Original Study

Outcomes Following SBRT vs. IMRT and 3DCRT for Older Patients with Stage IIA Node-Negative Non-Small Cell Lung Cancer > 5 cm

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Abstract

Contemporary comparative data for radiotherapy modalities are scarce for larger non-small cell lunger cancer (NSCLC) tumors. Using the SEER-Medicare database, we identified 584 patients with Stage IIA node-negative NSCLC > 5 cm in size who were treated with stereotactic body radiotherapy (SBRT), intensity-modulated radiotherapy (IMRT) or 3-dimensional conformal radiotherapy (3DCRT). While SBRT was associated with higher survival compared to IMRT or 3DCRT, concurrent chemoradiation with IMRT or 3DCRT had similar survival rates to SBRT. Nevertheless, the SBRT group experienced fewer complications than the 3DCRT or IMRT groups, suggesting that SBRT may be appropriate treatment strategy for older patients with larger tumors.

Background: To describe outcomes and compare the effectiveness of stereotactic body radiotherapy (SBRT) versus 3-dimensional conformal radiotherapy (3DCRT) or intensity-modulated radiotherapy (IMRT) in patients with stage IIA lymph node-negative (N0) non-small cell lung cancer (NSCLC) tumors > 5 cm. **Methods:** We used the SEER-Medicare database (2005-2015) to identify patients > 65 years with stage IIA (AJCC TNM7) N0 NSCLC > 5 cm tumors who were treated with SBRT, IMRT, and 3DCRT. We used propensity score methods with inverse probability weighting to compare lung cancer-specific survival (LCSS), overall survival (OS), and toxicity. **Results:** Of 584 patients, 88 (15%), 140 (24%), and 356 (61%) underwent SBRT, IMRT, and 3DCRT, respectively. The SBRT group was older ($P = .004$), had more comorbidities ($P = .02$), smaller tumors ($P = .03$), and more adenocarcinomas ($P < .0001$). We found a trend towards higher median unadjusted OS with SBRT compared to IMRT and 3DCRT (19 vs. 13 and 14 months, respectively, $P = .37$). In our propensity score-adjusted analyses, SBRT was significantly associated with better OS and LCSS compared to IMRT (HR_{OS}: 0.78, 95% CI: 0.68-0.89, HR_{LCSS}: 0.70, 95% CI: 0.60-0.81) and 3DCRT (HR_{OS}: 0.81, 95% CI: 0.72-0.93, HR_{LCSS}: 0.80, 95% CI: 0.68-0.93). SBRT-treated patients also had lower overall adjusted complication rates compared to IMRT (OR: 0.74, 95% CI: 0.55-0.99) and 3DCRT (OR: 0.53, 95% CI: 0.40-0.71). **Conclusion:** For patients with NSCLC tumors > 5 cm, SBRT trends towards fewer toxicities and improved survival compared to other forms of radiotherapy. Our findings support SBRT as an appropriate treatment strategy for older patients with larger inoperable NSCLC tumors.

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Abbreviations: 3DCRT, 3-dimensional conformal radiotherapy; ARD, absolute risk difference; CI, confidence interval; CPT-4, Current Procedural Terminology, 4th edition; EBRT, external beam radiation treatment; HR, hazard ratio; ICD-9, International Classification of Diseases, 9th revision; ICD-O, International Classification of Diseases for Oncology; IMRT, intensity-modulated radiotherapy; IPW, inverse probability weighting; LCSS, lung cancer-specific survival; N0, node-negative; NCI, National Cancer Institute; NSCLC, non-small cell lung cancer; OR, odds ratio; OS, overall survival; PET, positron emission tomography; RCT, randomized controlled trial; SBRT, stereotactic body radiotherapy; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; SEER, Surveillance, Epidemiology and End Results; SPACE, Scandinavian Stereotactic Precision and Conventional Radiotherapy Evaluation; US, United States.

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Introduction

The incidence of early-stage non-small cell lung cancer (NSCLC) in older individuals is expected to increase as screening guidelines are adopted in the United States (US) and around the world.[1] Older NSCLC patients often have multiple age- and smoking-related comorbidities that may make them high risk for surgical resection.[2] In these challenging clinical scenarios, patients are considered for treatment with radiotherapy (RT) as a non-invasive option. Stereotactic body radiotherapy (SBRT) is a newer form of RT that is increasingly used to treat medically inoperable early-stage NSCLC; however, its role in treating larger tumors has not been fully elucidated.[3-10]

SBRT delivers high dose radiation, in 1 to 5 sessions or fractions, making it an attractive choice for treating patients with smaller NSCLCs who have increased surgical risk. In stage I NSCLCs, single-arm studies have shown SBRT to be well tolerated and associated with excellent local control rates.[11-13] However, as most prospective studies limited tumors to < 5 cm in size,[10-13] SBRT was not considered a feasible option in clinical practice for larger tumors. As a result, non-surgical candidates with larger tumors typically underwent conventionally fractionated 3-dimensional conformal radiotherapy (3DCRT) or intensity-modulated radiotherapy (IMRT) delivered over several weeks.[14-18] Standard fractionation 3DCRT, while no longer the technical standard,[19] delivers radiation beams that conform to the shape of tumors. Traditional IMRT is an advanced conformal radiotherapy method that utilizes varying intensities of radiation beams to achieve target coverage and is typically reserved for locally advanced tumors. While conventional fractionation IMRT and 3DCRT are generally well tolerated, local control rates with these RT modalities remain suboptimal for larger tumors, even with chemotherapy.[20-25]

Emerging data from small, single-institution case series suggest that SBRT may be a safe and effective option in patients with tumors > 5 cm.[5-9] Therefore, SBRT may be a promising yet underutilized strategy for treating larger NSCLC tumors if more high quality data is generated. In this study, we used population-based data from the Surveillance, Epidemiology and End Results (SEER)-Medicare database to compare survival and tolerability of SBRT vs. conventional IMRT and 3DCRT in patients > 65 years of age with stage IIA node-negative (N0) NSCLCs > 5 cm in size.

Materials and Methods

Patient Characteristics

We conducted a comparative effectiveness study using nationally representative data from the SEER-Medicare database, a population-based tumor registry linked to Medicare claims that provides clinical information and longitudinal outcomes of cancer patients > 65 years old within representative areas of the US (approximately 34% of the population).[26,27] Study subjects were diagnosed between 2005 and 2015 with histologically confirmed, stage IIA (defined using AJCC TNM staging criteria, seventh edition),[41] N0 NSCLCs between > 5 cm and ≤ 7.0 cm in size and treated with SBRT, IMRT, or 3DCRT. International Classification of Diseases, ninth revision (ICD-9) and Current Procedural Terminology, fourth edition (CPT-4) codes from SEER-Medicare data were used to identify treatment modalities: 1) SBRT (ICD-9: 92.3, 92.30-92.39; CPT-4: 61793, 77373, 77435, G0173, G0251, G0339, G0340, 0082T); 2) IMRT (CPT-4: 77301, 77418, 77338, 0073T, G0174), and 3) 3DCRT (CPT-4: 77295). As SBRT can be planned with IMRT and 3DCRT techniques, patients who had a SBRT billing code, in addition to procedural codes for 3DCRT or IMRT, were considered treated with SBRT. Patients were excluded if they: (1) participated in health maintenance organizations or without Part B Medicare coverage due to lack of complete claims data; (2) resided in nursing homes or receiving hospice care due to concerns for poor performance status; (3) were treated with neoadjuvant chemotherapy for the lung cancer, as these cancers could represent tumor downstaging; and (4) were diagnosed with tumors located at the main bronchus, carina and hilus of the lung, which are typically not amenable to SBRT due to their central location.[28,29] These tumors were identified using SEER codes per International Classification of Diseases for Oncology (ICD-O: C340 and C34).[30-32]

From SEER, we retrieved patient demographic information, including age, sex, race, and marital status. Socioeconomic status was estimated by grouping patients into quartiles based on the median incomes of the census tract or zip code in which they lived. Rural residence at time of diagnosis was defined using rural-urban continuum codes (4-9).[33,34] Comorbidities were assessed from Medicare claims data using a validated claims-based adaptation of the National Cancer Institute (NCI) comorbidity index.[35] Data from the Hospice and Home Health Agency files were used to identify use of home health services (ie, medical social services, home health aide, durable medical equipment, skilled nursing, physical therapy, intravenous therapy, and home oxygen) as indicators for poor functional status.[36] Cancer characteristics, including tumor size, stage, site, and histology were obtained from SEER. Histologic subtypes were determined with SEER codes according to the ICD-O.[30] Diagnosis and staging evaluation (ie, positron emission tomography [PET] scan and mediastinoscopy) were obtained from Medicare claims.[37]

Study Outcomes

For the primary outcome, we assessed both lung cancer-specific survival (LCSS) and overall survival (OS). LCSS and OS were determined as the interval from date of treatment to date of death from lung cancer or from any cause, respectively. Study participants who were alive at the last follow-up date (December 31, 2015) were treated as censored observations. Cause of death was obtained from SEER that includes data reported in death certificates. For the secondary outcome, we examined post-treatment complications within 12 months of treatment using Medicare claims data; these included: (1) radiation pneumonitis; (2) radiation fibrosis; (3) esophagitis; (4) pneumothorax; (5) bleeding (pulmonary hemorrhage or hemoptysis); and (6) rib fracture.

Statistical Analyses

Baseline characteristics of patients in each treatment group (SBRT, IMRT, 3DCRT) were compared using the $\chi 2$ test or analysis of variance for categorical and continuous variables, respectively. As several patient and tumor characteristics may have affected decisions regarding which form of RT was utilized, we used propensity score methods to control for potential selection bias. Propen-

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Table 1 Characteristics of Older Patients with Stage IIA Node-Negative NSCLC > 5 cm in Size Treated with SBRT vs. IMRT vs. 3DCRT

	Cohort N = 584	SBRT[a] N = 88	IMRT[b] N = 140	3DCRT[c] N = 356	*P*-value	Adjusted *P*-value[d]
Age, year, mean ± std[e]	77 ± 6	80 ± 6	78 ± 7	77 ± 6	.004	.33
Female, No. (%)	248 (42.5)	41 (46.6)	62 (44.3)	145 (40.7)	.54	.86
Married, No. (%)	276 (47.3)	39 (44.3)	60 (42.9)	177 (49.7)	.32	.45
Non-White, No. (%)	87 (14.9)	11 (12.5)	22 (15.7)	54 (15.2)	.78	.95
Median Income, No. (%)					.10	.84
First Quartile	181 (31.0)	28 (31.8)	40 (28.6)	113 (31.7)		
Second Quartile	168 (28.8)	21 (23.9)	44 (31.4)	103 (28.9)		
Third Quartile	117 (20.0)	13 (14.8)	24 (17.1)	80 (22.5)		
Fourth Quartile	118 (20.2)	26 (29.5)	32 (22.9)	60 (16.9)		
Rural residence		< 11 (< 12.5)[f]	17 (12.1)	47 (13.2)	.40	.99
NCI[g] comorbidity index, No., (%)					.02	.56
0 to < 1.0	400 (68.5)	51 (58.0)	90 (64.3)	259 (72.8)		
1.0 to < 2.0		< 11 (< 12.5)	< 11 (< 7.9)	23 (6.5)		
≥2.0		≥ 11 (≥ 12.5)	≥ 11 (≥ 7.9)	74 (20.8)		
Tumor Size					.03	.08
5.1 cm - 6.0 cm	371 (63.5)	65 (73.9)	79 (56.4)	227 (63.8)		
>6.0 – 7.0 cm	213 (36.5)	23 (26.1)	61 (43.6)	129 (36.2)		
Tumor Site					.28	.94
Upper lobe	338 (57.9)	43 (48.9)	81 (57.9)	214 (60.1)		
Lower lobe		≥ 11 (≥ 12.5)	≥ 11 (≥ 7.9)	123 (34.6)		
Other[h]		< 11 (< 12.5)	< 11 (< 7.9)	19 (5.3)		
Histology, No. (%)					<.001	.36
Adenocarcinoma	160 (27.4)	44 (50.0)	32 (22.9)	84 (23.6)		
Squamous cell		≥ 11(≥ 12.5)	91 (65.0)	205 (57.6)		
Other[j]		< 11 (< 12.5)	17 (12.1)	67 (18.8)		
PET[i]-scan, No. (%)	427 (73.1)	67 (76.1)	118 (84.3)	242 (68.0)	.001	.001
Mediastinoscopy, No. (%)	32 (5.5)	< 11 (< 12.5)	< 11 (< 7.9)	16 (4.5)	.38	.79
Home health aide or durable medical equipment	123 (21.1)	20 (22.7)	31 (22.1)	72 (20.2)	.82	.93
Skilled nursing services		< 11 (< 12.5)	13 (9.3)	22 (6.2)	.46	.53

[i] Large cell, not otherwise specified, or other
[a] Stereotactic body radiotherapy
[b] Intensity-modulated radiotherapy
[c] 3-dimensional conformal radiotherapy
[d] Adjusted using propensity score methods
[e] Standard deviation
[f] SEER prevents the reporting of the actual number for any variables associated with < 11 patients
[g] National Cancer Institute
[h] Middle site, not otherwise specified, or overlapping lesion of lung
[i] Positron emission tomography
[j] Large cell, not otherwise specified, or other

sity scores were estimated for each patient using nominal logistic regression indicating the probability of undergoing the treatment they received, conditional on patient characteristics (ie, sociodemographics and comorbidity score), tumor characteristics (ie, size, location, histology) and use of pretreatment evaluation (ie, PET/CT, mediastinoscopy) (see Table 1 for all covariates). We did not include adjuvant chemotherapy as a variable in our propensity score model, as this would not influence treatment allocation. To account for concurrent chemotherapy, we performed subgroup analyses stratifying the sample by SBRT vs. IMRT- or 3DCRT-based chemoradiation. We defined concurrent chemotherapy as initiation of treatment within 14 days of starting RT. For study outcomes, we adjusted for allocation bias using inverse probability weighting (IPW); weights for each patient were calculated as the inverse of the estimated probability for undergoing the type of treatment they received. We then examined the balance of covariates across groups (and subgroups) after adjustment and removal of extreme weights.

For our survival analysis, we used unadjusted Kaplan-Meier estimates and the log-rank method to compare 1-year, 3-year, and 5-year LCSS and OS for each treatment group. Cox proportional

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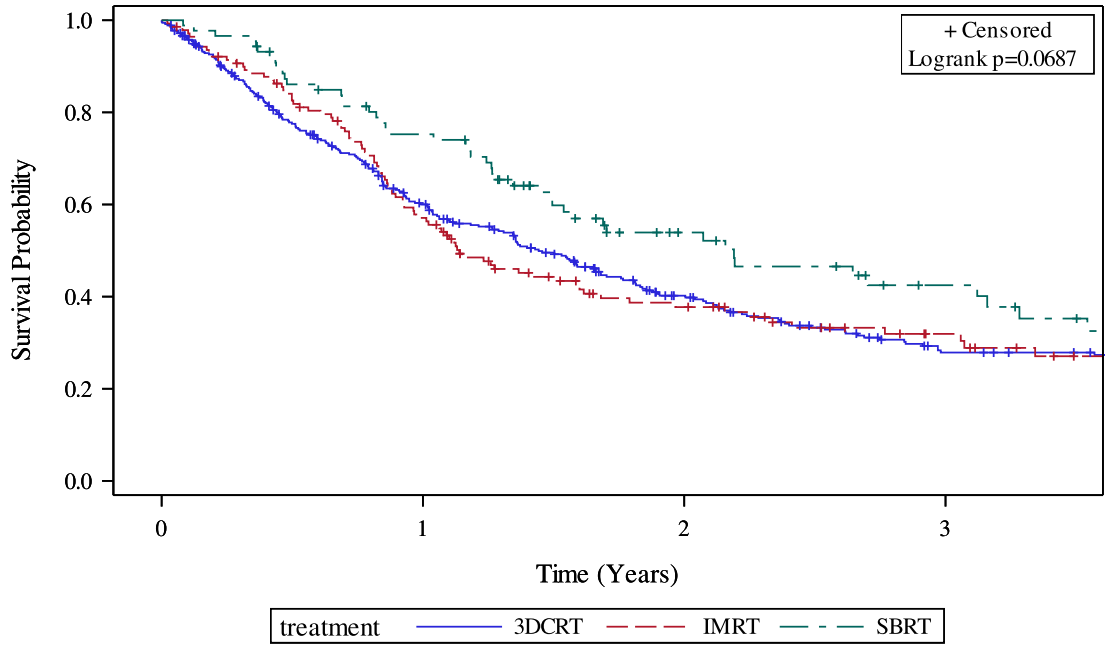
Figure 1 Unadjusted Kaplan-Meier estimates of lung cancer-specific survival in older patients with NSCLC > 5 cm tumors treated with SBRT vs. IMRT vs. 3DCRT. Green, red, and blue reflect unadjusted Kaplan-Meier estimates for SBRT, IMRT and 3DCRT respectively. The number at risk through 3 years and survival estimates are below the graph



3DCRT	356	190	102	59
IMRT	140	76	39	21
SBRT	88	62	30	18

	SBRT[a] N=88	IMRT[b] N=140	3DCRT[c] N=356	P-value
Median follow-up time, months (IQR)[d]	17.7 (9.7-32.2)	13.0 (8.0-25.9)	12.8 (5.4-26.4)	
Median, months (95% CI)[e]	26.3 (17.9-37.9)	13.7 (11.6-19.2)	17.3 (14.2-20.4)	0.07
1-year, %	67 (76.1)	82 (58.6)	222 (62.4)	
3-year, %	45 (51.1)	54 (38.6)	135 (37.9)	
5-year, %	40 (45.5)	50 (35.7)	124 (34.8)	

[a] Stereotactic body radiotherapy
[b] Intensity-modulated radiotherapy
[c] 3-dimensional conformal radiotherapy
[d] Interquartile range
[e] Confidence interval

hazards model was then used to compare unadjusted and adjusted survival. For our secondary outcome, we describe the proportion of patients in each group that experienced complications. Unadjusted and adjusted overall complication rates were compared. To maintain patient confidentiality, SEER prevents the reporting of the actual number for any variables associated with < 11 patients. Therefore, we report crude absolute risk differences (ARDs) between treatment groups for each complication. This study was determined exempt by the institutional review board of the Icahn School of Medicine at Mount Sinai.

Results

Overall, 584 patients met inclusion criteria, of which 88 (15%) received SBRT, 140 (24%) were treated with IMRT, and 356 (61%) underwent 3DCRT (Supplementary Figure 1). For patients treated with IMRT and 3DCRT, 47 (34%) and 121 (34%) received concurrent chemotherapy, respectively. Comparisons of baseline characteristics between the groups are summarized in Table 1. Patients who received SBRT were older ($P = .004$) and were associated with more comorbidities ($P = .02$). The mean NCI comorbidity index and standard deviation (std) for patients treated with SBRT

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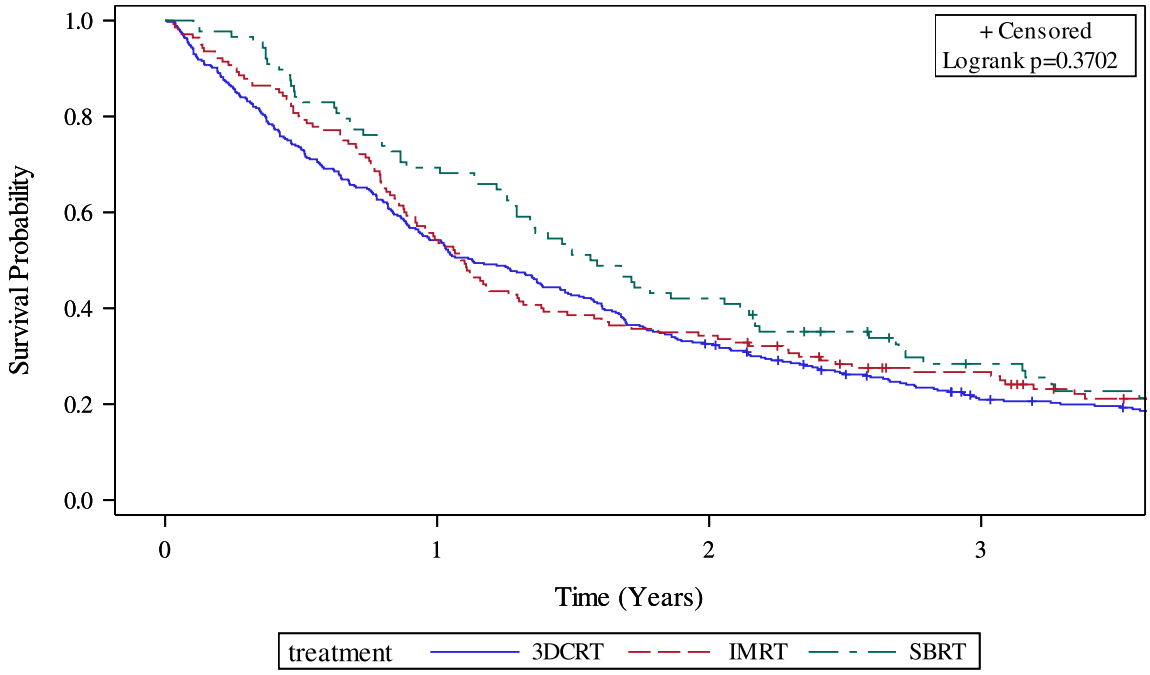
Figure 2 Unadjusted Kaplan-Meier estimates of overall survival in older patients with NSCLC > 5 cm tumors treated with SBRT vs. IMRT vs. 3DCRT. Green, red, and blue reflect unadjusted Kaplan-Meier estimates for SBRT, IMRT and 3DCRT respectively. The number at risk through 3 years and survival estimates are below the graph



	SBRT[a] N=88	IMRT[b] N=140	3DCRT[c] N=356	P-value
Median follow-up time, months (IQR)[d]	18.9 (9.4-33.1)	13.1 (8.0, 30.7)	13.6 (5.5-29.9)	
Median, months (95% CI)[e]	18.9 (15.5-25.4)	13.1 (11.0-15.6)	13.6 (11.4-16.6)	0.37
1-year, %	61 (69.3)	76 (54.3)	193 (54.2)	
3-year, %	26 (29.5)	38 (27.1)	77 (21.6)	
5-year, %	13 (14.8)	28 (20.0)	53 (14.9)	

[a] Stereotactic body radiotherapy
[b] Intensity-modulated radiotherapy
[c] 3-dimensional conformal radiotherapy
[d] Interquartile range
[e] Confidence interval

were 1.5 ± 2.1 compared to 1.4 ± 2.2 for IMRT and 0.88 ± 1.7 for 3DCRT. The SBRT group also had smaller tumors ($P < .03$) that were more frequently of adenocarcinoma origin ($P < .0001$) compared to patients who received IMRT and 3DCRT. Median tumor size was 5.6 cm (interquartile range [IQR]: 5.3-6.1 cm) for SBRT, 6.0 cm (5.5-6.6 cm) for IMRT and 6.0 cm (5.5-6.4 cm) for 3DCRT. Patients who received SBRT were also more likely to have been evaluated by PET scans compared to IMRT and 3DCRT ($P < .0001$). We found no significant differences in the distribution of other baseline characteristics ($P > .05$ for all comparisons).

In the total cohort, unadjusted LCSS and OS and median follow-up time are found in Figure 1 and 2, respectively. Subgroup unadjusted survival analyses can be found in the e-supplementary material (Supplementary Table 1). Overall, for the unadjusted survival analyses, 1-year, 3-year and 5-year LCSS were 76.1%, 51.1% and 45.5% respectively, for SBRT-treated patients, compared to 58.6%, 38.6% and 35.7% for IMRT-treated patients, and 62.4%, 37.9% and 34.8% for patients who received 3DCRT (Figure 1). The unadjusted median LCSS was longer in the SBRT group when compared to both IMRT and 3DCRT (26 vs. 14

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Table 2 Adjusted Survival of Older Patients with Stage IIA Node-Negative NSCLC > 5 cm in Size Treated with SBRT vs. IMRT vs. 3DCRT

Hazard Ratio, 95% CI[a]	SBRT[b] vs. IMRT[c]		SBRT vs. 3DCRT[d]	
	Unadjusted	Adjusted[e]	Unadjusted	Adjusted
Total Cohort	N=88 vs. 140		N=88 vs. 356	
Lung Cancer-Specific Survival	0.70 (0.50-1.00)	0.70 (0.60-0.81)	0.70 (0.51-0.96)	0.80 (0.68-0.93)
Overall Survival	0.88 (0.66-1.18)	0.78 (0.68-0.89)	0.84 (0.65-1.08)	0.81 (0.72-0.93)
SBRT vs. concurrent chemoradiation	N = 88 vs. 47		N = 88 vs. 121	
Lung Cancer-Specific Survival	1.02 (0.63-1.65)	1.11 (0.87-1.41)	0.89 (0.62-1.28)	1.21 (0.96-1.53)
Overall Survival	1.27 (0.85-1.91)	1.15 (0.93-1.41)	1.01 (0.81-1.47)	1.20 (0.99-1.47)
SBRT vs. no concurrent chemoradiation	N = 88 vs. 93		N = 88 vs. 235	
Lung Cancer-Specific Survival	0.57 (0.40-0.83)	0.60 (0.51-0.71)	0.61 (0.44-0.84)	0.75 (0.63-0.89)
Overall Survival	0.72 (0.53-0.98)	0.68 (0.58-0.79)	0.71 (0.55-0.93)	0.74 (0.64-0.86)

[a] Confidence interval
[b] Stereotactic body radiotherapy
[c] Intensity-modulated radiotherapy
[d] 3-dimensional conformal radiotherapy
[e] Adjusted using inverse probability weighting

vs. 17 months, respectively; $P = .07$). One-year, 3-year and 5-year OS rates were 69.3%, 29.5% and 14.8%, respectively for SBRT-treated patients vs. 54.3%, 27.1% and 20.0%, for IMRT-treated patients vs. 54.2%, 21.6% and 14.9% for 3DCRT-treated patients (Figure 2). Median unadjusted OS was higher in the SBRT group when compared to IMRT and 3DCRT (19 vs. 13 vs. 14 months, respectively; $P = .37$). Adjusted analyses using the Cox regression model and IPW demonstrated SBRT was associated with significant improvement in LCSS and OS when compared to IMRT (LCSS hazard ratio [HR]: 0.70, 95% confidence interval [CI]: 0.60-0.81; OS HR: 0.78, 95% CI: 0.68-0.89) and 3DCRT (LCSS HR: 0.80, 95% CI:0.68-0.93, OS HR: 0.81, 95% CI: 0.72-0.93; Table 2). In the subgroup analyses (Table 2), LCSS and OS remained higher for SBRT compared to IMRT or 3CDRT with no concurrent chemotherapy. However, there were no differences in survival among patients who received SBRT vs. IMRT with concurrent chemotherapy (LCSS HR: 1.11, 95% CI: 0.87-1.41, OS HR: 1.15, 95% CI: 0.93-1.41) or 3DCRT with concurrent chemotherapy (LCSS HR: 1.21, 95% CI: 0.96-1.53, OS HR: 1.20, 95% CI: 0.99-1.47).

Patients treated with SBRT had lower numerical overall complications within 12 months of treatment compared to those treated with IMRT and 3DCRT (20.5% vs. 23.6% vs 29.2%, $P = .17$) (Table 3). Compared to patients treated with IMRT, SBRT-treated patients had significantly higher unadjusted ARDs for pneumothorax than IMRT (ARD: -6.5%, 95% CI: -12.5 to -0.5%). Compared to 3DCRT-treated patients, the SBRT group had significantly lower unadjusted ARDs for radiation fibrosis (ARD: 2.3%, 95% CI: 0.7%-3.8%) and esophagitis (ARD: 8.1%, 95% CI: 0.7%-3.8%). After adjusting for potential confounders with IPW, SBRT was associated with lower overall treatment-related toxicity when compared to IMRT (odds ratio [OR]: 0.74, 95% CI: 0.55-0.99) and 3DCRT (OR: 0.53, 95% CI: 0.40-0.71). This significant result was also observed in the SBRT vs. concurrent chemoradiation subgroup analysis (SBRT vs. IMRT OR: 0.52, 95% CI: 0.34-0.80; SBRT vs. 3DCRT OR: 0.64, 95% CI: 0.42-0.96). When stratifying the cohort to SBRT vs. IMRT and 3DCRT with no concurrent chemotherapy, SBRT-treated patients had lower adjusted complication rates compared to 3DCRT (OR: 0.68, 95% CI: 0.49-0.94) but not IMRT (OR: 1.07, 95% CI: 0.76-1.50).

Discussion

A significant percentage of patients diagnosed with larger localized NSCLC tumors are not able to tolerate surgical resection due to age- and/or smoking-related comorbidities. While these patients can undergo standard 3DCRT or IMRT with or without concurrent chemotherapy, SBRT has emerged as a potential alternative. Though SBRT has been increasingly used for larger tumors in clinical practice,[3,4] there is limited comparative data. Using nationally representative data from SEER-Medicare, this study shows that older patients who received SBRT for NSCLCs > 5 cm and ≤ 7.0 cm in size were associated with better LCSS and OS compared to those who received 3DCRT or IMRT. SBRT was also associated with reduced adjusted rates of overall complications, compared to those receiving IMRT and 3DCRT. Patients who received concurrent chemotherapy with IMRT or 3DCRT seemed to have similar survival but higher complication rates. Our findings therefore provide support that SBRT may be considered an acceptable non-invasive treatment strategy for older patients with stage IIA N0 NSCLC > 5 cm tumors.

SBRT is currently used in smaller (< 5 cm) NSCLC tumors and is supported by a growing body of data demonstrating excellent local control and improvement in survival. In the Radiation Therapy Oncology Group (RTOG) 0236 trial, the 3-year and 5-year primary tumor control rates with SBRT were 98% and 93%, respectively, while the 5-year primary tumor and involved lobe rate was 80%.[11-13] Compared to other forms of RT, the CHISEL phase III randomized controlled trial (RCT) demonstrated a 2-year OS in < 5 cm NSCLCs of 77% (95% CI: 67-88) for patients treated with SBRT compared to 59% (95% CI: 44-78) for patients treated with 3DCRT.[38] However, the Scandinavian Stereotactic Precision and Conventional Radiotherapy Evaluation (SPACE) trial,

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Table 3 Treatment-Related Toxicities within 12 Months in Older Patients with NSCLC > 5 cm Treated with SBRT vs. IMRT vs. 3DCRT

	Outcome			3DCRT[c] N = 356	*P*-value	
					Unadjusted	Adjusted[d]
	Any complication, No. (%)	18 (20.5)	33 (23.6)	104 (29.2)	.17	<.0001
		SBRT[a] N=88	IMRT[b] N=140	3DCRT[c] N=356	*P*-valuee	
Total Cohort		SBRT[a] N=88	IMRT[b] N=140	3DCRT[c] N=356	*P*-value	Adjusted *P*-value[d]
	Any complication, No. (%)	18 (20.5)	33 (23.6)	104 (29.2)	.17	<0.001
					SBRT vs. 3DCRT	
Adjusted Odds Ratio[d] (95% CI)[e]	Any complication	0.74 (0.55-0.99)			0.53 (0.40-0.71)	
Unadjusted % Absolute Risk Difference, (95% CI)	Bleeding	1.3% (-3.1%-5.7%)			0.8% (-2.8%-4.4%)	
	Radiation Pneumonitis	0.8% (-5.6%-7.1%)			0.5% (-5.0%-5.9%)	
	Radiation Fibrosis	1.4% (-0.5%-3.4%)			2.3% (0.7%-3.8%)	
	Esophagitis	6.5% (-0.8%-13.7%)			8.1% (2.1%-14.1%)	
	Pneumothorax	-6.5% (-12.5% to -0.5%)			-2.9% (-9.0%-3.2%)	
	Rib Fracture	-3.2% (-7.2%-0.9%)			2.5% (-0.4%-5.5%)	
SBRT vs. concurrent chemoradiation						
SBRT vs. concurrent chemoradiation		SBRT N= 88	IMRT N = 47	3DCRT N = 121	*P*-value	
SBRT vs. concurrent chemoradiation		SBRT N=88	IMRT N=47	3DCRT N=121	*P*-value	Adjusted *P*-value
	Any complication, No. (%)	18 (20.5)	15 (31.9)	40 (33.1)	.14	.009
		SBRT vs. IMRT			SBRT vs. 3DCRT	
Adjusted Odds Ratio (95% CI)	Any complication 0.52 (0.34-0.80)				0.64 (0.42-0.96)	
SBRT vs. no concurrent chemoradiation						
SBRT vs. no concurrent chemoradiation		SBRT N = 88	IMRT N = 93	3DCRT N = 235	*P*-value	
SBRT vs. no concurrent chemoradiation		SBRT N=88	IMRT N=93	3DCRT N=235	*P*-value	Adjusted *P*-value
	Any complication, No. (%)	18 (20.5)	18 (19.4)	64 (27.2)	.22	.009
		SBRT vs. IMRT			SBRT vs. 3DCRT	
Adjusted Odds Ratio (95% CI)	Any complication	1.07 (0.76-1.50)			0.68 (0.49-0.94)	

[a] Stereotactic body radiotherapy
[b] Intensity-modulated radiotherapy
[c] 3-dimensional conformal radiotherapy
[d] Adjusted using inverse probability weighting
[e] Confidence interval

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which used a different biological effective dose and fraction schedule and enrolled patients with poorer performance status than the CHISEL trial, found no significant OS differences between patients treated with SBRT and patients treated with 3DCRT.[39] While these studies have helped provide support for SBRT as the curative treatment option over 3DCRT for smaller inoperable NSCLC tumors, no prospective studies to date have directly compared SBRT to conventionally fractionated IMRT for smaller early-stage NSCLC tumors.

Data evaluating SBRT outcomes in patients with NSCLC > 5 cm is limited mostly to single-institution case series without a comparator arm. Among 40 patients with larger NSCLCs treated with SBRT at an academic medical center, OS was 60% at 18 months.[9] Other case series of similar numbered patients demonstrated 1-year survival rates between 65% and 81%.[5,6] A recent study using the National Cancer Database (NCDB) comprising 201 patients who either received SBRT with chemotherapy or SBRT alone for NSCLC ≥ 5 cm reported 1-year OS of 77% in the SBRT-only group (N = 171).[7] However, this study did not report LCSS rates and was unable to assess for toxicities related to SBRT. In the study reported here, we used nationally representative data from the SEER-Medicare registry directly comparing older patients receiving SBRT vs. 3DCRT or IMRT for local treatment of NSCLCs > 5 cm in size. We found data consistent with survival rates reported in previous case series examining SBRT in tumors > 5 cm in size. Importantly, this present study advances our current understanding by showing that SBRT may be associated with higher survival compared to IMRT and 3DCRT overall but not when compared to patients receiving SBRT vs. concurrent chemoradiation with IMRT or 3DCRT.

Treatment-related toxicities are an important consideration in the management of older patients with NSCLC. In the RTOG 0236 trial for smaller NSCLC tumors, 16.4% of non-operable patients receiving SBRT experienced ≥ grade 3 adverse event, while a significantly less subset (7.7%) of potentially operable patients in RTOG 0618 experienced a protocol-specified grade 3 adverse event, suggesting that performance status and comorbidities have an important association with SBRT tolerability.[11,12] In our study, specifically looking at older patients at the highest risk of toxicities, we found that patients who received SBRT experienced significantly lower rates of overall treatment-related toxicity within the first 12 months compared to patients receiving 3DCRT and IMRT, including those receiving concurrent chemotherapy. This finding was particularly evident after adjusting for important confounding factors between treatment groups, suggesting that SBRT is a safer and well-tolerated modality that may be used to treat larger tumors in older patient populations.

This study has strengths and limitations. We used nationally representative, population-based data to study treatment outcomes of different RT modalities in a real-world patient population, providing our study important external validity. Moreover, our study focuses on older patients (> 65 years), an important subset most likely to derive benefit from RT given both the high incidence of lung cancer and significant challenges with surgical management in this age group. The main limitation, inherent to all observational data, is lack of treatment randomization creating baseline differences between treatment groups that may impact treatment allocation and outcomes. To account for this selection bias, we used robust propensity score models and IPW methods of all measured variables. However, despite accounting for the most important patient baseline characteristics and tumor factors, there potentially may remain unmeasured confounders. For example, while we excluded centrally located tumors that are often associated with worse outcomes and increased toxicities using ICD codes, tumor location may not be completely captured based on these data and therefore may impact our findings. Additionally, SEER-Medicare does not provide data or validated surrogate variables that would reliably estimate dose and fractionation for RT, and receipt of palliative vs. curative IMRT or 3DCRT treatment is not clear. However, (1) it is unlikely that patients who received IMRT were given palliative doses based on guideline recommendations to use external beam radiation treatment (EBRT; most commonly 2DCRT) for this indication;[40] (2) we stratified patients who received concurrent chemotherapy who are unlikely to receive palliative doses; and (3) all patients had localized tumors without lymph node involvement and therefore were eligible and should receive curative intent treatment. Lastly, our ability to detect differences only in overall but not individual complication rates and ARDs (ie, rib fracture, esophagitis, etc.) across groups is likely due to low incidence rates. Though patients may have experienced late toxicities, we detected few complications occurring after 12 months, which may be due to short follow-up time. Despite these limitations, given that no RCTs have compared RT modalities for the treatment of larger > 5 cm tumors, our results provide national data describing real-world outcomes in this understudied population.

Conclusion

In summary, this population-based study demonstrated that SBRT is associated with better survival when compared to IMRT and 3DCRT in patients with larger NSCLCs > 5 cm in size after adjusting for important clinical confounders. Survival outcomes were similar when comparing patients who underwent SBRT vs. IMRT and 3DCRT with concurrent chemotherapy. However, with a lower overall incidence of treatment-related toxicities associated with SBRT than with IMRT or 3DCRT, SBRT may be an appropriate option for treating older patients with larger inoperable NSCLC tumors. These results should be validated by future prospective studies, which should also consider evaluating long-term outcomes, patterns of recurrence, and cost-effectiveness of these radiotherapies.

Clinical Practice Points

- Older patients with non-small cell lung cancer (NSCLC) are often at high risk for surgery due to multiple age- and smoking-related comorbidities.
- Although stereotactic radiotherapy (SBRT) has emerged as a non-invasive alternative for early-stage small NSCLC tumors, there is limited data for the treatment of larger tumors.
- Using SEER-Medicare data, we examined outcomes in patients > 65 years with Stage IIA node-negative NSCLC tumors > 5 cm who received SBRT vs. intensity-modulated radiotherapy (IMRT) or 3-dimensional conformal radiotherapy (3DCRT).

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- In the overall cohort (N=584), SBRT was associated with higher survival compared to IMRT and 3DCRT.
- Subgroup analysis showed no difference in survival between patients who received SBRT (N=88) vs. concurrent chemoradiation with IMRT (N=47) or 3DCRT (N=121).
- SBRT was associated with fewer complications than IMRT or 3DCRT, including those receiving concurrent chemoradiation.

Author Contributions

JHT, GM, HSP, JPW, RRV contributed to the conception/design of the work, statistical analysis, interpretation of data of the work, and drafting of the work. DCM, KR, and QW contributed to the interpretation of data for the work and revising it for important intellectual content. All authors had final approval of the version to be published and agreement to be accountable for all aspects of the work.

Data Availability

Research data cannot be shared in accordance with NCI SEER-Medicare policies.

Disclosure

RRV serves on advisory boards for Bristol-Myers Squibb (BMS), AstraZeneca, Merck and Novocure, on speaker's bureau of AstraZeneca, received consulting honorarium from Onconova Therapeutics, and research grants from BMS, Lung Cancer Research Foundation and AstraZeneca. JPW received consulting honorarium from Banook, Atea, PPD, and Sanofi and research grants from Sanofi, Regeneron and Arnold Consulting. HSP serves on an advisory board for Galera Therapeutics, received honorarium from BMS, Guidepoint, Grand Rounds Health, Healthcasts, Healthline and RadOncQuestions, consulting fees from AstraZeneca, speaking fees from BMS and research grants from RefleXion Medical and U.S. FDA. DM receives a research grant from the NIH T32 program. JHT, GM, QW, and KR have no conflicts of interest to declare.

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Supplementary materials

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