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A Pilot Trial of Serial FDG-PET in Patients with Medically Inoperable Stage I Non-Small Cell Lung Cancer Treated with Hypofractionated Stereotactic Body Radiotherapy (SBRT)

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Abstract

Purpose—Routine assessment is made of tumor metabolic activity as measured by 18F-Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) in Stage I non-small cell lung cancer (NSCLC). This report describes PET correlates prospectively collected after SBRT for patients with medically inoperable NSCLC.

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No copyrighted information or patient photos were used.

Ethical Guidelines The Indiana University institutional review board approved these trials and all patients provided written informed consent to participate in both the phase II and functional imaging trials. The trial met the ethical standards on human experimentation set forth in the Helsinki Declaration of 1975, as revised in 2000.

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Methods and Materials—14 consecutive patients with medically inoperable Stage I NSCLC were enrolled. All patients received SBRT to 60-66 Gy in 3 fractions. Patients underwent serial planned FDG-PET/CT fusion imaging pre-SBRT and at 2, 26 and 52 weeks following SBRT.

Results—With median follow-up of 30.2 months, no patients experienced local failure. One patient developed regional failure, one developed distant failure, and one developed a second primary. The median tumor pre-SBRT maximum standardized uptake value (SUV_{max}) was 8.70. Post-SBRT median SUV_{max} values at 2, 26 and 52 weeks were 6.04, 2.80, and 3.58 respectively. Patients with low pre-SBRT SUV were more likely to experience initial 2-week rises in SUV, while patients with high pre-SBRT SUV commonly had SUV declines 2 weeks post treatment ($p = 0.036$). Six of 13 patients had primary tumor $SUV_{max} > 3.5$ at 12 months post SBRT, but remained without evidence of local disease failure on further follow-up.

Conclusions—A substantial proportion of patients may have moderately elevated FDG-PET SUV_{max} at 12 months without evidence of local failure on further follow-up. Thus, slightly elevated PET SUV_{max} should not be considered a surrogate for local treatment failure. Our data do not support routine serial FDG-PET/CT for follow-up of patients receiving SBRT for stage I NSCLC.

Keywords

Lung cancer; Non-small cell lung cancer; FDG PET; Stereotactic body radiation therapy; Body radiosurgery

Introduction

Lung cancer is the leading cause of cancer-related death in the United States, with an estimated 213,380 new lung cancer cases and 160,390 deaths due to lung cancer in 2007¹. The standard of care for early stage non-small cell lung cancer (NSCLC) is surgical resection, which results in an approximately 60-80% 5-year overall survival (OS) ²⁻⁵. However, many patients with early stage lung cancer are ineligible for surgery because of cardiovascular, pulmonary and other medical comorbidities. In medically inoperable patients, treatment with conventionally fractionated external beam radiation therapy (EBRT) results in roughly 10-30% 5-year OS⁶⁻¹¹.

Hypofractionated Stereotactic Body Radiation Therapy (SBRT) is a technique gaining wider acceptance in the treatment of early stage NSCLC. SBRT commonly uses 3-5 large fractions of stereotactically delivered radiation to total doses between 48 and 66 Gy. Results of SBRT from a large Japanese retrospective multi-institutional series show local control (LC) rates of 86% at 5 years and overall survival (OS) of 47% at 5 years¹². At Indiana University (IU), we have conducted prospective studies of SBRT, including a phase I study^{13, 14}, in which our dose-fractionation schedule was established, and a recently-reported phase II trial of SBRT in patients with medically inoperable stage IA and IB NSCLC¹⁵. Our results revealed a Kaplan-Meier 3-year local control rate of 88.1%. Our 3-year OS of 42.7% was consistent with the Japanese data. An analysis of serial pulmonary function data confirmed that it is safe to deliver this treatment to patients with low baseline pulmonary function¹⁶. Data from other centers in Europe, Japan, China, and the US show promising efficacy and low toxicity¹⁷⁻²¹.

As more patients are treated with SBRT for early stage NSCLC, it is critical to make an accurate assessment of local effects, both in terms of tumor control and normal tissue damage. The biologic effects of hypofractionated SBRT may differ considerably from conventional EBRT on both tumor and normal tissue. It is often difficult to distinguish local atelectasis and fibrosis from persistent or recurrent tumor. There is some indication that standardized uptake values (SUV) from 18F-Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) after

conventional radiotherapy for lung cancer may be useful as a surrogate for tumor response²². However, data are limited on the results of FDG-PET imaging specifically following SBRT.

To evaluate the effect of SBRT on both normal tissues and tumor, a pilot companion study to the IU phase II SBRT protocol was created. This protocol enrolled consecutive consenting patients from the phase II protocol and followed them pre and post-treatment with serial FDG-PET. The companion protocol's objective was to characterize the effect of SBRT on tumor metabolic activity as a function of time and to correlate the change in metabolic activity with local control, survival, and toxicity data from the phase II protocol. Our aim is to report the utility of FDG-PET in the evaluation of patients following SBRT for early stage NSCLC.

Methods and Materials

Eligibility Criteria

Patients eligible and scheduled to be treated on the IU phase II study of SBRT for early stage NSCLC were eligible for the companion study of functional imaging as long as they had no contraindications to functional imaging (allergy to imaging agents), were willing to fulfill protocol requirements, and consented to both protocols. Criteria for entry into the Phase II trial included biopsy proven AJCC stage I (T1 or T2, N0, M0) NSCLC with a technically resectable primary tumor deemed to be medically inoperable due to underlying medical problems that would prohibit a potentially curative resection. Medically operable patients who refused surgery were not eligible. Additional inclusion criteria included age ≥ 18 years, Karnofsky Performance Status (KPS) ≥ 60 and ability to fit inside the stereotactic body frame. Additional exclusion criteria included previous lung/mediastinal radiotherapy, concomitant antineoplastic therapy or chemotherapy within 8 weeks of SBRT, active infection and pregnant women. The IU institutional review board approved these trials and all patients provided written informed consent to participate in both the phase II and functional imaging trials. Pretreatment evaluation included medical history, physical examination, weight, KPS, complete blood count, liver function, FDG-PET CT, and pulmonary function testing including arterial blood gas measurements, spirometry, lung volumes and diffusion capacity of the lung for carbon monoxide (DLCO).

Toxicities were reported using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0 and toxicity grading was confirmed by an independent data safety monitoring committee. Local enlargement (LE) was defined as a 25% or greater increase in the sum of the products of perpendicular diameters of the initial lesion or the reappearance of a lesion after it was found to be in complete response. Local failure (LF) required both LE and hypermetabolic activity on PET similar to or greater than pre SBRT staging activity. Biopsy evidence of viable carcinoma was also proof of LF. Regional progression was defined as evidence of adenopathy in the natural lymphatic drainage for the primary tumor on either CT (progressive enlargement and size at least 1.0 cm in dimension) or new characteristic FDG-PET uptake. Metastatic dissemination was defined as tumor on examination or imaging characteristic of metastatic dissemination from NSCLC.

Treatment

Details of the IUMC SBRT radiation therapy have been published elsewhere^{13, 14}. Briefly, patients were positioned in the Stereotactic Body Frame (Elekta, Stockholm, Sweden) with a vacuum pillow to create reproducible immobilization. Prepatellar and sternal positioning marks were permanently applied. Abdominal clamping pressure was applied until the motion of the diaphragm was reduced to 1.0 cm or less on fluoroscopy. CT-guided simulation was performed. Atelectasis was not included in gross tumor volume (GTV). No nodal irradiation was attempted. The clinical target volume (CTV) was equal to the GTV without any volume

expansion. An additional 0.5 cm in the axial plane and 1.0 cm in the longitudinal plane were added to the GTV/CTV to constitute the planning target volume (PTV). Three-dimensional treatment planning with 7–10 noncoplanar compensated beams stereotactically directed toward the tumor was performed. Dose was typically prescribed to the 80% isodose line. At least 95% of the PTV was covered by the prescription dose. Inhomogeneity corrections were not used in treatment planning. Maximum point doses per fraction to the following critical normal structures were observed: spinal cord 6 Gy, esophagus 9 Gy, brachial plexus 8 Gy, heart 10 Gy, trachea and ipsilateral bronchus 10 Gy. All stage IA patients were treated to 60Gy in three fractions and all stage IB patients were treated to 66Gy in three fractions.

Patient Evaluation and Imaging

All patients on the prospective companion trial of functional imaging were scheduled for FDG-PET imaging immediately before SBRT and then two weeks, six months and 12 months following SBRT. All patients fasted for a minimum of 4–6 hours prior to intravenous injection with 0.14 mCi/kg of [^{18}F]-2-fluorodeoxyglucose (FDG) and imaging was initiated 60 minutes after injection. The patients were studied on a 16-slice dual modality PET/CT (Siemens Biograph®, Siemens, Malvern, Pennsylvania) with LSO (Lutetium Oxyorthosilicate) crystals. PET emission images were obtained from the base of the brain to the mid-thigh region on all patients at a scan duration of 4 minutes per bed position (15 cm). CT imaging with conventional settings for mA and kVp was obtained over the same anatomic areas and used for attenuation correction of the PET emission image data. All patients were positioned in the stereotactic body frame with a vacuum pillow in a set up identical to the SBRT treatment position for all PET-CTs with the exception of one patient whose six and 12 month images were performed without the stereotactic body frame because of vacuum pillow deflation. All PET-CT studies included the area of the body from the base of the brain to mid-thigh region. The degree of metabolic uptake in both the tumor site and surrounding normal tissues was quantified using standardized uptake values (SUV). The maximum SUV (SUV_{max}) for the target lesions and reference tissues was obtained using a 3-D voxel region of interest (VOI) placed simultaneously on the three orthogonal projections. In order to ensure that changes in tumor SUV_{max} were not caused by a generalized and unrelated increase or decrease in tissue FDG uptake, the tumor FDG uptake was normalized to FDG uptake of several reference tissues. Ratios of tumor SUV_{max} to the SUV_{max} of the reference tissues lung, blood and liver were calculated. In addition to the above described imaging, all patients were seen in follow-up 6 weeks following SBRT and then every three months for the first two years. Alternating chest x-ray (CXR) or chest CT was performed with each follow-up. Adverse toxic events were graded according to the NCI-CTC and assigned as to treatment relatedness. An independent data safety monitoring committee reviewed the assignments of all adverse events.

Statistical Methods

Descriptive statistics were reported as medians and ranges. Associations between baseline and week-2 SUV levels were explored via the Spearman correlation coefficient. We performed calculations using a two-sided significance level of 0.05. All analyses were performed with SAS version 9.0 (SAS Institute, Cary, NC).

Results

Patient Characteristics

Between November 2002 and August 2004, 70 patients with medically inoperable Stage I NSCLC were enrolled on the IUMC phase II trial of SBRT. From September 2003 to August 2004, 14 patients from this Phase II trial were enrolled on this prospective study of functional imaging. These 14 patients constitute the basis of this report. The median age was 72.5 years

(range, 55 to 86 years) and the baseline patient, tumor and SBRT treatment characteristics of the 14 functional imaging patients are presented in Table 1.

Local Control, Survival and Toxicity Analysis

With median follow-up of 30.2 months (range 13 – 60.5 months), no patients in this group have failed locally. One patient had a distant failure at 12.7 months; his official report lists local and regional failure as well, however there was no increased SUV or size in the primary site or in any mediastinal lymph nodes. This has been scored as a distant failure only. One patient developed what was deemed to be a second primary at 25.9 months post-treatment. One patient had a regional failure at 20.7 months post-SBRT. One patient had progressively increasing SUV and an evolving mass at the site of treatment. This was suspicious for recurrence, but biopsy showed only necrosis. The patient died of an apparent infection, so no further follow up was available. Nine patients have died, two with active NSCLC and seven of unrelated causes.

Toxicity profiles have been very favorable with four adverse events in three patients that were grade 3 or above, only one of which was felt to be possibly related to radiotherapy (Table 2.) No patient had an adverse event related to functional imaging. Three patients were oxygen dependent prior to SBRT and at last follow-up, six patients were oxygen dependent. Given the paucity of adverse events, we are unable to comment on any association between SUV response and normal tissue toxicity.

FDG PET

All 14 patients underwent pre-SBRT PET per protocol. The median tumor SUV_{max} was 8.70 (range 1.37 to 15.22). A total of 40 post-SBRT PET examinations were performed. Two patients failed to receive one post-SBRT PET examination each (week-2 and week 52). SUV_{max} values generally decreased over time (Figure 1).

Post-SBRT median SUV_{max} values at 2, 26 and 52 weeks were 6.04, 2.80, and 3.58 respectively. SUV_{max} values were also recorded for the normal tissues blood, lung and liver. Ratios of tumor SUV_{max} to normal tissue SUV_{max} were computed (Table 3). The ratios of tumor SUV_{max} to blood, lung and liver SUV_{max} also decreased over time.

Four of 14 patients had an initial SUV_{max} rise at 2 week imaging. Spearman correlation coefficient analysis showed that preSBRT SUV_{max} is inversely correlated with week-2 SUV_{max} ($p=0.036$ and $r=-0.608$).

A post-hoc unplanned analysis of mean lung dose (MLD) as extracted from planning computer dose volume histogram data showed no statistically significant relationship between ipsilateral MLD and SUV response ($p = 0.999$).

No patients had local failure, so it is difficult to comment on the SUV characteristics of local failure. One patient had an initial decline in SUV followed by progressive rise in SUV. However, biopsy showed only necrosis. Since the patient died of an apparent infection, no further follow-up was available. 6 of 13 patients had primary tumor SUV_{max} of greater than 3.5 at 12 months post SBRT but no evidence of local failure on further follow-up. Five patients had PET/CT examinations after the completion of this study at 18, 20.6, 20.9, 26.2, and 31 months post-SBRT. Two patients' scans were read as having no abnormally increased FDG uptake in the area of the previously treated tumor (no SUV_{max} was listed). The other three patients had SUV_{max} values of 3.05, 2.5, and 2.5 at 18, 20.6, and 31 months post-SBRT, respectively.

Discussion

With the expanded use of SBRT to treat early stage lung cancer, accurate response assessment is critical. While both the IU phase II and companion trial of functional imaging allowed re-biopsy to evaluate suspicion for local recurrence, re-biopsy was rarely pursued given biopsy risks in this frail population, sampling error concerns, and patient preference. Using CT alone for follow-up, months may be required to know the success or failure of RT-based treatment. CT may be unable to provide accurate response evaluation early enough to allow for some salvage strategies²².

Some have proposed that biochemical changes such as metabolic status measured by FDG-PET may occur much sooner than CT evaluation of tumor size and that FDG-PET may serve as an early marker of tumor response^{22, 23}. PET has been evaluated for response assessment following conventionally fractionated thoracic radiotherapy²²⁻²⁷. Choi and colleagues describe how the residual metabolic rate of glucose utilization, as measured by PET, two weeks following preoperative radiotherapy or chemoradiotherapy predicted pathologic tumor response at surgery for locally advanced NSCLC²². Mac Manus and team report their prospective NSCLC trial of early (median 10 weeks following RT-based treatment) PET and found that post-RT PET predicted overall survival better than weight loss, performance status, tumor stage, or CT evaluation²⁷. Hicks reported additional data from this same series of patients showing that by using a meticulous PET-based visual response assessment technique, they were able to distinguish normal tissue inflammation from tumor²³.

Because the radiobiology of hypofractionated SBRT with single daily doses at times in excess of 20 Gy differs considerably from that of conventional (roughly 2 Gy per day) fraction sizes²⁸, it is unclear whether the above data are directly applicable in evaluating tumor response with PET following SBRT. The large fraction sizes used in SBRT may produce segmental atelectasis or focal fibrosis²⁹. In our experience, it may be difficult to distinguish such local SBRT-related phenomena from persistent or recurrent tumor. Other groups have also described this problem and some suggest that progress in lung cancer has been slowed by quandaries over radiation fibrosis versus residual disease¹⁷.

Data on PET following hypofractionated SBRT for early NSCLC are limited. Ishimori and team reported nine patients treated with SBRT for early stage NSCLC who were followed with both ¹¹C-methionine PET and FDG-PET. They report continuous SUV decreases over time for five patients, SUV rises at 1-2 weeks for two patients and SUV rises 3 months or more following SBRT in two patients³⁰. At IU, we have also retrospectively reviewed PET imaging in our patients treated on institutional SBRT prospective protocols³¹. Excluding the 14 patients that are the subject of this prospective report of PET and SBRT, we analyzed data from 57 patients with PET pre-SBRT and 28 patients with post-SBRT PET. Our analysis, with a median follow-up of 42 months, shows that isolated nodal recurrence following PET-staged I NSCLC is uncommon (10%). In our retrospective series we also note that 14% of SBRT patients maintain moderate SUVs (>2.5) 22-26 months following SBRT but on longer follow-up (42-49 months) all of these patients remain alive without evidence of local, regional or distant failure. A much more heterogeneous patient population, consisting of primary and recurrent NSCLC and lung metastases, was evaluated by Coon et al³². They treated their patients with SBRT, delivering 60 Gy in 3 fractions. With a median follow-up of 12 months, they reported on 28 patients that had both pre- and post-treatment PET/CT scans. Patients with stable disease had a mean SUV decrease of 28%; those with partial response had a decrease of 48%, those with complete response had a decrease of 94%, and those with progressive disease had a decrease of only 0.4%.

Our current series has a longer period of imaging follow-up than the series by Ishimori et al and Coon et al. This prospective series also has the advantage of all PET studies being performed on the same scanner, making comparisons between pre- and post-treatment scans more reliable. Our data indicate that more than half of patients maintain a moderately elevated SUV_{max} of > 3.5 one year following SBRT. The results of our own prospective phase II trial, as well as large series with longer follow-up from Japan and Sweden, report the local control of SBRT to be greater than 80%^{12, 15, 33, 34}. Taken together, these observations would seem to indicate that a substantial proportion of patients who do not go on to develop local failure maintain persistently elevated SUV out to at least one year. This confirms initial findings from our retrospective review of PET and SBRT in a similar patient population³¹.

Possible explanations for these persistent SUV elevations include non-malignant stromal cells/normal tissue with unresolved post SBRT metabolic changes, reproductively dead but metabolically active tumor cells, and very indolent but reproductively capable tumor cells. The observation that many patients treated with SBRT for early NSCLC maintain a persistent SUV above the institutional baseline is significant as we evaluate definitions of local failure in an attempt to direct salvage strategies. While it would be incorrect to classify all patients with a post-SBRT SUV above base-line as treatment failures, this does not mean that PET has no utility following SBRT. In our experience, at some point, the vast majority of locally recurrent NSCLCs will show progressive elevations in SUV.

The ability of PET/CT to predict local control or toxicity cannot be addressed with our data, as we found no local recurrences and toxicity rates were low. We did observe one patient to have a progressive rise in SUV of the treated lesion. This was accompanied by CT findings demonstrating increased size, which could be consistent with atelectasis, scar formation, infection, or tumor growth. Due to these suspicious CT and PET findings, we obtained a biopsy, which revealed only necrosis. Because the patient died of an apparent infection and his biopsy showed necrosis, he was classified as not having had a local recurrence. However, it is possible that his biopsy result represented a sampling error, as his SUV rise is consistent with that seen in other patients who have had biopsy proven recurrence.

This small prospective trial shows that it is feasible and low-risk to use PET/CT to serially image patients undergoing SBRT for early stage NSCLC. However, our results cannot be used to support routine use of PET/CT to follow patients after SBRT treatment. At our own institution, contrasted chest CT scans are obtained in follow-up. If there is a suspicious change seen on CT, a follow-up PET/CT is obtained. It remains an open question as to whether PET/CT could be used to predict response or toxicity, as has been observed in non-SBRT series²²⁻²⁷. Further study with larger patient numbers and longer planned follow-up would be necessary to better characterize the role of PET/CT in this setting before recommending routine use of serial PET/CT post-SBRT in all patients.

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Figure 1. SUV_{max} over time

The maximum standardized uptake value (SUV_{max}) of the 14 study patients at the time of their pre- and post-SBRT PET/CT scans is graphed. At 12 months post-SBRT, many patients still had SUV_{max} values of 3.5 or above, despite a lack of local failure seen on extended follow-up.

Table 1

Patient Characteristics

Characteristic	no. of patients
Age at treatment	
Median	72.5 years (range 55-86 years)
Gender	
Female	9
Male	5
Reason for medical inoperability	
FEV1 $\leq$ 40%	9
chronic cardiovascular disease	3
severe COPD	2
Pre SBRT FEV1 % predicted	
Median	40% (range 23-76%)
Pre SBRT FEV1	
Median	0.9 L (range 0.53 to 2.01 L)
Pre SBRT FVC % predicted	
Median	62% (range 31-121%)
Pre SBRT DLCO % predicted	
Median	52% (range 27-92%)
Baseline Oxygen Dependence	
Yes	3
Histology	
squamous	5
adenocarcinoma	4
unspecified	5
Stage	
IA	5
IB	9
GTV volume	
Median	13.6 cm ³ (range 2.4-211.8 cm ³)
PTV volume	
Median	56.1 cm ³ (range 17.3-394.1 cm ³)

Characteristic	no. of patients
Total dose in three fractions	
60 Gy	5
66 Gy	9

Abbreviations: no. = number; FEV1 = forced expiratory volume in one second; COPD = chronic obstructive pulmonary disease; SBRT = stereotactic body radiotherapy; FVC = forced vital capacity; DLCO = diffusion capacity of the lung for carbon monoxide; GTV = gross tumor volume; PTV = planning tumor volume

Table 2

Toxicity Analysis

n=14	Grade * 1	Grade 2	Grade 3	Grade 4
Fatigue	8	0	0	0
Skin Erythema	1	1	0	0
Subcutaneous Fibrosis	0	0	0	0
Esophagitis	1	0	0	0
Radiation Pneumonitis	1	0	0	0
Decline in PFTs	3	3	0	0
Radiation Fibrosis	0	0	0	0
Other Adverse Events	7	4	4 [†]	0

* Grade refers to toxicities reported using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0

[†] These grade 3 “other adverse events” included one patient with pleural effusion which was felt to be possibly related to SBRT, and three patients with toxicity felt to be unrelated to SBRT: one patient with bronchitis, one with infectious pneumonia and one with a congestive heart failure/emphysema exacerbation (the patient with pleural effusion also had bronchitis, so two grade 3 toxicities were scored in this one patient).

Abbreviations: PFT = pulmonary function testing; SBRT = stereotactic body radiotherapy

Table 3**SUV Trends Over Time**

	SUV _{max}		Ratio of tumor SUV _{max} to reference organs		
	median	range	<u>tumor</u> blood	<u>tumor</u> lung	<u>tumor</u> liver
pre-SBRT	8.70	1.37 – 15.22	3.34	12.72	2.85
2 weeks post	6.04	0.14 – 10.87	2.34	8.99	1.81
26 weeks post	2.80	1.12 – 9.18	1.35	6.20	1.08
52 weeks post	3.58	0.06 – 14.61	1.07	4.15	0.85

Abbreviations: SUV = standardized uptake value; SUV_{max} = maximum standardized uptake value; SBRT = stereotactic body radiotherapy