Cost of Intensity-modulated Radiation Therapy for Older Patients with Stage III Lung Cancer

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Abstract

Rationale: In the treatment of stage III non-small cell lung cancer (NSCLC), three-dimensional conformal radiotherapy (3D-RT) is the standard method for radiation delivery; however, intensity-modulated radiotherapy (IMRT) has been rapidly adopted. These two modalities may lead to similar survival, warranting a closer scrutiny of the costs involved.

Objectives: The purpose of this study is to compare radiotherapy-related and total costs of older patients with NSCLC treated with 3D-RT versus IMRT.

Methods: We conducted a population-based study of all Medicare beneficiaries aged 65 years or older in a Surveillance, Epidemiology and End Results region. Patients were diagnosed with stage III NSCLC diagnosed between 2002 and 2009. Patients received IMRT or 3D-RT in combination with chemotherapy within 4 months of diagnosis. Radiotherapy-related and total adjusted cost and survival

of patients receiving 3D-RT versus IMRT were compared using propensity scores methods.

Measurements and Main Results: Of the 2,418 patients in study, 314 (13%) received IMRT. Adjusted analyses showed no difference in overall survival (hazard ratio, 0.97; 95% confidence interval [CI], 0.85–1.12) in patients treated with 3D-RT versus IMRT. After adjusting for propensity scores, RT-related costs (estimated difference, \$6,850; 95% CI, \$5,532–\$8,168) and total costs (estimated difference, \$8,713; 95% CI, \$4,376–\$13,051) were significantly higher among patients undergoing IMRT.

Conclusions: The rapid adoption of IMRT for the treatment of stage III NSCLC has occurred in the absence of evidence from prospective randomized trials. Our results show that IMRT is associated with similar survival but increased costs, underscoring the need for continued research in IMRT and other new technologies.

Keywords: lung neoplasms; radiotherapy; cost-benefit analysis

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The rising costs of health care, particularly in the realm of cancer diagnosis and treatment, are garnering an increasing focus from policy makers (1). When contemporary estimates of cancer incidence, patterns of care, survival rates, and expected demographic changes are

taken into account, cancer costs are projected to increase by 28% in 2020 to \$158 billion U.S. dollars (1). However, studies have demonstrated that there is a wide variation in the extent to which increased cancer spending has resulted in an improvement in cancer care, as

measured by survival rates and quality of life (2).

Examining the effectiveness and value associated with the treatment of non-small cell lung cancer (NSCLC) is of particular importance. NSCLC continues to be the leading cause of fatal cancer in the United

States and disproportionately affects the elderly (3). Most patients present with locally advanced unresectable disease requiring relatively costly chemoradiation therapy (CRT), although long-term survival remains limited (4, 5). Three-dimensional radiation therapy (3D-RT) is considered the minimum standard of care (5).

Intensity-modulated radiation therapy (IMRT) has emerged as an alternative and increasingly popular form of radiotherapy for NSCLC (6). IMRT involves sophisticated planning that creates steep dose gradients enabling the delivery of higher radiation doses primarily focalized to the tumor.

Despite its increased adoption, current evidence supporting the use of IMRT for patients with loco-regionally advanced (stage III) NSCLC is limited. The early adoption of IMRT was based on computer simulation modeling studies, which estimated that IMRT might deliver higher radiation doses to the tumor while minimizing lung toxicity (7–9). A few single tertiary center retrospective reviews involving a relatively small number of patients suggested that IMRT may be associated with lower rates of toxicity and improved survival (10, 11). However, more recently, two large population-based analyses in patients with NSCLC found similar survival after 3D-RT and IMRT, although one did show a survival benefit in patients with larger tumors (6, 12). A separate population-based analysis examining the rates of complications also found conflicting evidence regarding a reduction in toxicity with IMRT (13). Results from a randomized trial of 3D-RT versus IMRT have shown that IMRT is associated with a quality-of-life benefit but no survival benefit (14, 15).

The increasing adoption of IMRT and conflicting evidence regarding toxicity warrant closer scrutiny. In this study, we used a population-based sample of Medicare patients with stage III NSCLC who were treated with CRT to estimate radiation-related and total costs of IMRT compared with 3D-RT as observed in routine clinical practice in a broad and diverse population. We also assessed survival in the two treatment groups to evaluate potential differences in costs in relation to patients' outcomes.

Methods

The study was conducted using data from the Surveillance, Epidemiology, and End

Results (SEER) registry, linked to Medicare claims (16). SEER is a national cancer database consisting of 17 regional registries and currently represents approximately 26% of the U.S. population. We identified all patients with histologically confirmed, unresected stage III NSCLC diagnosed between 2002 and 2009 and treated with CRT either with 3D-RT or IMRT. We further limited the cohort to Medicare beneficiaries with both Part A (inpatient) and Part B (outpatient) coverage and excluded patients in health maintenance organizations as they lacked complete claim information, precluding an estimate of costs and clinical outcomes. We also excluded patients receiving hospice care or in a nursing home.

Sociodemographic information (age, sex, race, ethnicity, marital status, and estimated income) was obtained from the SEER and Medicare databases. To evaluate comorbidities at treatment initiation, we used the Deyo adaptation of the Charlson comorbidity index, applying lung cancer-specific weights (17, 18). We used Medicare claims to identify patients who received home health services (limited to homebound patients), which we used as a proxy for limited functional status (19).

Histology was ascertained using codes available in SEER. Cancers were staged using detailed information provided in SEER on tumor location, size, local extension, and lymph node involvement. NSCLCs were classified based on the seventh edition of the American Joint Committee on Cancer system (20).

We used Medicare data to ascertain the diagnostic and staging workup of study patients, including use of bone scan, positron emission tomography, and mediastinoscopy (21). Patients were defined as treated with primary RT if they were coded in SEER as having received primary treatment with external beam radiation or if Medicare claims for RT were present within 4 months of diagnosis (22). RT technique was classified as 3D-RT (Current Procedure Terminology-4 code 77295 or 77290) or IMRT (Current Procedure Terminology-4 code 77301) using planning codes in an effort to conduct an intention-to-treat analysis (i.e., patients were assigned to treatment group on the basis of first planning procedure regardless of type of RT received) (23). Patients were categorized as having received chemotherapy if there were Medicare claims indicating chemotherapy use within 4 months of diagnosis (24).

The study outcomes, radiotherapy-related and total direct medical costs, took the perspective of Medicare as the payer and were estimated using Medicare reimbursement data obtained from claims from inpatient, outpatient, physician services, durable medical equipment, hospice, and home health agency files (25). We included all costs incurred in the 12 months after radiotherapy planning initiation, as this period captures most treatments provided as part of the primary cancer therapy as well as potential treatment-related complications. Costs were standardized to 2010 dollars using the Consumer Price Index and adjusted for geographic differences in Medicare reimbursement rates according to the U.S. Census Bureau regions (26).

We created two categories of costs: radiotherapy-related and total costs. Radiotherapy costs included claims for planning or delivery of RT, as determined by Healthcare Common Procedure Coding System codes, in addition to claims that identified inpatient hospitalizations related to radiotherapy, outpatient visits for radiotherapy, and outpatient visits with radiation oncologists (*see* Table E1 in the online supplement) (27).

Because a comparison of treatment costs should be considered in light of potential health benefits arising from IMRT, we also considered two secondary outcomes, overall survival and toxicity. We calculated overall survival as the interval from the CRT planning date to the date of death recorded by Medicare. We identified the occurrence of RT-related toxicity, which we defined as pneumonitis or esophagitis requiring hospitalization within 12 months of treatment initiation using Medicare claims (International Classification of Disease-9 code 508.0 and 530.10, respectively) (28).

Statistical Analysis

We compared baseline characteristics of the patients who received 3D-RT versus IMRT using the chi-square or *t* test. We used propensity score methods to control for potential differences in baseline characteristics of patients who received 3D-RT versus IMRT. Propensity scores for IMRT were generated with a logistic model that included patients' sociodemographic characteristics, comorbidities, use of home services, type of diagnostic and staging evaluation, cancer-related characteristics, and year of diagnosis (29). We then

evaluated if the distribution of baseline characteristics between groups was well balanced after adjusting for propensity scores.

Costs were modeled using a generalized linear model (GLM) with an identity link and γ -distributed variance function. First, we used the propensity score as a covariate in a GLM. Second, we matched patients receiving IMRT and 3D-RT by their propensity score and then compared the costs with a GLM using a robust variance estimator to account for clustering (30). Third, we compared the costs using probability weighting by the inverse of the propensity score. In addition, we conducted secondary stratified analyses by stage (IIIA vs. IIIB) as well as year of diagnosis (diagnosed in years 2002–2006 and 2007–2009). Cox regression models were fitted to compare overall survival of patients treated with 3D-RT versus IMRT, adjusting for propensity scores. Adjusted odds ratios of radiation pneumonitis and esophagitis after 3D-RT versus IMRT were compared using logistic regression.

Statistical analyses were performed in SAS (SAS Institute, Cary, NC) using two-sided P values. This study was determined

to be exempt from the Icahn School of Medicine at Mount Sinai Institutional Review Board before study commencement.

Results

Selection of the study cohort is shown in Figure 1. Of the 2,418 patients with unresected stage III NSCLC included in the study, 314 (13%) underwent IMRT. Patients who received IMRT were more likely to be women ($P < 0.01$); however, there were no significant differences in the distribution of other sociodemographic characteristics or comorbidities among the two groups ($P > 0.05$ for all comparisons; Table 1). Consistent with the recent uptake of IMRT, this approach was more frequently used among patients diagnosed between 2007 and 2009 ($P < 0.001$). The distribution of tumor characteristics was similar among IMRT- and 3D-RT-treated patients ($P > 0.05$ for all comparisons). IMRT-treated patients were more likely to undergo positron emission tomography and bone scan as a part of their staging workup ($P < 0.001$). After adjusting for propensity scores, most baseline

characteristics were well balanced across groups.

The median unadjusted overall survival for patients treated with 3D-RT versus IMRT was 16 months (interquartile range [IQR], 21 mo) and 15 months (IQR, 22 mo), respectively ($P = 0.08$). Cox regression adjusting for propensity scores showed no significant difference in overall survival (hazard ratio [HR], 0.97; 95% confidence interval [CI], 0.85–1.11) of patients treated with 3D-RT versus IMRT. In our stratified analyses, IMRT and 3D-RT were associated with similar overall survival among patients with stage IIIA (HR, 0.99; 95% CI, 0.83–1.19) and IIIB (HR, 0.95; 95% CI, 0.76–1.17) disease. The unadjusted rate of severe radiation pneumonitis was 8.7% for patients who received 3D-RT compared with 8.6% among patients treated with IMRT ($P = 0.95$). After adjusting for propensity scores, IMRT was associated with similar rates of radiation pneumonitis (OR, 1.07; 95% CI, 0.69–1.67). There were too few cases of esophagitis to report and maintain confidentiality in accordance with National Cancer Institute guidelines.

The median unadjusted radiotherapy-related costs in the IMRT group were

Figure 1. Cohort diagram. 3D-RT = three-dimensional conformal radiotherapy; HMO = health maintenance organization; IMRT = intensity modulated radiotherapy; NSCLC = non-small cell lung cancer; SEER = Surveillance, Epidemiology, and End Results. *According to American Joint Committee on Cancer, 7th ed. [†]Exclusion criteria were sequentially applied as listed.

Table 1. Baseline characteristics of patients with stage III non–small cell lung cancer according to treatment

Characteristic	3D-RT (n = 2,104)	IMRT (n = 314)	P Value	Adjusted P Value*
Age, median (IQR), yr	78 (8)	77 (8)	0.86	0.99
Female	919 (44)	162 (52)	0.009	0.99
Married	1,193 (57)	175 (56)	0.75	0.99
Race/ethnicity				
White	1,808 (86)	257 (82)	0.14	0.99
Black	170 (8)	32 (10)		
Hispanic	59 (3)	≥11 (≥4) [†]		
Other	67 (3)	≤11 (≤4)		
Median income				
First quartile [‡]	498 (24)	77 (25)	0.11	0.99
Second quartile	523 (25)	63 (20)		
Third quartile	551 (26)	78 (25)		
Fourth quartile	531 (25)	96 (31)		
Comorbidity score				
≤1	894 (42)	134 (43)	0.75	0.99
1–2	621 (30)	87 (28)		
>2	589 (28)	93 (30)		
Year of diagnosis				
2002–2006	1,219 (58)	71 (23)	<0.001	0.56
2007–2009	885 (42)	243 (77)		
Diagnostic/staging workup				
PET scan	1,178 (56)	262 (83)	<0.001	0.008
Bone scan	715 (34)	67 (21)	<0.001	0.06
Mediastinoscopy	387 (18)	61 (19)	0.66	0.68
Histology				
Adenocarcinoma	801 (38)	125 (40)	0.57	0.99
Squamous cell	1,131 (54)	170 (54)		
Large cell	101 (5)	≤11 (≤4)		
Other	71 (3)	≤11 (≤4)		
Tumor site				
Upper	1,215 (58)	193 (61)	0.52	0.99
Middle	71 (3)	≤11 (≤4)		
Lower	516 (25)	75 (24)		
Other	302 (14)	≥11 (≥4)		
Tumor status				
T1	316 (15)	52 (17)	0.38	0.99
T2	594 (28)	101 (32)		
T3	486 (23)	71 (23)		
T4	580 (28)	72 (23)		
Not reported	128 (6)	18 (6)		
Nodal status				
N0	155 (7)	≤18 (≤4)	0.11	0.99
N1	110 (5)	15 (5)		
N2	1,408 (67)	212 (68)		
N3	379 (18)	69 (22)		
Not reported	52 (2)	≤18 (≤4)		
Stage				
IIIA	1,283 (61)	201 (64)	0.30	0.99
IIIB	821 (39)	113 (36)		

Definition of abbreviations: 3D-RT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; IQR = interquartile range; PET = positron emission tomography. Data presented as n (%) unless otherwise noted.

*Adjusted for propensity scores.

[†]Cells with ≤11 patients not reported to maintain patient confidentiality.

[‡]Lowest income quartile.

\$16,343 (IQR, \$12,384) and \$8,277 (IQR, \$5,937) in the 3D-RT group (Table 2).

After adjusting for propensity score, radiotherapy-related costs in the IMRT group were \$15,336 (95% CI, \$13,850–

\$16,833) and \$8,486 (95% CI, \$7,168–\$9,804) in the 3D-RT group. The adjusted difference in radiotherapy-related costs was \$6,850 (95% CI, \$5,532–\$8,168). Similar results were obtained after matching by

propensity scores and using inverse probability weighting. The median unadjusted total costs per treated patient in the IMRT treatment group was \$50,978 (IQR, \$41,397) and \$39,504 (IQR, \$35,354) in the 3D-RT group. After adjusting for propensity score, the overall adjusted cost per treated patient in the IMRT treatment group was \$59,036 (95% CI, \$53,536–\$64,537), and the overall adjusted costs in the 3D-RT group was \$50,322 (95% CI, \$45,985–\$54,660). The adjusted difference in the total costs in the IMRT group compared with the 3D-RT group was \$8,713 (95% CI, \$4,376–\$13,051).

Analyses matching by propensity scores and using inverse probability weighting of propensity scores showed similar results. In analyses limited to patients with stage IIIA disease, the adjusted difference in total (\$8,734; 95% CI, \$3,485–\$13,983) and RT-related (\$7,529; 95% CI, \$5,940–\$9,117) costs were similar. In analyses limited to patients with stage IIIB disease, the adjusted difference was \$8,388 (95% CI, \$785–\$15,991) for the total costs and \$5,313 (95% CI, \$3,013–\$7,613) for the RT costs. Analyses conducted after stratifying by year of diagnosis produced similar results.

Discussion

The rapid adoption of IMRT for the treatment of stage III NSCLC has occurred in the absence of evidence from prospective randomized trials. Our study is the first, to our knowledge, to examine the cost implications of the use of this technology in lung cancer, the number one cause of cancer deaths. Our population-based study shows that IMRT is associated with increased treatment costs but does not result in a survival or toxicity advantage compared with 3D-RT. Although a randomized trial of IMRT versus 3D-RT in younger patients (median age of 66 yr) found that IMRT had a decreased rate of esophageal toxicity, there was no evidence of survival benefit (15). Given the increased time and technical demands involved in planning as well as the higher costs, these results suggest that the continuing replacement of 3D-RT with IMRT should be reconsidered until the potential advantages of this technique are confirmed in prospective studies in elderly patients.

The value of IMRT has been investigated in the treatment of many cancers, including gynecologic, urologic,

Table 2. Propensity score analysis: comparison of total and radiotherapy-related costs of patients with unresected stage III non-small cell lung cancer treated with three-dimensional versus intensity-modulated radiotherapy

Model	N	Total Costs Difference (95% Confidence Interval)	Radiotherapy Costs Difference (95% Confidence Interval)
Primary analyses			
Adjusted for propensity scores	2,417	\$8,713 (\$4,376–\$13,051)	\$6,850 (\$5,532–\$8,168)
Inverse probability weighting by propensity scores	2,402	\$7,206 (\$4,468–\$9,950)	\$6,479 (\$5,751–\$7,207)
Matched by propensity scores	1,525	\$9,281 (\$5,033–\$13,531)	\$7,288 (\$6,180–\$8,397)
Secondary stratified analyses			
Stage IIIA	1,481	\$8,734 (\$3,485–\$13,983)	\$7,529 (\$5,940–\$9,117)
Stage IIIB	934	\$8,388 (\$785–\$15,991)	\$5,313 (\$3,013–\$7,613)
Year of diagnosis 2002–2006	1,286	\$6,091 (\$1,910–\$14,092)	\$3,460 (\$2,549–\$4,372)
Year of diagnosis 2007–2009	1,126	\$10,957 (\$5,956–\$15,958)	\$7,755 (\$6,396–\$9,113)

All costs in 2010 U.S. Dollars.

and gastrointestinal, among others, and has not been shown to be consistently cost effective (31–33). However, there are no previous studies examining the cost effectiveness of IMRT in the treatment of NSCLC. Our findings should be considered within the ongoing national conversation about health care costs, reimbursement, and comparative effectiveness. Although some advanced technologies improve patients' outcomes, they are a major driver of increased health care spending in the United States (34). Oftentimes, many novel devices or surgical techniques are rapidly adopted without the same level of evidence required for chemotherapy (35).

In the case of IMRT, which was adopted based on theoretical predictions of decreased toxicity, recent data as well as our results suggest there is no improvement in survival (6, 13, 36, 37). Given similar outcomes, and the higher costs of IMRT, additional scrutiny regarding use and reimbursement policies for this treatment is needed. Efforts to move toward value-based care should consider a revision of reimbursement rates closer to those for 3D-RT. Another strategy would be to expand the Centers for Medicare and Medicaid Services Coverage with Evidence Development program, in which Medicare coverage of an item or service only occurs in the context of a clinical study (38).

Strengths and Limitations

There are strengths and limitations to our study findings that should be noted. It is possible that without randomization, differences in costs were driven by systematic differences in the characteristics of patients treated with 3D-RT versus IMRT. Patient and physician preferences, as

well as patient and tumor (size, geometry, and proximity to critical structures) characteristics, could have influenced the decision to use IMRT, creating systematic differences among treatment groups.

However, a variety of aspects of our study minimized allocation bias.

First, current guidelines have no specific indications for 3D-RT versus IMRT, mitigating the potential for allocation bias (5). Second, in our analytic design, we limited the study to patients treated with CRT, thus excluding patients with poor performance status who may have received palliative RT. We also excluded patients who were in hospice or a nursing home and controlled for use of home services, a proxy for poor performance status (19). Similarly, we adjusted for detailed tumor characteristics (including size, location, and local extension) and comorbidities (including chronic obstructive lung disease) that may have impacted the use of 3D-RT versus IMRT, survival, and costs. Finally, we used propensity score methods to adjust for potential differences in the baseline characteristics of IMRT- and 3D-RT-treated patients. We note, however, that propensity scores do not account for the effect of unmeasured covariates, a known limitation of this method.

We were unable to report the frequency of esophagitis requiring hospitalization, likely because most cases of esophagitis were managed in the outpatient setting. However, we limited our assessment to severe toxicity requiring hospitalization, as claim-based algorithms have only been validated in that setting. In addition, any costs from the outpatient treatment of esophagitis would have been captured in our analysis. Our analyses were based on intention to treat, a

preferred strategy given that the actual RT dose received may also be influenced by early discontinuation due to toxicity, potentially introducing additional bias.

Similarly, we identified RT technique using planning codes to simulate intention to treat; however, 100 and 94% of patients included in the IMRT and 3D-RT groups, respectively, had subsequent matching RT delivery claims. It is a limitation of the SEER-Medicare dataset that information regarding doses of chemotherapy and radiotherapy are unavailable, as it is possible that individuals received subcurative treatment doses. However, using population-based data, our study represents treatment doses as used in clinical practice. As our study examines the outcomes of individuals older than 65 years, it is difficult to generalize our findings to younger patients. One study that did include younger patients found no difference in overall survival but reported an advantage of IMRT in patients with T3 and T4 disease (12). Similarly, our sample contained a low percentage of minority patients, likely a reflection of poor access to care.

Conclusions

In summary, using a large population-based sample, we found that IMRT costs are approximately \$8,000 higher per patient, but this RT modality is not associated with improved survival or toxicity in patients older than 65 years with stage III NSCLC treated with CRT. Our results underscore the need for continued research in IMRT and other new technologies in the elderly as well as a reassessment of reimbursement rates. ■

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