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Outcomes following Stereotactic Body Radiotherapy vs. Limited Resection in Older Patients with Early Stage Lung Cancer

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Abstract

Background—Limited resection and stereotactic body radiotherapy (SBRT) have emerged as treatment options for older early stage non-small cell lung cancer (NSCLC) patients who are not good candidates for lobectomy.

Methods—We used the Surveillance, Epidemiology and End Results-Medicare registry to identify patients >65 years of age with stage I–II NSCLC and negative lymph nodes treated with SBRT vs. limited resection. We fitted a propensity score model predicting use of SBRT and compared adjusted overall survival of patients treated with SBRT vs. limited resection. Secondary analyses stratified the sample by type of limited resection (wedge vs. segmentectomy), age (≤75 vs. >75 years), and tumor size (<3 vs. ≥3 cm). We also compared rates of surgical complications and SBRT-related toxicity in the two groups.

Results—We identified 2,243 patients of which 362 (16%) received SBRT. SBRT-treated patients were older, had higher comorbidity scores and larger tumors ($p<0.001$ for all comparisons). Adjusted analyses showed no differences in survival (hazard ratio [HR]:1.19; 95% confidence interval [CI]: 0.97–1.47) among patients treated with SBRT vs. limited resection. While survival of patients who underwent SBRT vs. wedge resection was not different (HR: 1.22; 95% CI: 0.98–1.52), SBRT was associated with worse outcomes when compared to segmentectomy (HR: 1.55; 95% CI: 1.18–2.03). Adverse events were most often respiratory and more frequent in the patients treated with limited resection (28% vs 14%, $p<0.001$).

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Conclusion—SBRT is better tolerated and associated with similar survival when compared to wedge resection but not to segmentectomy in older patients with node negative NSCLC.

Keywords

Non-small cell lung cancer; radiotherapy; wedge resection; segmentectomy; radiosurgery

Background

The prevalence of early stage non-small cell lung cancer NSCLC is expected to increase given current trends in population aging and the widespread implementation of computed tomography (CT) screening.[1] While standard curative treatment for lung cancer is lobectomy, full resection is often precluded in older patients by multiple comorbidities, frailty, high operative risk, and/or borderline lung function. These patients are frequently offered less aggressive but still effective approaches such as limited resection (segmentectomy or wedge resection) and more recently, stereotactic body radiation therapy (SBRT). SBRT delivers targeted radiation to the tumor in doses varying from 30–54 Gy divided in 1 to 5 fractions.[2] Compared to standard radiotherapy, SBRT uses a higher dose per fraction and delivers the treatment via multiple beams providing higher radiation doses to the tumor while minimizing normal tissue exposure.

In single arm phase I/II trials of inoperable patients,[3–5] SBRT has been shown to provide 3-year survival rates of 56–60%. However, two phase III studies comparing SBRT to lobectomy and one phase III study comparing SBRT to sub-lobar resection in potentially operable patients have been closed due to slow patient accrual.[6, 7] Similarly, there is limited information regarding SBRT-related toxicities, particularly among less selected older individuals treated in the community. Despite the lack of comparative data, use of SBRT for early stage lung cancer is rapidly increasing.

In this study, we used population-based cancer data to compare survival and toxicity of SBRT vs. limited resection among older patients with node negative stage I–II NSCLC.

Methods

The study used data from the Surveillance, Epidemiology, and End Results (SEER)-Medicare registry. Cancer information in the linked database originates from 17 regional registries that combined represent approximately 26% of the United States population.[8] The study cohort consisted of patients with histologically confirmed, primary NSCLC diagnosed between 2002 and 2009 that underwent limited resection (wedge or segmentectomy) or SBRT. The study was limited to NSCLCs ≤5 cm in size without nodal involvement (N0) or distant metastases. Patients who received pre-operative chemotherapy or radiotherapy (RT) as well as patients who underwent conventional RT were excluded. Patients receiving hospice care or residing in a nursing home were excluded as they are not usually candidates for curative treatments. To capture data regarding treatment and comorbidities, patients had both Parts A (inpatient) and B (outpatient) Medicare coverage within 1 year of diagnosis. We excluded patients enrolled in health maintenance organizations, as Medicare does not collect claims on these individuals.

We obtained patient sociodemographic information from SEER-Medicare. The burden of coexisting illnesses was calculated for each patient based on the Deyo adaptation of Charlson's comorbidity index using inpatient, outpatient and physician Medicare claim files.[9] We used information from Hospice and Home Health Agency files to identify use of home health services, we used these as a proxy for poor functional status.[10]

Histological subtype was coded using International Classification of Disease for Oncology, 3rd edition based on data extracted from SEER. Cancer stage was classified according to the 7th edition of the American Joint Committee on Cancer Criteria based on detailed tumor extension, size, lymph node involvement and systemic dissemination information reported by SEER.[11] The extent of pre-treatment staging was determined based on claims indicating use of bone scan, positron emission tomography (PET), endobronchial ultrasound guided trans-bronchial lymph node aspiration (EBUS), esophageal ultrasound guided lymph node aspiration (EUS), and mediastinoscopy.

Surgical treatment within 6 months of diagnosis was ascertained from SEER and Medicare surgical codes.[12] Receipt of SBRT within the same timeframe was ascertained using the Healthcare Common Procedure Coding System code 77435, current procedural terminology-4 codes 77373, G0173, G0251, G0339, G0340, 61793, 0082T and ICD-9 procedure codes 92.3, 92.30–92.39.[13]

Overall and lung cancer-specific survival were calculated from the date of treatment initiation to the date of death reported in Medicare and SEER, respectively. For analyses of lung-cancer specific survival, deaths from other causes were classified as censored. The cause of death was obtained from death certificate data provided by SEER.

Surgical adverse events were defined as presence of cardiovascular complications, thromboembolic events, respiratory complications, transfusions, and extra-pulmonary infections based on inpatient and outpatient claims within 90 days of treatment.[14, 15] Similarly, we identified potentially radiation-related adverse events using inpatient and outpatient claims for esophagitis, radiation pneumonitis and hemoptysis within the same timeframe.

Statistical Analysis

Characteristics of patients treated with SBRT vs. limited resection were compared using the chi-squared or t-test. As patient and tumor characteristics were likely related to the decision of using SBRT vs. limited resection, we used propensity score methods to control for allocation bias. The probability of undergoing SBRT was estimated using logistic regression including patient characteristics (socio-demographics, comorbidity index, use of home services), tumor information (size, extension, location, and histology), use of preoperative tests, time from diagnosis to treatment initiation, and year of diagnosis. Then, we used Cox regression to compare survival of patients treated with SBRT vs. limited resection. Four different and complementary methods were used to perform these analyses. First, we included the propensity score as a continuous covariate in the Cox model. Second, we divided patients into quintiles based on propensity scores and compared survival using a stratified Cox model. Third, we used inverse probability weighting in the cox model after deleting observations with extreme weights. Lastly, we matched patients based on their propensity scores using a greedy algorithm and compared survival using a Cox model for correlated data. We also conducted secondary analyses stratifying the sample according to age (≤75 or >75 years), type of surgery (segmentectomy or wedge resection), and tumor size (<3 cm vs. ≥3 cm).

Patients receiving wedge resection or segmentectomy usually undergo pathological lymph node evaluation. Conversely, most SBRT treated patients are staged clinically and therefore, may be more likely to have undetected N1 disease, a risk factor for worse survival. In order to assess potential impact of differential staging, we performed secondary analyses limiting the cohort to SBRT patients who underwent more comprehensive mediastinal staging (i.e., PET, EBUS, EUS or mediastinoscopy). Additionally, we performed a sensitivity analysis to assess whether different rates of undetected N1 disease in SBRT-treated patients vs. those who underwent surgery could explain survival differences between the two groups.

Toxicity rates were estimated among patients receiving SBRT vs. limited resection and compared using a logistic regression model adjusted for propensity scores.

Based on the expected number of patients treated with SBRT vs. limited resection and assumed number of deaths in the cohort, we estimated that the study will have >80% power to detect an increased hazard of death among patients SBRT treated patients of 1.25 at a 0.05 significance level. Analyses were done with SAS software version 9.3 using two tailed p-values. The study was exempt by the institutional review board.

Results

We identified 2,243 patients >65 years of age with confirmed node negative stage I or II NSCLC ≤5 cm in size. Of these, 362 (16%) received SBRT. Baseline patients' characteristics are summarized in Table 1. Patients who received SBRT were older, more likely to be female, unmarried, had higher comorbidity scores, and had larger tumors (p<0.001 for all comparisons). PET use was similar among patients in the two treatment groups (p=0.45). While a larger number of patients treated with limited resection underwent a staging mediastinoscopy (p<0.001), few patients (<3%) in either group had EBUS or EUS. Among the patients receiving limited resection 1,337 (71%) underwent wedge resection and 544 (29%) had a segmentectomy. After adjusting for propensity scores the distribution of baseline characteristics was similar in both groups (Table 1).

Cox regression showed no significant differences in overall (hazard ratio [HR]: 1.19, 95% confidence interval [CI]: 0.97–1.47) or lung cancer-specific (HR: 1.46, 95% CI: 0.97–2.19) survival among patients treated with SBRT vs. limited resection, after adjustment for propensity scores. Stratified analysis by propensity score quintiles also showed no significant differences in overall survival (HR: 1.20, 95% CI: 1.00–1.45) among groups but worse lung cancer-specific survival (HR: 1.45, 95% CI: 1.01–2.10) in SBRT treated patients. Using inverse probability weighting, we found both overall (HR: 1.00, 95% CI: 0.85–1.18) and lung cancer specific (HR: 1.36, 95% CI: 0.98–1.89) survival was not significantly different in both treatment arms. Finally, propensity score matching also showed similar results for overall survival (HR; 1.20, 95% CI: 0.98–1.49) and lung cancer specific survival (HR: 1.48, 95% CI: 0.97–2.42) (Table 2).Findings remained consistent in secondary analyses stratifying patients by age (>75 or ≤75 years) and tumor size (>3 cm or ≤3 cm; Table 2).

When analyses were stratified by type of surgery, SBRT-treated patients had significantly worse overall (HR: 1.55, 95% CI 1.18–2.03) and lung cancer-specific (HR: 1.80, 95% CI 1.09–2.97) survival compared to patients treated with segmentectomy. However, overall (HR: 1.22, 95% CI: 0.98–1.52) and lung cancer-specific (HR: 1.45, 95% CI: 0.95–2.21) survival after wedge resection and SBRT were not significantly different.

Analyses restricted to SBRT patients who underwent mediastinal lymph node staging showed no significant differences in overall (HR: 1.17, 95% CI: 0.91–1.49) or lung cancer-specific (HR: 1.52, 95% CI: 0.93–2.47) survival when SBRT was compared to limited resection. Because SBRT patients are less likely to have invasive staging compared to the patients treated by limited resection, we performed a sensitivity analysis to explore the effect on survival of differential misclassification of N1 nodal status in the two groups. Survival after SBRT approached that of limited resection as the assumed proportion of N1 cases among clinically-staged SBRT-treated patients increased (Table 3). However, SBRT was not superior to limited resection in any of the plausible scenarios explored.

Respiratory complications within 3 months of treatment occurred most often in those treated with surgery (28%) compared to SBRT (14%; p< 0.0001; Table 4). Cardiovascular events occurred in 3% of patients treated with surgery however this complication was rare (<1%) after SBRT. SBRT was relatively well tolerated with <3% of patients developing radiation pneumonitis and no patients were treated for hemoptysis or radiation-induced esophagitis.

Discussion

The incidence of early stage lung cancer is expected to considerably increase with the widespread implementation of low dose CT screening.[1] As a result, clinicians will more frequently be faced with difficult treatment decisions, particularly for older smokers some of whom may have borderline lung function or comorbidities. Less invasive procedures such as SBRT and limited resection provide attractive treatment options for older patients because of their lower rates of perioperative morbidity. However, these procedures lead to higher rates of long-term cancer recurrence compared to lobectomy, a problem that may be less significant in older patients who may have a limited life expectancy. Using population-based cancer data, we showed that SBRT and wedge resection are associated with similar long-term survival, while segmentectomy performs better than SBRT. Moreover, SBRT was relatively well tolerated and associated with low rates of severe toxicity. Our findings provide further evidence regarding the potential role of SBRT in the treatment of older early stage patients.

Both potentially operable[16] and inoperable[3–5, 17] early stage NSCLC patients have been treated with SBRT in small[5, 16] studies that have shown comparable survival rates compared to historical controls treated with limited resection. Outcomes following SBRT are in general better than those observed among unresected stage I patients treated with conventional radiotherapy providing improved[18, 19] or similar survival and less toxicity.[20] Following these promising initial results, phase III randomized trials comparing SBRT to lobectomy or limited resection were initiated by large oncological groups. However, two studies were terminated early due to poor accrual[6, 7] and only one phase III study is ongoing but no longer recruiting patients.[21, 22]

Other investigators have assessed the potential benefits of SBRT using observational data from single institutional series.[23–25] Population studies found improved survival among inoperable early stage lung cancer patients diagnosed in consecutive periods.[26, 27] As improvements in survival coincided with the introduction of SBRT, the investigators attributed these findings to an uptake of this technique. These studies, however, were greatly limited by a lack of patient level treatment data. Shirvani and colleagues used a prior release of the SEER database (including cases diagnosed during or before 2007) to compare survival in patients receiving lobectomy, limited resection, conventional RT and SBRT.[28] The study, which included a relatively small number (n=124) of SBRT cases, showed similar outcomes following limited resection vs. SBRT. However, this study had limited long-term follow-up information (as SBRT uptake mostly occurred after 2007), did not report toxicity data, and was limited to early SBRT adopters, a factor that may limit the representativeness of their findings. Un update of the study showed SBRT was inferior to lobectomy but they did not directly compare SBRT to limited resection, nor did they provide information on the effect of wedge resection or segmentectomy individually.[29] In the current study, we evaluated SBRT in a larger cohort of older patients and assessed longer-term survival outcomes. The median follow up was 38 months in the patients treated with limited resection and 27 months in the patients treated with SBRT. The longest follow up time in the study was 9 years in either arm. This limits our ability to extrapolate results over a longer time horizon. In addition, we evaluated the impact of differential nodal evaluation. Staging of SBRT patients relies heavily on imaging, which can be inaccurate and underestimate the extent of mediastinal nodal involvement. Sensitivity for identification of mediastinal lymph node involvement in lung cancer is 55% for CT scan and 77% for PET.[30] Differential understaging (patients with N1 disease being classified as N0) may lead to an apparent worse survival among SBRT-treated patients. We addressed this potential bias by performing stratified and sensitivity analyses, which confirmed that limited resection and SBRT are associated with similar long-term outcomes despite potential misclassification of lymph node status in the SBRT treated arm.

We also assessed the effectiveness of SBRT vs. segmentecomy or wedge resection separately. Segmentectomy is considered superior oncologically than wedge resection as it provides a larger parenchymal margin and an increased nodal yield.[31, 32] Previous data has shown that lobectomy and segmentectomy for small clinical stage I NSCLC are equivalent, while wedge resection showed inferior outcomes.[33–35] Consistent with these findings, our results suggest that segmentectomy, should be preferred over SBRT even among older individuals.

Toxicity is particularly important when considering cancer treatment options with similar long-term survival. We used inpatient and outpatient claims data within 3 months of treatment to capture rates of SBRT-related toxicity. Respiratory complications were common in both groups, likely reflecting a high prevalence of underlying lung disease. However, SBRT was associated with lower rates of respiratory and cardiovascular complications. There were very few (<3%) reported cases of radiation pneumonitis post-SBRT and none required admission. However, it is possible that some SBRT-treated patients had milder adverse events not captured by our claims-based criteria. Despite our limitations, our data strongly suggest that SBRT is relatively well tolerated and infrequently associated with hospital admissions. Thus, future studies should compare quality of life and explore the cost-effectiveness of SBRT vs. limited resection.

Comparative effectiveness studies are often limited by allocation bias due to systematic differences in the characteristics of patients treated with SBRT vs. limited resection. These differences may become confounders of the effect of type of therapy. In this study, we used propensity score methods to balance the distribution of measured prognostic factors across study arms. Moreover, we limited the cohort to patients who could have been candidates for either treatment and had detailed tumor information. However, we could not control for unmeasured covariates. Thus, the level of evidence provided by our study does not match those obtained from randomized controlled trials. Nevertheless, no data about the comparative effectiveness of SBRT is available from prospective trials, as these were prematurely terminated. Thus, our and prior observational studies provide the best available information regarding the potential role of SBRT. Additionally, the large numbers of elderly patients in the registry allowed for appropriately powered comparisons among specific treatments. This is of particular advantage for the analysis of outcomes such as adverse events, which have low frequency. Another advantage is that survival and toxicity rates reported in our study represent those expected among patients encountered in routine care.

Currently more than half of American radiation oncologists offer SBRT; use of this technique has considerably increased in the last 5 years.[36] We found that SBRT is better tolerated and associated with similar survival when compared to wedge resection but not to segmentectomy in older patients with node negative NSCLC. Our results allow for a better assessment of the potential benefits and risks of SBRT vs. limited resection in older patients who are not candidates for lobectomy.

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Table 1

Characteristics of Study Patients Treated with Limited Resection vs. Stereotactic Body Radiotherapy

Characteristic	Limited Resection N=1881	SBRT N=362	P-value	Adjusted[1] P-value
Age, years, mean (SD)	76 (5.7)	78 (6.5)	<0.001	0.99
Female, No. (%)	1072 (57)	235 (65)	0.01	0.99
Married, No. (%)	994(53)	156 (43)	<0.001	0.99
Race/ethnicity, No. (%)			0.01	0.99
White	1679 (89)	313 (86)		
Black	99 (5)	29 (8)		
Hispanic	38 (2)	>11 (>3)[2]		
Other	65 (4)	≤11 (≤3)		
Median Income, No. (%)			0.09	0.99
First Quartile	405 (22)	94 (26)		
Second Quartile	444 (24)	90 (25)		
Third Quartile	480 (25)	92 (25)		
Fourth Quartile	551 (29)	85 (23)		
Comorbidity Score, No. (%)			<0.001	0.99
≤1.0	591 (31)	67 (18)		
1.0–2.0	582 (31)	121 (33)		
>2.0	708 (38)	174 (48)		
Histology, No. (%)			<0.001	0.99
Adenocarcinoma	1075(57)	208 (57)		
Squamous cell	595 (32)	136 (38)		
Large Cell	52 (3)	>11 (>3)		
Other	159 (8)	≤11 (≤3)		
Size, cm, No. (%)			<0.001	0.99
≤2.0	1091(58)	137 (38)		
2.1–3.0	530 (28)	144 (40)		
3.1–5.0	260 (14)	81 (22)		
PET[3] scan, No. (%)	822 (44)	166 (46)	0.45	0.99
Bone scan, No. (%)	220 (12)	33 (9)	0.16	0.99
Mediastinoscopy, No. (%)	218 (12)	≤11 (≤3)	<0.001	0.93

[1]Adjusted for propensity scores

[2]Exact number of patients not reported in cells with ≤ 11 individuals to maintain patients' confidentiality

[3]PET: Positron Emission Tomography

Table 2

Comparison of Survival of Older Patients Treated with Limited Resection vs. Stereoactic Body Radiotherapy

Propensity Score Model	No.	Overall Survival HR[1] (95% CI)[2]	Lung Cancer-specific Survival HR (95% CI)
Primary Analyses			
Adjusted	2243	1.19 (0.97–1.47)	1.46 (0.97–2.19)
Stratified	2243	1.20 (1.00–1.45)	1.45 (1.01–2.10)
Matched	972	1.20 (0.98–1.49)	1.48 (0.97–2.42)
Inverse Probability Weighted	2240[3]	1.00 (0.85–1.18)	1.36 (0.98–1.89)
Secondary Analyses			
Age ≤75 years	1066	1.11 (0.77–1.61)	1.44 (0.70–2.97)
Age >75 years	1177	1.24 (0.95–1.60)	1.49 (0.91–2.42)
Size ≤3 cm	1902	1.21 (0.95–1.53)	1.38 (0.65–2.96)
Size >3 cm	341	1.18 (0.75–1.86)	1.62 (1.01–2.61)
Wedge Resection vs. SBRT	1699	1.22 (0.98–1.52)	1.45 (0.95–2.21)
Segmentectomy vs. SBRT	906	1.55 (1.18–2.03)	1.80 (1.09–2.97)
Limited resection vs. SBRT with lymph node evaluation[4]	2059	1.17 (0.91–1.49)	1.52 (0.93–2.47)

[1] HR: hazard ratio,

[2] CI: confidence interval,

[3] Observations with extreme weights were deleted,

[4] Lymph node evaluation included pre-treatment endobronchial ultrasound guided lymph node biopsy, endoscopic ultrasound guided lymph node biopsy, mediastinoscopy or PET scan in the patients treated with SBRT

Table 3

Sensitivity Analyses Modeling the Impact of Increased N1 Disease in SBRT-treated patients

Probability of N1 Disease (%)		Increased Hazard of Death with N1 Disease	Adjusted Hazard Rate for SBRT vs. Limited Resection (95% CI)[3]
SBRT[2]	Limited Resection[1]		
20%	10%	1.3	1.14 (0.94–1.15)
20%	10%	1.5	1.12 (0.92–1.37)
20%	10%	2.0	1.07 (0.88–1.31)
30%	10%	1.3	1.11 (0.91–1.35)
30%	10%	1.5	1.07 (0.88–1.31)
30%	10%	2.0	0.99 (0.81–1.21)
40%	10%	1.3	1.08 (0.88–1.32)
40%	10%	1.5	1.02 (0.84–1.25)
40%	10%	2.0	0.92 (0.75–1.12)
50%	10%	1.3	1.05 (0.86–1.28)
50%	10%	1.5	0.99 (0.81–1.2)
50%	10%	2.0	0.86 (0.74–1.05)

[1]Probability of N1 disease was held constant as patients with limited resection as these patients are pathologically staged during surgery,

[2]SBRT: Stereotactic Body Radiotherapy,

[3]CI: confidence interval

Table 4

Adverse Events Following Treatment

Type of Toxicity	Limited Resection N=1881	SBRT N=362	P-value[1]
Transfusion, No. (%)	32 (1)	-	-
Reoperation, No. (%)	15 (1)	-	-
Extrapulmonary complications, No. (%)	201 (9)	21 (1)	<0.001
Cardiovascular complications, No. (%)	75 (3)	<11 (<3)	0.21
Thromboembolic complications, No. (%)	117 (5)	25 (7)	0.37
Respiratory Complications, No. (%)	621 (28)	50 (14)	<0.001
Hemoptysis, No. (%)	-	0	-
Radiation Pneumonitis, No. (%)	-	<11 (<3%)	-

[1] Adjusted for propensity scores