)
T4	10 (33)
N stage	
N1	5 (27)
N2	10 (33)
N3	15 (50)
AJCC 2000 stage	
IIIA	7 (23)
IIIB	17 (57)
IV	6 (20)
M1 stage ($\leq$2)	
Lung	2 (7)
Liver	3 (10)
Bone	2 (7)
Histological type	
Adenocarcinoma	11 (37)
Squamous cell	12 (40)
NSCLC, NOS	7 (23)

Abbreviations: AJCC = American Joint Committe on Cancer; NSCLC, NOS = non-small cell lung cancer, not otherwise specified.