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## Stereotactic Body Radiotherapy for Early-stage Non–small-cell Lung Cancer in Patients 80 Years and Older: A Multi-center Analysis

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### Abstract

Stereotactic body radiotherapy (SBRT) for early-stage non–small-cell lung cancer use is evolving, with implementation in a rising geriatric oncologic population. Our study investigated the use of SBRT for non–small-cell lung cancer in 58 consecutive patients ≥ 80 years old at 4 academic centers. SBRT was well-tolerated with expected toxicity rates, excellent disease-specific outcomes, and patients with higher performance status deriving the greatest benefit.

**Background**—Stereotactic body radiotherapy (SBRT) is the standard of care for medically inoperable early-stage non–small-cell lung cancer. Despite the limited number of octogenarians and nonagenarians on trials of SBRT, its use is increasingly being offered in these patients, given the aging cancer population, medical fragility, or patient preference. Our purpose was to investigate the efficacy, safety, and survival of patients ≥ 80 years old treated with definitive lung SBRT.

**Methods**—Patients who underwent SBRT were reviewed from 2009 to 2015 at 4 academic centers. Patients diagnosed at ≥ 80 years old were included. Kaplan-Meier and multivariate logistic regression and Cox proportional hazard regression analyses were performed. Recursive

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#### Disclosure

The authors have stated that they have no conflicts of interest.

#### Supplemental Data

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partitioning analysis was done to determine a subgroup of patients most likely to benefit from therapy.

**Results**—A total of 58 patients were included, with a median age of 84.9 years (range, 80.1-95.2 years), a median follow-up time of 19.9 months (range, 6.9-64.9 months), a median fraction size of 10.0 Gy (range, 7.0-20.0 Gy), and a median number of fractions of 5.0 (range, 3.0-8.0 fractions). On multivariate analysis, higher Karnofsky performance status (KPS) was associated with higher local recurrence-free survival (hazard ratio [HR], 0.92;  $P < .01$ ), regional recurrence-free survival (HR, 0.94;  $P < .01$ ), and overall survival (HR, 0.91;  $P < .01$ ). On recursive partitioning analysis, patients with KPS  $\geq 75$  had improved 3-year cancer-specific and overall survival (99.4% and 91.9%, respectively) compared with patients with KPS  $< 75$  (47.8% and 23.6%, respectively;  $P < .01$ ).

**Conclusion**—Definitive lung SBRT for early-stage non-small-cell lung cancer was efficacious and safe in patients  $\geq 80$  years old. Patients with a KPS of  $\geq 75$  derived the most benefit from therapy.

### Keywords

Geriatric oncologic; Nonagenarians; Octogenarians; Performance status; Radiation pneumonitis

## Introduction

Stereotactic body radiotherapy (SBRT) is the standard of care for medically inoperable early-stage non-small-cell lung cancer (NSCLC), with local control rates of approximately 90%.<sup>1-8</sup> The adoption of lung SBRT has been swift, with its use now being investigated in patients who are surgical candidates<sup>9,10</sup> as well as those who would otherwise choose no other therapy.<sup>11</sup> With an aging oncologic population,<sup>12</sup> the treatment of octogenarians and nonagenarians with definitive lung SBRT will become more common, either owing to medical fragility or patient preference. There is limited literature exploring the efficacy and safety of definitive lung SBRT in this population, with small numbers of these patients on prospective trials and concerns about the utility of this treatment in patients who may die of competing risk factors.<sup>1,2,13</sup>

The objectives of this study were to evaluate the efficacy of definitive lung SBRT in patients  $\geq 80$  years old at the time of treatment in a high-volume multicenter academic practice. Additionally, given safety concerns in a potentially more medically fragile group, we sought to explore the toxicity of lung SBRT in this population and examine patient, tumor, and treatment factors associated with treatment-related toxicity.

## Methods and Materials

### Patient Selection

Under an institutional review board-approved protocol, the records of patients from 2009 to 2015 treated with definitive lung SBRT at Emory University Hospital, Emory University Hospital Midtown, Grady Memorial Hospital, and Emory St. Joseph's Hospital were reviewed. We excluded patients who started treatment before 80 years of age. Staging was

based on the seventh edition of the American Joint Committee on Cancer guidelines.<sup>14</sup> Treatment simulation, planning, and delivery was done per modern clinical trial standards.<sup>15</sup> All patients were followed with periodic physical exams and surveillance computed tomography (CT) imaging.

### Statistical Analysis

All statistics were computed using SAS software version 9.4 (Cary, NC). Patient characteristics examined included gender, age, history of prior cancer, history of prior lung cancer, history of prior thoracic radiation, active smoking status, smoking pack-years, Karnofsky performance status<sup>16</sup> (KPS) at time of initial consult (score, 0-100), and use of an angiotensin-converting-enzyme inhibitor (ACE-I) at time of initial consult. ACE-I usage was investigated owing to the evolving literature of its association with radiation pneumonitis (RP).<sup>17,18</sup> Tumor characteristics examined included histology (adenocarcinoma, squamous cell carcinoma, and not biopsied), T stage (T1a/T1b, T2a/T2b, and T3), tumor size, and tumor location. Treatment characteristics examined included method of mediastinal staging (positron emission tomography [PET]-CT with or without pathologic sampling), radiation dose per fraction, number of fractions delivered, and treatment delivery modality (intensity-modulated radiotherapy or volumetric arc therapy). Of note, age, KPS at the time of consult, smoking pack-years, tumor size, number of radiation fractions delivered, and radiation dose per fraction were treated as continuous variables. Local recurrence-free survival (LRFS) was defined as time from last treatment date to recurrence at treated site, death, or last follow-up. Regional recurrence-free survival (RRFS) was defined as time from last treatment date to recurrence in the same lobe of treatment, ipsilateral hilum, mediastinum, death, or last follow-up. Metastatic recurrence-free survival (MRFS) was defined as time from last treatment date to recurrence in the contralateral lung, any distant site of disease, death, or last follow-up. Death was included in these endpoints given the low event rate of tumor failures. Cancer-specific survival (CSS) was defined as time to death from causes other than lung cancer or last follow-up. Overall survival (OS) was defined as time to death or time to last follow-up from diagnosis. RP was defined using Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 grade 2 or higher. Survival estimates for endpoints of local control (absence of failure at the treated site), regional control (absence of failure at the lobe of treatment, ipsilateral hilum, or mediastinum), distant control (absence of failure at contralateral lung or distant sites), CSS, and OS were estimated using the Kaplan-Meier product limit method, and survival distributions were compared using the log-rank test.<sup>19</sup> Univariate association (UVA) of each variable with LRFS, RRFS, MRFS, CSS, and OS were assessed using Cox proportional hazard models and log rank tests. UVA logistic regression was assessed for RP. Multivariable (MVA) logistic regression and proportional hazard models were generated, using a backward selection with an alpha removal of 0.2. Recursive partitioning analysis was done to determine the relationship between KPS at time of consult to CSS and OS and generate 2 stratified classes.<sup>20,21</sup> Significance was assessed at the 0.05 level. Graphics were created using R version 2.15.1.

## Results

### Patient Characteristics

After review of 266 patient charts, 58 patients met the study inclusion criteria, with the rest excluded for being treated before the age of 80 years. The median follow-up time was 19.9 months (range, 6.9-64.9 months), median age at time of treatment was 84.9 years (range, 80.1-95.2 years), median KPS at time of consult was 75 (range, 50-100), and median tumor size was 2.05 cm (range, 0.8-6.3 cm). All patients were staged prior to therapy with a PET-CT scan. The other patient, tumor, and treatment characteristics of our study population are summarized in Table 1.

### Local Recurrence

There were 6 tumor recurrences at the treated site (10.4%), with median time to recurrence of 17.7 months (range, 5.0-62.4 months). On UVA, having prior lung cancer (hazard ratio [HR], 2.46; 95% confidence interval [CI], 1.06-5.72) and having any prior cancer (HR, 4.09; 95% CI, 1.50-11.13) were associated with shorter LRFS whereas higher KPS at time of consult (HR, 0.92; 95% CI, 0.89-0.96) was associated with longer LRFS (See Supplemental Table 1 in the online version). On MVA, T1a or T1b tumors (HR, 0.20; 95% CI, 0.04-0.90), and higher KPS at time of consult (HR, 0.92; 95% CI, 0.89-0.96) were associated with longer LRFS, whereas adenocarcinomas (HR, 6.36; 95% CI, 1.57-25.76) were associated with shorter LRFS (Table 2).

### Regional Recurrence

There were 12 regional tumor recurrences (20.7%), with median time to recurrence of 14.8 months (range, 2.2-64.2 months). On UVA, having prior cancer (HR, 3.08; 95% CI, 1.28-7.42), history of prior lung cancer (HR, 2.58; 95% CI, 1.15-5.77), and right middle lobe tumor location (HR, 5.49; 95% CI, 1.09-27.65) was associated with shorter RRFS, whereas higher KPS at time of consult (HR, 0.93; 95% CI, 0.90-0.96) was associated with longer RRFS (See Supplemental Table 2 in the online version). On MVA, only higher KPS at time of consult (HR, 0.94; 95% CI, 0.90-0.97) was associated with longer RRFS (See Supplemental Table 3 in the online version).

### Metastatic Recurrence

There were 6 metastatic disease recurrences (10.4%), with median time to recurrence of 18.1 months (range, 2.2-64.2 months). On UVA, history of prior cancer (HR, 3.56; 95% CI, 1.28-9.89) and history of prior lung cancer (HR, 3.75; 95% CI, 1.47-9.57) was associated with shorter MRFS, whereas higher KPS at the time of consult (HR, 0.91; 95% CI, 0.87-0.95) was associated with longer MRFS (See Supplemental Table 4 in the online version). On MVA, only higher KPS at time of consult (HR, 0.91; 95% CI, 0.87-0.95) was associated with longer MRFS.

### CSS

There were 9 deaths attributable to lung cancer (15.5%). On UVA, a history of prior cancer (HR, 4.20; 95% CI, 1.05-16.84) was associated with lower CSS, whereas higher KPS at time

of consult (HR, 0.94; 95% CI, 0.89-0.99) was associated with higher CSS (See Supplemental Table 5 in the online version). On MVA, history of prior lung cancer (HR, 7.75; 95% CI, 1.61-37.20) and older age (HR, 1.19; 95% CI, 1.01-1.42) was associated with lower CSS, whereas not being an active smoker (HR, 0.14; 95% CI, 0.02-0.87) was associated with higher CSS (Table 3). Two- and 3-year rates of CSS were 81.6% (95% CI, 64.5%-91.0%) and 72.6% (95% CI, 52.1%-85.4%), respectively.

## OS

There were 20 deaths at the time of analysis. On UVA, history of prior cancer (HR, 3.30; 95% CI, 1.19-9.11) and history of prior lung cancer (HR, 3.00; 95% CI, 1.22-7.36) were associated with lower OS, whereas higher KPS at time of consult (HR, 0.91; 95% CI, 0.88-0.95) was associated with higher OS (See Supplemental Table 6 in the online version). On MVA, only higher KPS at time of consult (HR, 0.91; 95% CI, 0.88-0.95) was associated with higher OS. Two- and 3-year rates of OS were 69.3% (95% CI, 53.6%-80.6%) and 56.4% (95% CI, 37.6%-71.6%), respectively. Figure 1 summarizes disease outcomes and survival endpoints for our series.

## Effect of KPS on CSS and OS

Given the association of KPS with all outcomes, we performed recursive partitioning analysis to determine a cutoff for CSS and OS significance. A KPS of 75 was the cutoff for 2 distinct groups of patients. Patients with KPS  $\geq$  75 had significantly improved CSS and OS (Figure 2). For patients with KPS < 75, the 2- and 3-year CSS rates were 67.2% (95% CI, 40.0%-84.2%) and 47.8% (95% CI, 19.1%-71.9%), respectively, whereas for patients with KPS  $\geq$  75, the 2- and 3-year CSS rates were both 96.2% (95% CI, 75.7%-99.4%). For patients with KPS < 75, the 2- and 3-year OS rates were 49.9% (95% CI, 29.0%-67.6%) and 23.6% (95% CI, 5.3%-49.2%), respectively, whereas for patients with KPS  $\geq$  75, the 2- and 3-year OS rates were both 91.1% (95% CI, 68.4%-97.7%).

## RP and Other Treatment-related Toxicity

Overall, 20 patients (34.5%) developed grade 2 RP, with only 2 patients (3.5%) developing grade 3 RP. The median time to RP development was 5.2 months (range, 1.7-21.1 months). On logistic regression, UVA of variables associated with RP, T1 tumors (odds ratio [OR], 0.04; 95% CI, 0.01-0.41) were associated with lower rates of RP, whereas larger tumors (OR, 1.58; 95% CI, 1.01-2.48) and not being on an ACE-I (OR, 3.71; 95% CI, 1.12-12.27) were associated with higher rates of RP (See Supplemental Table 7 in the online version). On MVA, T1 tumors (vs. T3) (OR, 0.03; 95% CI, 0.01-0.37) were associated with lower rates of RP, whereas not being on an ACE-I (OR, 5.83; 95% CI, 1.29-26.32) was associated with higher rates of RP (Table 4).

There were a total of 7 other non-RP treatment-related toxicities (12.1%). Specifically, there were 3 grade 1 chest wall pain (mild pain) toxicities, 1 grade 2 chest wall pain (moderate pain limiting an instrumental activity of daily living) toxicity, 2 grade 3 chest wall pain (severe pain limiting self-care) toxicities, and 1 grade 3 esophagitis (severely altered swallowing requiring PEG tube placement) toxicity. There were no grade 4 or 5 toxicities

among the entire cohort at last follow-up. All patients completed their entire prescribed course of radiation.

## Discussion

The present study specifically addresses octogenarians and nonagenarians managed with definitive lung SBRT for early stage NSCLC in a multi-center setting. We demonstrated that treatment is efficacious, with overall tumor outcomes in line with other series reporting outcomes after definitive lung SBRT.<sup>1-3,5,7,9,10,22,23</sup> We also demonstrated that KPS at the time of consult was not only associated with OS outcomes but also disease-specific outcomes. Using recursive partitioning analysis, we showed that patients with KPS  $\geq 75$  have significantly improved CSS and OS.

Importantly, this study also examines prior lung cancer and prior thoracic radiation as patient factors, a common clinical scenario in patients  $\geq 80$  years old with early-stage lung cancer. In terms of treatment tolerance and toxicity, we found treatment was well-tolerated in this elderly cohort, with expected rates of RP and other treatment-related toxicities.<sup>2,3,24,25</sup> To our knowledge, this is the largest study examining definitive lung SBRT in octogenarians and nonagenarians in the United States with full disease and treatment toxicity information.

Patients  $\geq 80$  years old have not been well-represented on the landmark randomized trials establishing the effectiveness of lung SBRT. In the phase II multi-center study (RTOG 0236) by Timmerman et al,<sup>1,2</sup> they examined biopsy-proven T1-2N0M0 NSCLC in medically inoperable patients treated with SBRT to a total dose of 54 Gy in 3 fractions. Of the 55 evaluable patients, they found a 3-year primary tumor control rate of 97.6%, 3-year lobar control rate of 90.6%, and 3-year OS rate of 55.8%. The median age of patients on this trial was 72 years, with 86% of patients having a Zubrod performance status of 0 to 1. Despite the age difference in our series (median age, 84.9 years), we observed similar tumor control outcomes, with 10.4% local failures, 20.7% regional failures, and a 3-year OS rate of 56.4%, suggesting that lung SBRT is similarly efficacious in octogenarians. In the recently reported prospective trial JCOG0403 of biopsy-proven T1N0M0 NSCLC, patients were treated to 48 Gy delivered over 4 fractions.<sup>10</sup> They accrued 100 inoperable patients and 64 operable patients and showed a 3-year OS rate of 59.9% in inoperable patients and 76.5% in operable patients. Whereas the median age of 78 years in this study was higher than RTOG 0236, only 28% and 31% of the inoperable and operable patients, respectively, were over 80 years old. Ongoing randomized trials in lung SBRT including RTOG 0813 and RTOG 0618 do not have a distinct age cutoff, but it is difficult to report the number of patients  $\geq 80$  years old at this time, as recently reported results of RTOG 0813 in abstract form comment that “patients were elderly” without additional information.<sup>26</sup>

There are few studies examining lung SBRT in elderly patients. In a study by Hayashi et al, they examined outcomes of 81 patients treated with lung SBRT.<sup>25</sup> They dichotomized patients at 85 years, with 20 patients being placed in a “very elderly” cohort of  $\geq 85$  years old. They showed that 3-year local control rates were worse in the “very elderly” cohort compared with others (83.1% vs. 93.8%, respectively) as was 3-year OS rates (40.7% vs. 75.0%, respectively). These results differ from our series, with 3-year OS rate of 56.4%

(95% CI, 37.6%-71.6%). This difference is intriguing as no patient in the “very elderly” group in their series had a Zubrod performance status score of > 1, only 20% had tumors larger than T1, and all were treated with effective SBRT doses. In fact, our series represents a more high-risk cohort, with 32.8% having tumors larger than T1, with similarly good performance status (median, KPS 75). It is likely that the difference in outcomes could be attributed to either the 5-year difference in age (85 years old vs. 80 years old) or from the small number of patients in their “very elderly” cohort. These differences highlight one of the challenges with oncologic management: determine a subgroup of patients who are likely to experience a survival benefit despite competing risk factors, which generally would be much greater in an aging population. In an effort to answer this, we performed a recursive partitioning analysis using KPS to determine a threshold for improved outcomes. On this analysis, we found that patients with KPS  $\geq$  75 had improved CSS and OS (Figure 2). This finding will hopefully provide guidance for selecting a group of patients most likely to benefit from therapy. Other retrospective literature examining lung SBRT in older patients includes a database analysis examining 3147 patients  $\geq$  70 years old where 96 of the 258 patients treated with SBRT were  $\geq$  80 years old.<sup>27</sup> The authors found that SBRT had improved OS versus observation (HR, 0.64). In a recent series by Mancini et al, examining 251 patients treated with lung SBRT, they dichotomized patients at age 75. There were 126 patients  $\geq$  75 years old, with a median age of 82.1 years<sup>22</sup> defining their “elderly cohort.” They found no differences in 3-year local control among elderly and non-elderly cohorts (84.2% vs. 86.4%, respectively) or 3-year OS (47.5% vs. 41.0%, respectively). They did observe that distant disease control was improved in the elderly cohort, a finding also seen in other series.<sup>23,28</sup> We similarly found a low rate of distant recurrence (10.4%), with previous lung cancer history (HR, 3.75; 95% CI, 1.47-9.57) associated with increased rates. This finding is hypothesized to be related to less aggressive management of equivocal findings on follow up and more conservative restaging.<sup>22,23</sup>

One of the most significant concerns with treatment of octogenarians and nonagenarians is treatment-related toxicity. In a retrospective series from Japan examining 109 patients  $\geq$  80 years old with T1-2N0M0 NSCLC treated with lung SBRT there was a reported early grade 3+ RP rate of 4.6%.<sup>29</sup> The reported low rates of late toxicity, with grade 2 symptomatic rib fracture in 2 patients and grade 2 transient chest wall pain in 7 patients. In the previously mentioned series by Hayashi et al that stratified patients at age 85, there was an overall reported 11.1% grade 2+ RP rate. Interestingly in this series, they found a statistically significantly higher rate of grade 2+ RP in patients  $\geq$  85 years old (30.0%) compared with patients younger than 85 years old (4.9%). On MVA of patient and dosimetric factors, only age remained associated with RP.<sup>25</sup> This finding that age plays a role in increased toxicity contradicts the previously mentioned series by Mancini et al examining 251 patients with NSCLC treated with lung SBRT, where 126 patients were  $\geq$  75 years old represented their elderly cohort.<sup>22</sup> They found no differences in acute or late grade 3+ toxicity between elderly and non-elderly patients. In terms of acute grade 3+ toxicity, rates were 11.1% in patients  $\geq$  75 years old and 8.0% in patients < 75 years old, and similarly found no statistical difference in grade 3+ late toxicity with rates of 10.3% in patients  $\geq$  75 years old and 7.2% in patients < 75 years old. In this series, no elderly patient experienced chest wall pain. The results of our series, with an older cohort, found similarly low rates of grade 3+ RP (3.5%)

and low rates of any other grade 3+ toxicity (5.2%). In summary, most studies report acceptable grade 3+ toxicity rates of around 10%, regardless of the varying definitions of an “elderly cohort.”<sup>22,23,25,29</sup> Our series is also the first to report an association between elderly patients not on an ACE-I during lung SBRT (OR, 5.83; 95% CI, 1.29-26.32) and higher rates of RP. This is hypothesis generating, and supports the findings of recently published work looking at a broader patient population managed with lung SBRT.<sup>17</sup>

Our series has several strengths and limitations. The major strength of this series is the large number of patients aged 80 or older at the time of treatment in this specific clinical scenario of definitive lung SBRT, the largest such series reported in the United States. We have detailed information on patient characteristics, treatment type, outcome, and toxicity. Our series is one of the few in the literature, and the first examining elderly patients, to incorporate prior cancer history, prior lung cancer history, and previous thoracic radiation in variables analyzed. We felt this was important given the many complexities surrounding the management of octogenarians, including their higher likelihood for previous cancer diagnoses and therapies. The major limitation of our series is the inherent bias of retrospective reviews, including the reliance on medical record for accurate information on follow-up. Although we attempted to document many known variables related to outcomes, including KPS, smoking status, and previous malignancy, there are undoubtedly confounding factors that are not accounted for given the retrospective nature of our study. Additionally, we do not report on the central or peripheral location of the lung tumors, a factor known to be related to toxicity outcomes.<sup>3</sup>

## Conclusions

This series summarizes a large academic, multicenter experience in the management of octogenarians and nonagenarians treated with definitive lung SBRT for early-stage NSCLC. We demonstrate tumor control and survival outcomes similar to other series, including those with younger patients. Importantly we found that grade 3+ toxicity rates were low, indicating that this therapy is well-tolerated even in patients 80 years old. Using recursive partitioning analysis, we were able to find that patients with KPS 75 experience improved CSS and OS, suggesting that definitive lung SBRT is a reasonable option for octogenarians and nonagenarians meeting this criterion.

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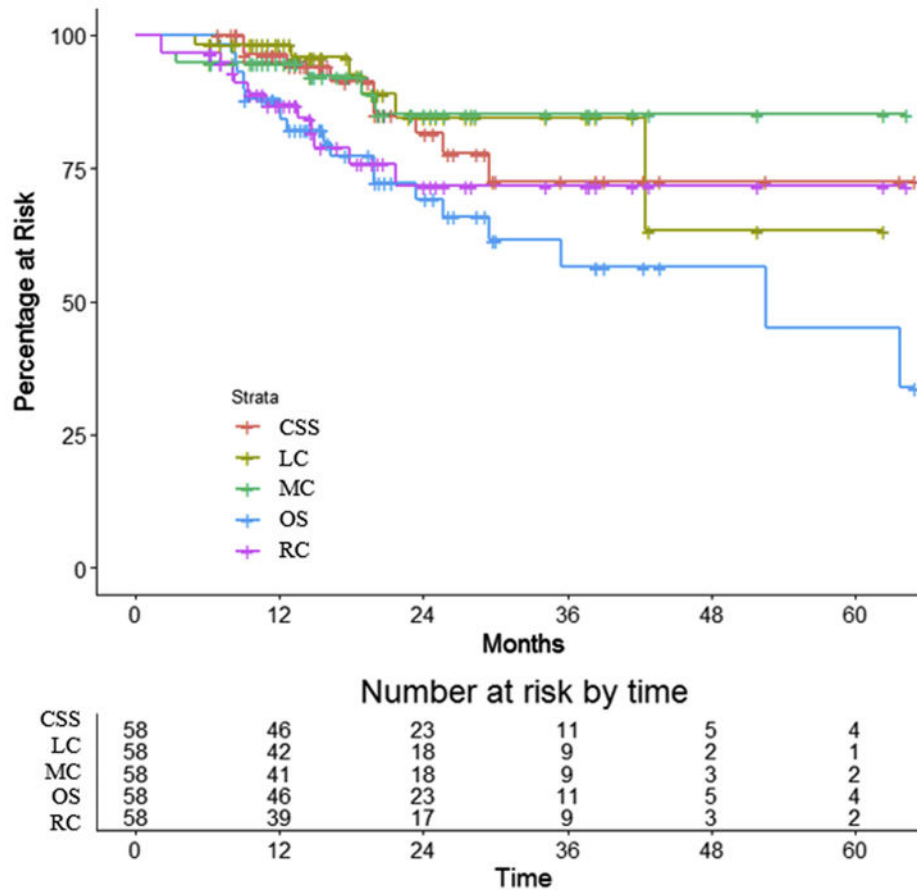


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### Clinical Practice Points

- SBRT is the standard of care for medically inoperable early stage NSCLC.
- Octogenarians and nonagenarians have not been well-represented on prospective trials of SBRT; however, this is becoming a more common clinical scenario with an aging cancer population and patient preference.
- The present study found that SBRT for patients 80 years old with NSCLC treated across 4 academic centers is generally well-tolerated with low rates of grade 3+ toxicity, despite our population having a high rate of previous cancer diagnoses as well as previous courses of thoracic radiation.
- Tumor control was excellent with SBRT, and patients with a KPS of 75 derived the most significant survival benefit with therapy.
- This series, in conjunction with series internationally, demonstrates that the use of SBRT should be considered for NSCLC in octogenarians and nonagenarians with reasonable performance status.



Endpoint	No. of Subjects	Event N (%)	Censored N (%)	1-year (95% CI), %	2-year (95% CI), %
CSS	58	9 (16)	49 (84)	81.6 (64.5-91.0)	72.6 (52.1-85.4)
LC	58	6 (10)	52 (90)	84.5 (65.3-93.5)	84.5 (65.3-93.5)
MC	58	6 (10)	52 (90)	85.1 (68.5-93.4)	85.1 (68.5-93.4)
OS	58	20 (34)	38 (66)	69.3 (53.6-80.6)	56.4 (37.6-71.6)
RC	58	12 (21)	46 (79)	71.7 (54.1-83.5)	71.7 (54.1-83.5)

**Figure 1.**

Local Control (LC), Regional Control (RC), Metastatic Control (MC), Cancer-specific Survival (CSS), and Overall Survival (OS) Among the Entire Cohort of Patients 80 Years and Older Treated With Definitive Lung Stereotactic Body Radiotherapy. LC, RC, MC, CSS, and OS Among All 58 Patients in the Study. LC Was Defined as Tumor Control at Treated Site. RC Was Defined as Tumor Control in the Same Lobe of Treatment, Ipsilateral Hilum, or Mediastinum. MC Was Defined as Disease Control in the Contralateral Lung or Free From Any Distant Site of Disease. CSS Was Defined as Survival in the Absence of Any Active Cancer at Any Site, With Other Deaths Censored. OS Was Defined as Time to Death

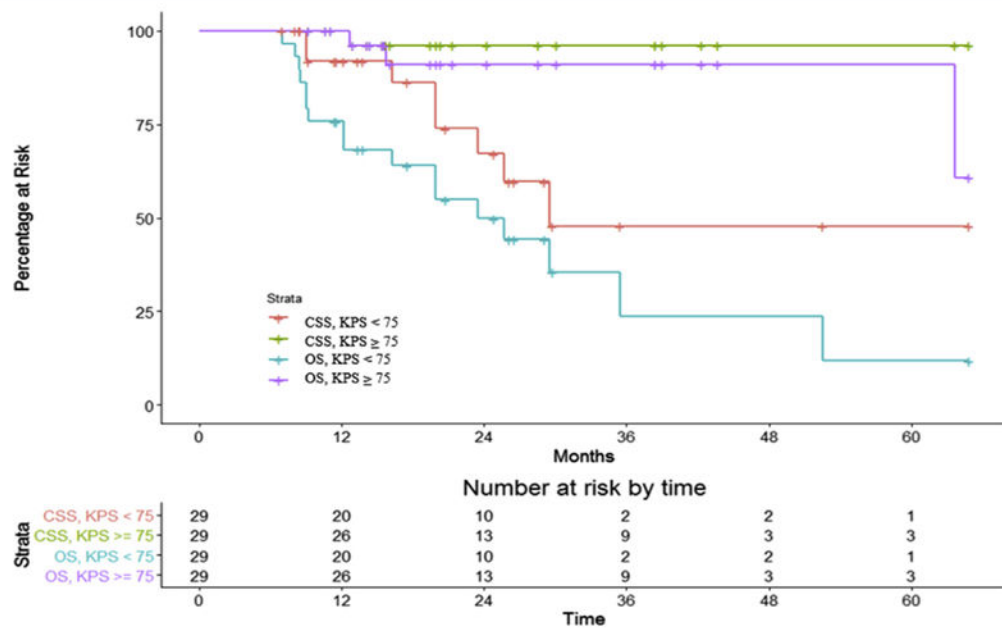
or Time to Last Follow up From Diagnosis. The 2- and 3-year Endpoints With 95% Confidence Intervals (CI) Are Listed Below:

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**Figure 2.** Cancer-specific Survival (CSS) and Overall Survival (OS) Among Patients Stratified by Karnofsky Performance Status (KPS) breakpoint of 75 on Recursive Partitioning Analysis. CSS and OS Were Analyzed Among the Entire Cohort of 58 Patients as Stratified by the KPS Breakpoint of 75 as Determined by Recursive Partitioning Analysis (RPA). CSS Was Defined as Net Survival Measuring Cancer Survival in the Absence of Other Causes of Death. OS Was Defined as Time to Death or Time to Last Follow-up From Diagnosis. The Determined RPA KPS of 75 Was also the Median KPS of the Entire Cohort, as Evidenced by the Equal Distribution of Patients in the Number at Risk Section at the Bottom of the Figure. For Patients With KPS < 75, the 2- and 3-year CSS Rates Were 67.2% (95% CI, 40.0%-84.2%) and 47.8% (95% CI, 19.1%-71.9%), Respectively, Whereas for Patients With KPS ≥ 75, the 2- and 3-year CSS Rates Were Both 96.2% (95% CI, 75.7%-99.4%). For Patients With KPS < 75, the 2- and 3-year OS Rates Were 49.9% (95% CI, 29.0%-67.6%) and 23.6% (95% CI, 5.3%-49.2%), Respectively, Whereas for Patients With KPS ≥ 75, the 2- and 3-year OS Rates Were Both 91.1% (95% CI, 68.4%-97.7%)

**Table 1**

Summary of the Patient, Tumor, and Treatment Characteristics of Our Study Population

Variable	N (%) = 58
Patient characteristics	
Gender	
Female	28 (48.3)
Male	30 (51.7)
History of prior cancer	
No	28 (48.3)
Yes	30 (51.7)
History of prior lung cancer	
No	37 (63.8)
Yes	21 (36.2)
History of prior thoracic radiation	
No	47 (81.0)
Yes	11 (19.0)
ACE-I usage	
No	32 (55.2)
Yes	26 (44.8)
Active smoker	
No	52 (89.7)
Yes	6 (10.3)
Smoking pack-years	
Median (range)	40.0 (0.0–130.0)
Tumor characteristics	
Histology	
Adenocarcinoma	23 (39.7)
Squamous cell carcinoma	17 (29.3)
Not biopsied	18 (31.0)
T stage	
T1a/T1b	39 (67.2)
T2a/T2b	12 (20.7)
T3	7 (12.1)
Tumor location	
Left lower lobe	11 (19.0)
Left upper lobe	8 (13.8)
Right lower lobe	14 (24.1)
Right middle lobe	2 (3.4)
Right upper lobe	23 (39.7)
Treatment characteristics	

Variable	N (%) = 58
Method of mediastinal staging	
PET-CT alone	37 (63.8)
PET-CT and pathologic sampling	21 (36.2)
Radiation dose per fraction in Gy	
Median (range)	10.0 (7.0–20.0)
Number of radiation fractions delivered	
Median (range)	5.0 (3.0–8.0)
Treatment modality	
IMRT	14 (24.1)
VMAT	44 (75.9)

Abbreviations: ACE-I = angiotensin-converting enzyme inhibitor; CT = computed tomography; IMRT = intensity modulated radiotherapy; KPS = Karnofsky performance status; PET = positron emission tomography; VMAT = volumetric arc therapy.

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**Table 2**

Multivariable<sup>a</sup> Analysis of Patient, Tumor, and Treatment Characteristics and Their Association With Local Recurrence-free Survival

Covariate	Level	Hazard Ratio (95% CI)	HR <i>P</i> Value
T stage	T1a or T1b	0.20 (0.04–0.90)	<b>.04</b>
	T2a or T2b	1.28 (0.23–6.97)	.78
	T3 or T4	–	–
Tumor histology	Adenocarcinoma	6.36 (1.57–25.76)	<b>.01</b>
	Not biopsied	1.02 (0.22–4.72)	.98
	Squamous cell carcinoma	–	–
History of prior lung cancer	Yes	2.38 (0.68–8.32)	.17
	No	–	–
History of prior cancer	Yes	2.93 (0.99–8.69)	.06
	No	–	–
KPS at the time of consult		0.92 (0.89–0.96)	<b>&lt;.01</b>

Bold *P*-values indicate statistical significance.

Abbreviations: CI = confidence interval; HR = hazard ratio; KPS = Karnofsky performance status.

<sup>a</sup>Backward selection with an alpha level of removal of .20 was used. The following variables were removed from the model: age, tumor location, prior lung radiotherapy, gender, radiation fractions and dose per fraction, tumor size, treatment modality.

**Table 3**

Multivariable<sup>a</sup> Analysis of Patient, Tumor, and Treatment Characteristics and Their Association With Cancer-specific Survival

Covariate	Level	Hazard Ratio (95% CI)	P Value
History of prior lung cancer	Yes	7.75 (1.61–37.20)	<b>.01</b>
	No	–	–
Active smoker	No	0.14 (0.02–0.87)	<b>.04</b>
	Yes	–	–
Age		1.19 (1.01–1.42)	<b>.04</b>

Bold *P*-values indicate statistical significance.

Abbreviation: CI = confidence interval.

<sup>a</sup>Backward selection with an alpha level of removal of 0.2 was used. The following variables were removed from the model: Karnofsky performance status at time of initial consult, tumor size, prior lung radiation.

**Table 4**

Multivariable<sup>a</sup> Analysis of Patient, Tumor, and Treatment Characteristics and Their Association With Developing Radiation Pneumonitis

Covariate	Level	Odds Ratio (95% CI)	P Value
T stage	T1a or T1b	0.03 (0.01–0.37)	<b>.01</b>
	T2a or T2b	0.07 (0.01–1.06)	.06
	T3	–	–
ACE-I usage	No	5.83 (1.29–26.36)	<b>.02</b>
	Yes	–	–

Bold P-values indicate statistical significance.

Abbreviations: ACE-I = angiotensin converting enzyme inhibitor; CI = confidence interval.

<sup>a</sup>Backward selection with an alpha level of removal of .20 was used. The following variables were removed from the model: age, radiation dose/fraction, number of radiation fractions, tumor size, gender, and smoking pack-years.

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