



Safety and Effectiveness of Cyberknife-Based Stereotactic Body Radiotherapy in Older Patients with Biopsy Proven Early Stage Non-Small Cell Lung Cancer: A Community Cancer Center Experience from the International Geriatric Radiotherapy Group

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Abstract

The aim of this article is to assess the safety and efficacy of cyberknife-based Stereotactic Body Radiotherapy (SBRT) among older patients (at least 70 years-old) whose medical conditions preclude surgery for their early stage Non-Small Cell Lung Cancer (NSCLC). A retrospective review of older patients with a median age of 82 (range: 70 to 88 year-old) who had cyberknife-based SBRT for early stage biopsy proven NSCLC in a community hospital was performed. Morbidity, complications, and local control were assessed. Among 33 older patients who had SBRT for early stage NSCLC, no patient developed grade 3 to 4 complications at a median follow-up of 19 months (range: 5 to 32 months). Only two patients (6%) developed local recurrences. Cyberknife-based SBRT is safe and effective for local control in older patients with early stage biopsy proven NSCLC whose medical conditions preclude surgery.

Keywords: Older; Lung cancer; Early stage; Co-morbidity; SBRT

Introduction

The prevalence of lung cancer increases with age. However, older lung cancer patients often face discrimination due to the perception that they may be too frail to receive curative therapy. Individuals who are 85 or older tend to receive supportive care [1], thus condemning them to a poor quality of life and death. As the prevalence of comorbidity factors also increases with age, primary care physicians may be reluctant to refer older lung cancer patients for curative treatment. Based on current data, for operable patients, surgery is the standard of care for early stage Non-Small Cell Lung Carcinoma (NSCLC) [2]. Indeed, for younger patients with good performance status, adequate pulmonary and cardiac function, lobectomy provides excellent local control and survival with reasonable complications [3]. However, surgical mortality is proportional to the number of comorbidity factors which makes older lung cancer patient a poor candidate for lobectomy [4,5]. In

the past, conventional radiotherapy for inoperable NSCLC has been reported to have a poor survival and a higher rate of complications because of inadequate radiation dose to the tumor and excessive lung dose [6,7]. However, there is currently an alternate choice for those patients whose medical conditions preclude surgery, Stereotactic Body Radiotherapy (SBRT) for early stage NSCLC. This advanced technique of radiotherapy delivers a high dose of radiation under image-guidance while sparing normal organs such as the lungs, and heart from excessive radiation. Prospective studies of SBRT for early stage NSCLC have been encouraging with good local control and minimal complications such as grade 3 to 4 pneumonitis and rib fractures [8,9]. However, most of those studies have been conducted in academic centers with a large body of experience stemming from treatment of a large number of patients of all age groups and physical conditions. In addition, besides RTOG 0236 which required histologic confirmation for inclusion into the trial, many institutions included lung lesions that were not biopsied, raising the question whether those lung masses were truly malignant.

We would like to report the safety and effectiveness of SBRT for older patients with biopsy proven early stage lung cancer who received treatment in a community cancer center in our international research network (<http://www.igrg.org>). Our experience may sway primary care physicians to refer older lung cancer patients with multiple comorbidity factors for curative radiotherapy instead of hospice care. In the time of Coronavirus Disease 19 (COVID-19) infection, SBRT may also offer a safer alternative to surgery as the procedure is performed as an outpatient.

Materials and Methods

A total of 55 patients with NSCLC were treated with Cyberknife at Brandon Regional Hospital in Florida from 2009 to 2012, of which 33 patients were 70 years old or older. All patients had adequate follow-up ranging from 5 to 32 months (median: 19 months). The institutional review board at Brandon Regional Hospital approved the study. All methods were performed in accordance with the institution relevant guidelines and regulations.

The patients were not candidates for surgery because of the presence of multiple co-morbidity factors alone or in combination with poor functional status. No patient declined surgery.

All patients had the following:

1. Proven biopsy NSCLC.
2. Signed informed consent before the procedure.
3. Staging Positron Emission Tomography/Computer Tomography (PET-CT) scan prior to the procedure.
4. Peripheral disease defined as 2 cm or more away from the main stem bronchus.

Prior to radiotherapy, all patients underwent placement of fiducial markers to localize tumor location. The fiducials were detected by orthogonal X-rays at the treatment room. The system included an infrared camera which monitored the chest wall movement. During treatment, the location of the fiducials was tracked in real time during the breathing cycle to allow treatment accuracy. The synchrony respiratory motion tracking system is used to tract the target in real time with respiration. Thus, 4-Dimension CT scan was not necessary for treatment planning.

Planning CT images were obtained with a slice thickness of 1.25

mm. Planning CT scan was performed 10 days after fiducial placement to minimize potential migration of the markers. The patients were immobilized with a body vacuum bag in the supine position with the arms positioned next to the body. The diagnostic PET-CT scan was fused to the planning CT scan to outline the Gross Tumor Volume (GTV). A margin of 5 mm was added around the GTV to outline the Planning Target Volume (PTV).

Stereotactic body radiotherapy was delivered by Cyberknife Robotic Radiosurgery Treatment Unit (Accuray Inc. Sunnyvale, USA). A total of 100 to 200 non-coplanar beams using Iris various aperture collimator ranging from 15 mm to 60 mm was delivered with a dose rate of 600 MU/minute.

Radiotherapy dose and fractionation was personalized to deliver a minimum of 100 Gy Biological Effective Dose (BED) dose based on the linear quadratic formula with α/β of 10 for early responding tissue. However, when the PTV is adherent or close to the chest wall, the dose was reduced to avoid pathological fracture which may lead to pneumonia and death in patients with restricted pulmonary reserve.

Acute and long-term toxicities were graded according to Radiotherapy Oncology Group (RTOG) severity scale (<http://ctep.cancer.gov>). Survival data was analyzed using Kaplan-Meier estimation.

Results

Except for three patients, all patients were smokers. Their age ranged from 70 to 88-years old (median: 82). All patients had severe co-morbidity factors ranging from 1 to 6 (median: 3). The most common comorbidity factors were Chronic Obstructive Pulmonary Disease (COPD) (n=20) and Coronary Artery Disease (CAD) (n=19). They were staged as IA (n=26) or IB (n=7) based on the 7th edition of American Joint Committee on Cancer. There were 11 squamous cell carcinoma, 8 adenocarcinoma, and one bronchoalveolar carcinoma. In 13 patients, the biopsy sample was not adequate enough to distinguish between adenocarcinoma and squamous cell carcinoma and was labeled NSCLC.

All patients tolerated the SBRT very well. There were no grade 3 to 4 complications during the treatment. At a median follow-up of 19 months (range 5 to 32 months), there was no long-term complications. Two patients (6%) developed local and mediastinal recurrences. Three patients developed distant metastases in the brain

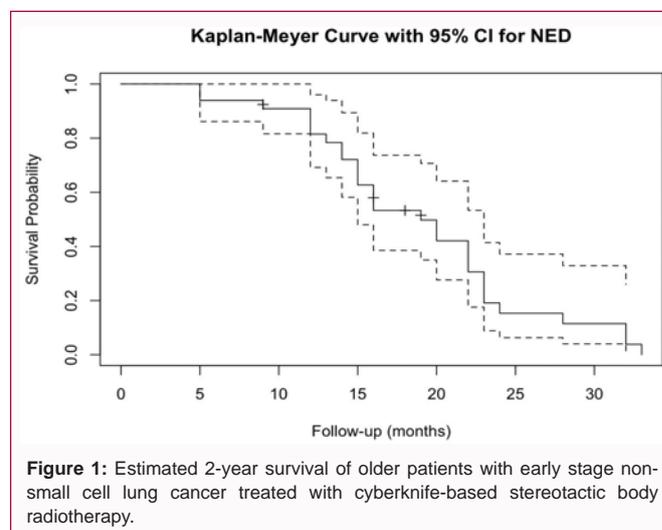


Table 1: Patient characteristics.

Patient number:	33
Age:	70-88 (Median:82)
Race:	
Caucasians	33
Sex:	
Female	22
Male	11
Stage:	
IA	26
IB	7
Histology:	
NSCL	13
Squamous	11
Adenocarcinoma	8
Bronchoalveolar	1
Location:	
RUL	9
RLL	9
RML	1
LUL	8
LLL	6
Peripheral:	33
Smokers	30
Radiation dose:	
12.50 Gy times 4 (BED=112.5)	14
12 Gy times 4 (BED=105.6)	5
10 Gy times 5 (BED=100)	6
20 Gy times 3 (BED=180)	4
18 Gy times 3 (BED=151.2)	2
16 Gy times 3 (BED=124.8)	1
9 Gy times 5 (BED=85.5)	1
Follow-up (months):	5-32 (Median:19)

NSCLC: Non-Small Cell Lung Cancer; RUL: Right Upper Lobe; RLL: Right Lower Lobe; RML: Right Middle Lobe; LUL: Left Upper Lobe; LLL: Left Lower Lobe, BED: Biologic Equivalent Dose

(n=1), bone (n=1), and liver (n=1). The two patients who developed local recurrences were treated to 85 Gy (stage IA) and 105 Gy (stage IB) respectively (biological equivalent dose). Those two patients also developed mediastinal recurrences. Overall, 28 patients (84.8%) had no evidence of disease at their last follow-up visit. The 2-year survival and disease-free survival was estimated to be 51.9% (Figure 1) and 80.4% (Figure 2) respectively. Table 1 and Table 2 summarize patient characteristics and treatment outcome respectively.

Discussion

The population in the United States (US) and Western Europe is getting older. The US Census Bureau estimates that by 2050, the population aged 65 and older is projected to be 83.7 million which is almost double its estimated population of 43.1 million in 2012 [10]. As the population gets older, the incidence of cancer also increases, and in particular lung cancer among former smokers. Two-thirds of new

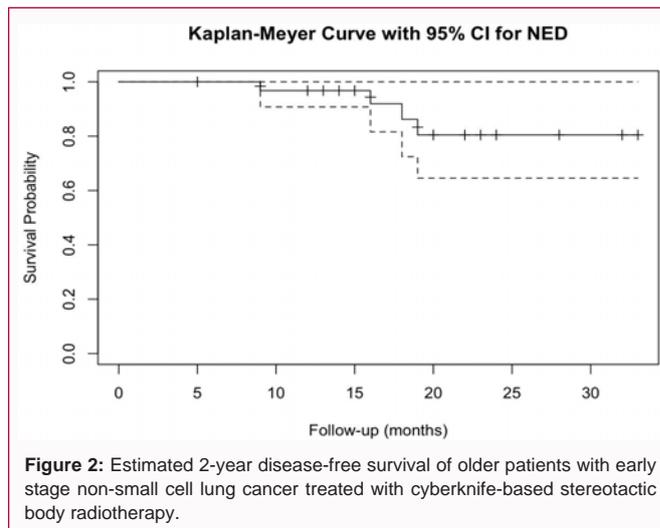


Figure 2: Estimated 2-year disease-free survival of older patients with early stage non-small cell lung cancer treated with cyberknife-based stereotactic body radiotherapy.

Table 2: Toxicity and efficacy of Cyberknife-based stereotactic body radiotherapy in elderly cancer patients with early stage non-small cell lung cancer.

Grade 3-5 toxicity:	0%
Late complications:	0%
Loco-regional recurrences:	2/33 (6%)
Distant metastases:	2/33 (6%)
No evidence of disease:	28/33 (84.8%)

lung cancer is diagnosed in patients over age 65 [11]. Among those patients, approximately 20% have early stage NSCLC [12]. Those patients may become frail because the morbidity index also increases with age and may not receive any treatment [4,5,13]. Frailty is defined as a state of increase vulnerability to a stressor event such as surgery, preventing the patient from returning to homeostasis because of the decline of multiple physiological systems. As half or more of older cancer patients are reported to be frail, they are at a particular risk of developing postoperative complications following surgery for lung cancer [14]. Thus, a treatment modality which minimizes toxicity and provides optimal local control would be ideal for those patients.

Stereotactic body radiotherapy has been introduced as an excellent treatment modality for patients with early stage NSCLC whom medical conditions preclude lobectomy. The combination of daily imaging combined with a steep dose gradient from the target volume allows delivery of a high radiation dose to the tumor, thus sparing the adjacent normal organs such as the lungs. Prospective studies on SBRT for early stage NSCLC have been encouraging with excellent local control and significant reduction of grade 3 to 4 pneumonitis [9].

Compared to Video-Assisted Thoracic Surgery (VATS) which carry minimal surgical morbidity, SBRT for early stage NSCLC has been reported to have less complications and similar survival especially for patients who were candidates for surgery but chose SBRT instead [8,15]. A pooled analysis of patients with early stages NSCLC also demonstrated similar survival between lobectomy and SBRT. In addition, the study corroborated SBRT low complication rates compared to lobectomy [16]. Thus, SBRT may be ideally suited for older lung cancer patients because of its minimal morbidity. However, most of the SBRT data reported in the literature has been focused in academic centers with a plethora of experience in managing patients with multiple comorbidity. As most of patients will be

treated at local community cancer centers with limited resources, our experience in managing those patients would be valuable in making SBRT recommendations.

Cyberknife-based SBRT has been reported to be a safe treatment modality with low complications rates even for central located lung tumors [17]. The real time tumor tracking and risk-adapted fractionation allows low to moderate toxicity following SBRT for lung cancer [18]. In our study, we did not observe any long-term grade 3 to 4 complications which may be due to many factors. All the lesions were located in the periphery of the lung away from critical structures such as the central airway and main blood vessels. In addition, we fractionated the treatment to minimize complications rates. For example, the patient who was treated to a BED of 85.5 Gy recurred locally following treatment because his lesion was located close to the chest wall, raising concern about the risk of rib fracture which could be debilitating. As total lung capacity decreases with age, in older patients the pain induced by the fracture may lead to hypoventilation, pneumonia, and possible death [19-21]. Finally, our median follow-up of 19 months is relatively short for this population with multiple co-morbidities who may die from inter-current disease before the development of complications.

To illustrate our last argument, the 2-year survival was only 51.9% while the 2-year disease-free survival was estimated to be 80.4%. Only two patients (6%) developed local recurrences. Those two patients also developed mediastinal recurrences which may be secondary to local recurrences. Our excellent local control may be due to the high BED as all but one patient were treated to a BED of 100 Gy or above [8]. Other studies of Cyberknife-based SBRT for early stage NSCLC also corroborated the high local control rate achieved with this technique of radiotherapy [22-24].

Our study illustrates the safety and efficacy of cyberknife-based SBRT for older patients with early stage NSCLC in a community setting. We chose the age of 70 as a cut-off because of anthropometric studies reporting increased weight loss and sarcopenia in men and women after the age of 70 [25,26]. Those patients are at increased risk of complications rates following surgery [27]. Our patient population also illustrates the operative risk of older patients with lung cancer undergoing surgery as the median co-morbidity factor was 3 (range: 1 to 6). The most common comorbidity factors were severe COPD and CAD precluding surgery. Rivera et al. [28] reported a 44% mortality rate following lung cancer surgery for older patients when they had three or more comorbidity factors. Our study also highlights the importance of a multidisciplinary approach involving all specialties such as thoracic surgeons, medical oncologists, radiation oncologists, and geriatricians for the management of older cancer patients [29]. The consensus reached by the tumor board has been reported to provide optimal outcome for patients with multiple comorbidities [30]. Despite the risk of treating those patients, Wang et al. [31] also corroborated the low morbidity of Cyberknife-based SBRT for patients with a presumed diagnosis of NSCLC based on PET-CT scan. However, compared to Wang et al. study, all of our patients had a biopsy proven NSCLC. When we review the literature of SBRT for elderly patients with early stage NSCLC, most studies are characterized by a high rate of presumed non-biopsied tumors which makes data interpretation difficult [32]. Those lesions may be benign or may represent a different histology such as small cell lung cancer with a different pattern of failures.

We would like to emphasize that older cancer patients are at

risk of death if infected during the COVID-19 pandemic because of their age and co-morbidity [33,34]. Delaying their treatment because of elective surgery cancellation may allow disease progression and compromise survival [35]. On the other hand, patients with asymptomatic infection may expose Health Care Workers (HCW) to infection because of the risk of aerosolization during intubation [36,37]. In addition, surgery for asymptomatic infected COVID-19 patients carries a high risk of mortality [38,39]. Thus, SBRT may offer a safe alternative to surgery for early stage NSCLC during this uncertain time provided that proper measures are taken to protect both patients and HCW from infection [40]. As an organization devoted to older cancer patients, the International Geriatric Radiotherapy Group would like to conduct SBRT for early stage NSCLC in its network of over 1100 institutions in 126 countries to assess its impact on patient quality of life [29].

The limitations of the current study include the retrospective nature of the study, the small number of patients, short follow-up, and absence of centrally located tumors. Nevertheless, our study highlights the safety and efficacy of SBRT for older patients with early stage NSCLC who were not candidates for surgery in a community cancer center.

Conclusion

Cyberknife-based stereotactic body radiotherapy is a safe and effective treatment modality for older patients with biopsy proven early stage NSCLC whose medical conditions preclude surgery. Prospective studies should be performed in the future to assess the impact of SBRT on patient quality of life.

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