ORIGINAL RESEARCH

Robotic stereotactic body radiation therapy for elderly medically inoperable early-stage non-small cell lung cancer

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Introduction: Stereotactic body radiation therapy (SBRT) is being increasingly applied in the treatment of non-small cell lung cancer (NSCLC) because of its high local efficacy. This study aims to examine survival outcomes in elderly patients with inoperable stage I NSCLC treated with SBRT.

Methods: A total of 31 patients with single lesions treated with fractionated SBRT from 2008 to 2011 were retrospectively analyzed. A median prescribed dose of 48 Gy was delivered to the prescription isodose line, over a median of four treatments. The median biologically effective dose (BED) was 105.6 (range 37.50–180), and the median age was 73 (65–90 years). No patient received concurrent chemotherapy.

Results: With a median follow up of 13 months (range, 4–40 months), the actuarial median overall survival (OS) and progression-free survival (PFS) were 32 months, and 19 months, respectively. The actuarial median local control (LC) time was not reached. The survival outcomes at median follow up of 13 months were 80%, 68%, and 70% for LC, PFS, and OS, respectively. Univariate analysis revealed a BED of >100 Gy was associated with improved LC rates ($P = 0.02$), while squamous cell histology predicted for worse LC outcome at median follow up time of 13 months ($P = 0.04$). Increased tumor volume was a worse prognostic indicator of both LC and OS outcomes ($P < 0.05$). Finally, female gender was a better prognostic factor for OS than male gender ($P = 0.006$). There were no prognostic indicators of PFS that reached statistical significance. No acute or subacute high-grade toxicities were documented.

Conclusion: SBRT is a safe, feasible, and effective treatment option for elderly patients with inoperable early stage NSCLC. BED, histology, and tumor size are predictors of local control, while tumor size and gender predict OS.

Keywords: SABR, CyberKnife, BED, gender, histology

Introduction

The standard treatment for stage I non-small cell lung cancer (NSCLC) is surgical resection.[1,2] Definitive anatomic resection carries a favorable local control (LC) rate and overall survival (OS).[1] Some patients, however, are medically inoperable because of an unacceptable risk of operative complications and mortality.[3,4] Alternative treatment options have traditionally included limited surgical resection[5] or conventional radiotherapy.[6] Both approaches, however, yield poorer outcomes.[5,6] Five-year survival rates of 45%–59% and 0%–42% are generally expected from limited surgical resection and conventional radiotherapy treatment, respectively, for inoperable stage I NSCLC.[7,8]

Stereotactic body radiation therapy (SBRT) was introduced for the treatment of inoperable early stage NSCLC over a decade ago.[9] Using image guidance, SBRT

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allows for the reduction of dose to critical structures thus enabling the delivery of much higher doses to the target.[10] LC outcomes from early SBRT studies have been confirmed in two recent multicenter Phase II SBRT trials.[11,12] Timmerman et al reported a primary tumor control rate of 97% and LC (in the involved lobe) of 91% at 3 years[11] following SBRT, whereas Baumann et al reported a 3-year LC rate of 92%.[12] OS rates with such techniques have been poor, but this has been attributed to medical comorbidities rather than disease progression or treatment-related toxicity.[9–11]

The CyberKnife system (Accuray Inc, Sunnyvale, CA, USA) integrates a robotically positioned linear accelerator (LINAC) with image-guided stereotactic localization. Its ability to dynamically track targets that move with breathing, with the Synchrony tumor tracking component, is a key feature of this system.[13] Retrospective studies using this system have shown favorable outcomes in LC and OS, of 91% and 75%, respectively.[14–30] The purpose of the present retrospective analysis was to evaluate the outcomes of patients with surgical high-risk, stage I NSCLC treated at our institution, using robotic hypofractionated SBRT.

Methods
Eligibility

After research ethics board approval was obtained, all patients with a diagnosis of clinically staged IA or IB NSCLC (per the American Joint Committee on Cancer, staging manual, 7th edition[31]) who were treated between 2008 and 2011 with curative-intent radiotherapy at the Virginia Hospital Center, were identified. Patients who had received hypofractionated radiotherapy were retrospectively reviewed. All such patients were either inoperable, as determined by thoracic surgeons, or had refused surgical intervention. All patients had a histologic diagnosis of NSCLC, and all had available a history; a physical examination; computed tomography (CT) imaging of the chest, abdomen, and pelvis; whole body positron emission tomography (PET) scan, brain magnetic resonance imaging (MRI) or CT. The exclusion criteria included recurrent lung cancers or lung metastases, metachronous lung cancer, loss to follow up, or postoperative radiation regimens. Patients treated previously with SBRT were not included in the study population. Charts were reviewed to determine patterns of disease failure, toxicity (as defined by the Common Terminology Criteria for Adverse Events, version 3.0), and outcome.

Fiducial placement

Most patients received fiducial placement (Gold Fiducial Markers, Best Medical International Inc, Springfield, VA, USA) into the adjacent soft tissue for real-time image guidance, either bronchoscopically, or percutaneously: Two to four gold fiducials, 0.8–1 mm in diameter by 3–7 mm in length, were usually placed in a noncollinear arrangement for best translational correction of the radiation beam position. To minimize fiducial migration, a 1–2 week period of time was allowed before simulation was commenced, in order to decrease procedural edema and permit fibrosis and fixation of the fiducials.

For lesions that were adjacent to and did not move independently of the spine (five of the 31 patients), spinal tracking (X-Sight™ Spine Prone Tracking System; Accuray Inc), which uses spine bony landmarks, was utilized instead. Pretreatment digitally reconstructed radiographs (DRRs) were generated from the CT scans. Three-dimensional target displacements and global rotations of the spinal structures were determined by comparing radiographs with the DRRs. Translations and global rotations were aligned during patient setup and corrected during treatment delivery.

Treatment planning

Fine-cut (1.25 mm) CT was used for targeting and treatment planning. The planning CT scans were done with intravenous (IV) contrast when needed to allow better distinction between tumor and adjacent vessels or atelectasis. The target lesion was outlined by a radiation oncologist and designated as the gross tumor volume (GTV). The target was generally drawn using CT pulmonary windows. However, a soft-tissue window with contrast was sometimes used to avoid inclusion of the adjacent vessels, atelectasis, or mediastinal or chest wall structures, within the GTV. This target included only abnormal CT signal consistent with gross tumor (ie, the GTV and the clinical target volume were identical). PET/CT fusion was done for all patients, and PET data were used in defining the GTV. An additional margin of 5 mm was added to the GTV to constitute the planning target volume (PTV), but adjustments were made by the treating physician, based on tumor location, proximity of critical structures, and tumor motion during treatment.

Dosimetry

Three-dimensional noncoplanar beam arrangements were custom designed for each case, to deliver highly conformal

prescription dose distributions. Generally, more beams were used for larger lesions. As such, prescription lines covering the PTV were typically around the 80% (but ranging between 60%–90%) line, rather than the more traditional 95%–100%. Higher isodoses (hotspots) were manipulated to occur within the target and not in adjacent normal tissue.

To ensure good coverage, the prescription isodose surface was chosen such that 95% of the PTV was conformally covered by the prescription isodose, and 99% of the PTV received a minimum of 90% of the prescription dose. For target dose heterogeneity, the prescription isodose surface selected had to be ≥60% and ≤90% of the dose at the center of mass of the PTV. Any dose >105% of the prescription dose was forced to occur primarily within the PTV itself and not within the normal tissues outside the PTV. Therefore, the cumulative volume of all tissue outside the PTV receiving a dose >105% of prescription dose should not have been more than 15% of the PTV volume. The following critical structures were contoured: the spinal cord, esophagus, brachial plexus, heart, trachea and proximal bronchial tree, whole lung, and skin. The dose tolerance to the critical structures was in accordance with the American Association of Physicists in Medicine Task Group 101.[32] Treatment conformity was determined in all patients using the New Conformity Index (NCI), which was calculated by the formula: treatment volume × prescription isodose line/volume of target covered by the prescription isodose line.[2]

Treatment delivery and follow-up studies

Tumors were actively tracked in real time during treatment using Synchrony™. For the treatments, the patient wore a tight-fitting elastic vest. Three beacons, emitting visible red light pulsed at 30 Hz, were placed on this vest. The beacon positions were monitored by a camera mounted at the foot end of the patient couch. This camera continuously recorded the position of the markers during the patients' respiration cycle. In parallel, a series of X-ray images of the internal fiducials was taken with the patient breathing freely. These images established the position of the fiducials and thus, the tumor at the time of these images. The time stamps of the beacon data (as captured by the camera) and the location data of the internal fiducials (as determined at the instant of the X-ray images) were synchronized. From a series of these images, a correlation model, between the external and internal positions, was established. Thus, using the instantaneous information from the external beacon, the position of the tumor was calculated. Using this dynamic model, the robot was able to track the tumor motion in real time, while the radiation was delivered. As treatment commenced, X-ray images were taken, either before each therapeutic beam or less frequently, for systematic breathers, updating the model. Clinical examinations and PET/CT imaging were performed at 3-month follow-up intervals from the end of the treatment.

Statistical analysis

Progression-free survival (PFS) was defined as the time from the first day of SBRT treatment to local, regional, or distant failure or last follow-up visit in living patients without evidence of recurrence or progression. The LC, local failure, regional failure, and distant failures were defined, as previously described elsewhere.[33] Patients were censored at the time of death. The OS was defined as the time from SBRT treatment until death or the last follow-up visit. Interpretation of the available fluorodeoxyglucose (FDG-PET)/CT and CT scans and correlative clinical examinations were used to assess for response of the treated lesion 3 months after SBRT. Tumor measurements at each follow up were carried out using the Response Evaluation Criteria In Solid Tumors (RECIST), according to which a complete response (CR) is defined as total tumor disappearance and a partial response (PR) is defined as a 30% or greater decrease in the longest tumor diameter. We defined CR as no evidence of disease in the treatment volume, by both radiographic and direct clinical examination. "No response" was defined as an absence of marked change or increase in the treated lesion. PR was defined as not meeting the criteria for CR or no response. A univariate analysis was conducted to evaluate the association between each survival outcome, and the following independent variables considered: histology (adenocarcinoma, SCC), gender (male, female), biologically effective dose (BED) (<100, >100 Gy), T stage (1, 2), age (in years), GTV (in cubic centimeters), SBRT dose (in Gy), smoking (in number of pack years), and Karnofsky Performance Status (KPS). All correlations were initially identified by Cox regression analysis and if significant, the logrank test was run for generation of Kaplan–Meier plots, for select factors. Acute toxicities that occurred during treatment or within the first 2 weeks following the end of treatment, including fatigue, chest pain, shortness of breath, cough, hemoptysis, wheezing, and esophagitis, were examined. Radiation pneumonitis was examined as a subacute toxicity in all patients. Analyses were performed in SAS version 9.2 (SAS Institute Inc, Cary, NC, USA).

Results

Patient characteristics

A total of 36 patients with inoperable early stage NSCLC were treated. Five patients were excluded from the analysis: one did not have a biopsy-proven tumor, two patients had no follow-up information, and two patients had two separate lesions. A total of 31 patients with stage I inoperable NSCLC were therefore included in this study. The baseline patient and disease characteristics are listed in Table 1. The group comprised 61% males and 39% females, and the median patient age at the time of treatment was 73 (range 65–90). The majority (96%) of patients were smokers, and the median KPS for all patients was 85. The histology varied between SCC (35.5%) and adenocarcinoma (64.5%). The majority of the tumors were peripheral (74%), while 26% qualified as central tumors. Most patients presented with T1 disease (74%), with a median tumor volume of 24.05 cm^3 (range 3.90–151) and a median maximum diameter of 2.42 cm (range 1.2–5.0).

Treatment characteristics

The treatment characteristics are presented in Table 2. A median prescribed dose of 48 Gy was delivered to the prescription isodose line over a median of four 1- to 2-hour treatments over 5–10 days (median 7 days). The median dose per fraction was 12 Gy (range 12–20 Gy). The median BED was 105.6 (range 37.50–180). On average (mean and median), 96% of the PTV was conformally covered by the prescription isodose line (range 94%–99.85%). The median NCI was 1.46 (range 1.27–2.69). The median percent of the total lung volume receiving 15 Gy or more was 6.5%. In general, tumors that were centrally located received slightly lower median BED and had better conformity (Table 2). There were no patients that received concurrent chemotherapy.

Clinical outcomes and prognostic factors

The median follow up was 13 months (4–40), with a median OS of 32 months and a median PFS of 19 months. The median

Table 2 Treatment characteristics for all patients and subdivided by tumor location (peripheral, central)

	Mean, median (range)
Prescribed dose on all patients, Gy	49.03, 48.00 (25–60)
Peripheral lesions	47.97, 48.00 (30–60)
Central lesions	44.67, 48.00 (25–50)
Prescription IDL on all patients, %	82.55, 82.00 (74–93)
Peripheral lesions	83.59, 83.00 (74–92)
Central lesions	82.00, 81.00 (74–93)
Number of fractions on all patients	4.09, 4.00 (3–5)
Peripheral lesions	4.26, 4.00 (3–5)
Central lesions	4.56, 5.00 (4–5)
Dose per fraction on all patients, Gy	12.8, 12.00 (5–20)
Peripheral lesions	11.77, 12.00 (6–20)
Central lesions	10.00, 10.00 (5–10)
BED on all patients	115.27, 105.60 (37.50–180)
Peripheral lesions	106.15, 105.60 (48–180)
Central lesions	91.04, 100.00 (37.50–105.60)
Coverage on all patients	96.42, 96.30 (94.30–99.85)
Peripheral lesions	96.34, 96.00 (94.30–99.30)
Central lesions	96.15, 96.40 (94.30–97.10)
NCI on all patients	1.56, 1.45 (1.27–2.69)
Peripheral lesions	1.57, 1.53 (1.27–2.69)
Central lesions	1.43, 1.43 (1.30–1.58)

Notes: The NCI is calculated by the formula: treatment volume × prescription isodose line/volume of target covered by prescription isodose line.[2]
Abbreviations: BED, biologically effective dose; IDL, isodose line; NCI, New Conformity Index.

LC was not reached. The 1-year OS, PFS, LC, and regional control rates were 70%, 68%, 80%, and 80%, respectively (Table 3 and Figure 1). Seven patients failed locally, and five of them were salvaged with SBRT reirradiation and to date, are alive, while two of the local failures died of the disease. Univariate analysis revealed that a BED of >100 Gy was associated with improved LC rates ($P = 0.02$). Histology was also a predictor of LC, with improved LC outcomes in tumors of adenocarcinomatous histology ($P = 0.04$) (Figure 2). Increased tumor volume was also a worse prognostic indicator for both LC and OS ($P < 0.05$). Female gender was a better prognostic factor for OS than male gender ($P = 0.006$)

Table 1 Patients' characteristics

Age (median, range)	(76, 65–90)
KPS (median, range)	(70, 60–100)
Gender (male, female)	(39%, 61%)
Smoker (yes, no) (median, range)	(96%, 4%) (40, 20–100)
Histology (adenocarcinoma, squamous)	(64.5%, 35.5%)
Clinical stage (T1N0, T2N0)	(74%, 26%)
Maximum diameter, cm (mean, median, range)	(2.42, 2.50, 1.2–5.0)
Volume, cc (mean, median, range)	(36.15, 24.05, 3.90–151)

Abbreviations: KPS, Karnofsky Performance Status.

Table 3 Clinical outcomes with actuarial rates at median follow up of 13 months

Median follow up (range in months)	13 (4–40)
Local control (%)	24/31 (80%)
Regional control (%)	26/31 (88%)
Distant control (%)	25/31 (84%)
Any progression (%)	10/31 (68%)
Overall survival (%)	21/31 (70%)
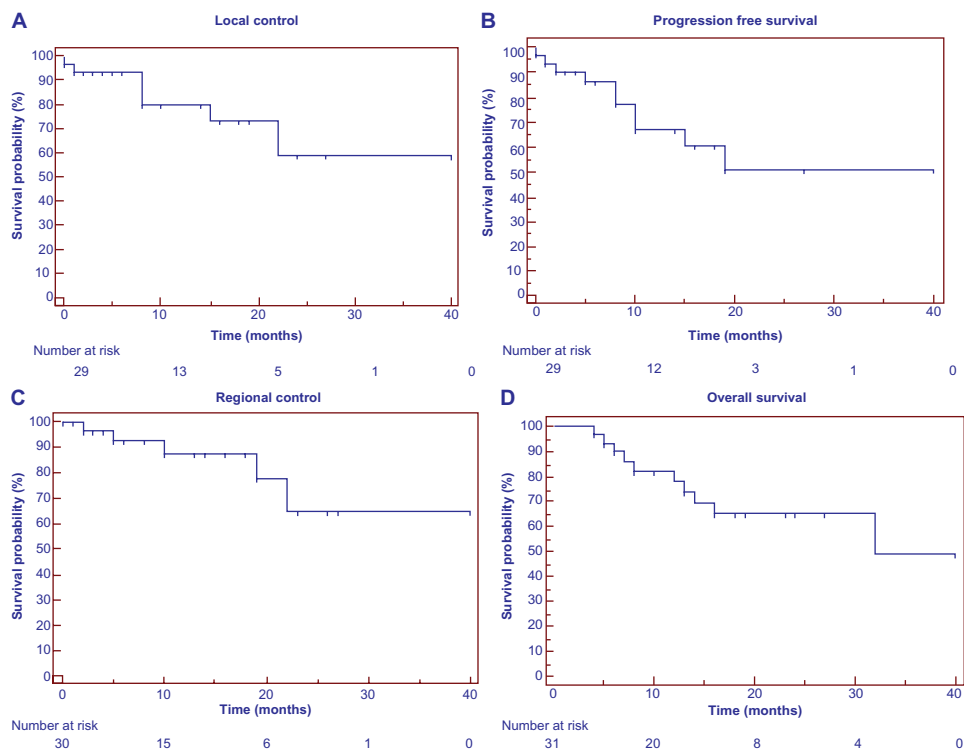
Figure 1 Survival outcomes of elderly inoperable patients with early stage lung cancer (n = 35); (**A**) local control; (**B**) progression-free survival; (**C**) regional control; (**D**) overall survival.

(Figure 3). There were no prognostic indicators of PFS that reached statistical significance.

Toxicity

Acute toxicities experienced by this patient population included fatigue that was experienced by four patients, and cough and chest pain that were reported by two patients. These symptoms self-resolved and did not require any medical intervention. Three patients experienced shortness of breath in the acute setting that was alleviated with bronchodilators. None of the patients experienced pneumonitis, esophagitis, or hemoptysis.
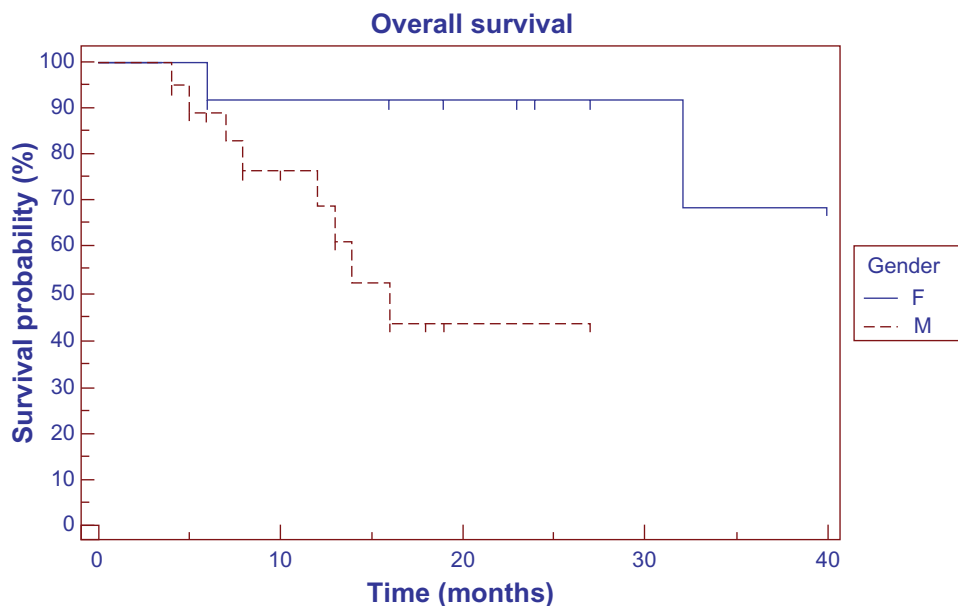
Discussion

For early stage patients who are medically inoperable, SBRT is becoming the standard of care.[9] The present study described
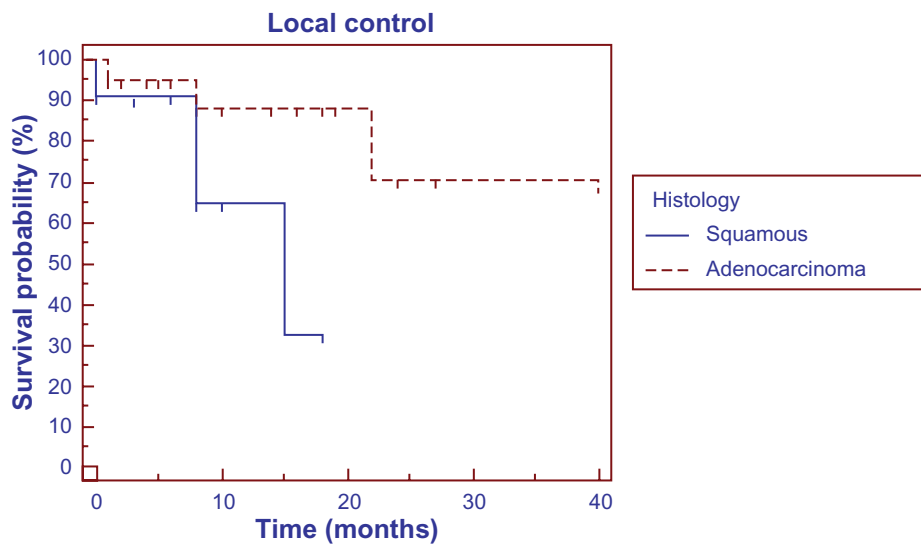
Figure 2 Local control and histology.

Overall survival

Figure 3 Overall survival and gender.

our recent experience with the definitive treatment of early-stage NSCLC inoperable elderly patients, using stereotactic radiosurgery with the CyberKnife system. The unique ability to dynamically track targets that move with breathing is a key feature that differentiates the CyberKnife from other commercially available image-guided platforms, which typically use either respiratory manipulation or respiratory gating in order to manage breathing-induced motion. The literature on SBRT use for early stage lung cancer reports 3-year LC and OS rates of 80%–98% and 43%–72%, respectively[9,11,34,35] Timmerman et al reported a 3-year LC rate of 91%–92% in two recent multicenter Phase II SBRT trials.[11,36] Similar LC outcomes have been reported with the CyberKnife system.[14–30] Our survival outcomes demonstrate equivalent OS rates but lower LC rates (80%) than that reported in the literature using this system. This could be due to the inherent heterogeneity between patient populations studied but could also be related to the fact that when SBRT was first utilized at our center, the dosing and the BED in particular were suboptimal.

Similar to previous reports, our results show that a BED of >100 Gy is a strong predictor of improved LC. With SBRT, the cumulative BED is significantly higher than that used with conventional radiation treatment. This high-precision SBRT delivery system allows for a sharp dose gradient at the edge of the target volume that enables the delivery of an ablative dose to the target, while minimizing treatment toxicity to a tolerable level. A BED above 100 Gy has been used as a cutoff for adequate dose; below this threshold, the

local recurrence risk is higher.[37–39] A recent meta analysis showed that a medium to medium-high BED, defined as BED range 83.2–146 Gy, correlated with improved survival in early stage NSCLC patients.[40] Our results also show a negative correlation between tumor volume, LC, and OS. This is consistent with the published literature demonstrating that the rates of local recurrence rates increase as tumor size increases.[37,39,41,42]

Our results show a correlation between a tumor histology of adenocarcinoma origin and improved LC rate. The association between tumor histology and radiation response has long been discussed, and it is generally believed that SCC is generally more responsive to radiation treatment.[43] A large multicenter retrospective analysis has shown patients with adenocarcinomatous histology to have significantly better overall prognosis to radiation treatment than those with squamous histology.[44] However, a recent prospective study examining the difference in SBRT response between the two histologies showed that although tumor shrinkage was faster for SCC than adenocarcinomas at 2 and 4 months, there was no difference in the mean tumor size at 6 months or in the 3-year LC.[45] Our results are likely biased by the small sample size and the low event rate; caution is therefore exercised in extrapolating any definitive conclusions from the data.

The strong correlation between female gender and improved OS reaffirms previously published results. In an analysis aimed at investigating the prognostic factors associated with improved survival outcomes in early stage NSCLC treated with SBRT, increased tumor diameter and

male gender were the only significant variables that negatively influenced OS on multivariate analysis.[42] Furthermore, a recursive partitioning analysis model showed gender to have a significant effect on OS outcome.[42] Similarly, a retrospective review of 831 nonmetastatic NSCLC patients treated with external beam radiation therapy (EBRT) at the MD Anderson Cancer Center showed gender to be an independent prognostic factor associated with survival outcomes;[46] among cases of medically inoperable Stage I NSCLC, the female patients had a better 5-year OS than did male patients (30.0% versus 13.1%, respectively).[46] Although our data agree with these published results, our sample size is comparatively small and limits the ability to draw any firm conclusion on the clinical significance of gender and survival outcomes in this patient population.

Conclusion

This study has demonstrated that the use of SBRT in inoperable, elderly patients with early stage NSCLC is well tolerated and provides acceptable LC outcomes. Our retrospective review is limited by potential selection bias, small sample size, and heterogeneous patient population and treatment parameters, and many issues remain to be elucidated. Our study lacked data on ethnic and racial background, and the impact of ethnicity and racial disparities on survival outcomes deserves investigation, especially as SBRT becomes a widely accepted application in early-stage NSCLC. Randomized, controlled trials are warranted in order to draw firm conclusions about the clinical benefit of SBRT in the treatment of this disease.

Acknowledgment

Disclosure

Dr Gagnon is on the clinical advisory board for US Radiosurgery. Actual or potential conflicts of interest do not exist for any other authors.

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