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Postoperative Radiotherapy for Elderly Patients with Stage III Lung Cancer

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Abstract

Background—The potential role of postoperative radiation therapy (PORT) for patients with completely resected stage III non-small-cell lung cancer (NSCLC) with N2 disease remains controversial. Using population-based data, we compared survival of a concurrent cohort of elderly patients with N2 disease treated with and without PORT.

Methods—Using the Surveillance, Epidemiology and End Results (SEER) registry linked to Medicare records we identified 1,307 cases of stage III NSCLC with N2 lymph node involvement diagnosed between 1992 and 2005. We used propensity score methods and instrumental variable analysis to compare survival of patients treated with and without PORT after controlling for selection bias.

Results—Overall, 710 (54%) patients received PORT. Propensity score analysis showed that PORT was not associated with improved survival of patients with N2 disease (hazard ratio [HR]: 1.11; 95% confidence interval [CI]: 0.97–1.27). Analyses limited to patients treated with or without chemotherapy, intermediate or high complexity RT planning, or adjusting for time trends showed similar results. The instrumental variable estimator for the absolute improvement in 1- and 3-year survival with PORT was −0.04 (95% CI: −0.15 to 0.08) and −0.08 (95% CI:−0.24 to 0.15), respectively.

Conclusions—These data suggest that PORT is not associated with improved survival of elderly patients with N2 disease. These findings have important clinical implications given that SEER data shows that a large percentage of elderly patients are currently treated with PORT despite the lack of definitive evidence about its effectiveness. The potential effectiveness of PORT should be further evaluated in randomized control trials.

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Keywords

Postoperative radiotherapy; N2 disease; lung cancer; survival

Introduction

Surgical resection is considered the standard of care for patients who are diagnosed with clinically early stage non-small cell lung cancer (NSCLC).[1] However, a considerable proportion of patients who undergo surgery for localized NSCLC are found to have involvement of N2 lymph nodes on pathologic staging.[2–4] These patients have higher rates of local recurrence and worse survival when compared with patients with pathologic N0 or N1 disease.[5, 6] Because of this increased risk of local recurrence, postperative radiation therapy (PORT) has been proposed as a means to improve the outcomes of resected patients with N2 lymph node involvement.[7]

There is considerable debate regarding the potential benefit and harms of PORT for patients with NSCLC. Although some studies have shown improvements in survival with PORT these findings have not been confirmed in other trials.[8–12] Current recommendations against the use of PORT are based on the results of a meta-analysis published in 1998 and subsequently updated to include more recent studies.[13, 14] This meta-analysis analyzed data from 2,343 patients with stage I to III NSCLC from 11 prospective trials (some initiated as early as 1965) and showed a significant adverse effect of PORT on survival. In subgroup analysis the detrimental survival effect seemed limited to those with stage I or II disease; the results for N2 positive patients favored PORT, although the difference was not statistically significant. However, these results are subject to several important limitations.[15, 16] The RT techniques used in many of the trials are not consistent with current standards (e.g. cobalt machines, single RT field) and some studies used larger than conventional daily fractions which could have resulted in suboptimal effectiveness while increasing toxicity. Additionally, most of these randomized controlled trials (RCTs) were limited to highly selected, younger patients who fulfilled the strict inclusion and exclusion criteria. Thus, there is limited data regarding the effectiveness of PORT for elderly patients with N2 disease treated in the community. More recently, several large RCTs have established adjuvant chemotherapy as the standard of care for stage IIIA NSCLC[17, 18] and thus, it is also important to reevaluate the role of PORT among patients treated with chemotherapy.

In this study, we used nationally representative data from the Using the Surveillance, Epidemiology and End Results (SEER)-Medicare registry to evaluate whether PORT was associated with improved survival among elderly patients with resected NSCLC and N2 lymph node involvement.

Methods

We used the National Cancer Institute's SEER database, which integrates data from 17 regional cancer registries.[19] SEER has been linked to Medicare enrollment and claims data using unique patient identifiers.[20] Among individuals aged 65 years in SEER, approximately 93% have been identified in the Medicare enrollment file and included in the SEER-Medicare registry.

Using SEER-Medicare we identified all primary cases of completely resected NSCLC with N2 lymph node involvement diagnosed between 1992 and 2005. We excluded cases diagnosed at autopsy or using death certificate data as well as patients in a health maintenance organization or who lacked Part B Medicare coverage (coverage for outpatient care) at the time of diagnosis for whom we were not able to ascertain comorbidities and

chemotherapy use. We also excluded patients who underwent limited resection (wedge resection or segmentectomy), received preoperative chemotherapy or radiation therapy, or died during the perioperative period (within 30 days of surgery). The final cohort consisted of 1,307 patients with resected N2 NSCLC.

Sociodemographic information was obtained from SEER and Medicare databases. To evaluate the burden of comorbidities, we used the Deyo adaptation of the Charlson comorbidity index, applying lung cancer-specific condition weights.[21, 22] In terms of histology, cases were classified as adenocarcinoma, bronchioalveolar cell carcinoma, squamous cell carcinoma, large cell carcinoma, or other histologic type. Stage was classified according to the most recent classification American Joint Committee on Cancer criteria.[6, 23]

Patients were classified as having undergone resection if SEER data or Medicare physician claims indicated the patient had a lobectomy or pneumonectomy (surgical codes 30 to 70). PORT use was ascertained from SEER and Medicare claims.[24] Patients were considered as being treated with PORT if they were coded by SEER as having received postoperative external beam radiation or if Medicare inpatient, outpatient, or physician claims contained any code indicating PORT use within four months of surgery.[25] RT complexity was determined using planning and simulation codes from Medicare physician claims.[26, 27] Postoperative use of chemotherapy (platinum-based or other regimens) was identified from Medicare claims using published algorithms.[28]

Postoperative events can influence decisions regarding PORT use. Thus, presence or absence of common surgical complications was identified using Medicare claims.[29–31] We also used Medicare data to ascertain use of home health services. To be eligible for Medicare home services, beneficiaries must be homebound; thus, we used this information as a proxy for poor performance status.

Statistical Analysis

Differences in distribution of baseline characteristics between patients who received or did not receive PORT were evaluated using the chi-square test. The Kaplan-Meier method was used to estimate unadjusted survival rates among patients in the two treatment groups. Survival was determined as the interval from the date of resection to the Medicare date of death. Those surviving past December 31, 2007 (date of the last follow-up) were classified as censored observations.

We used propensity score analyses to control for differences in the baseline characteristics of patients treated with and without PORT. Propensity scores can be thought of as a measure of the likelihood that a patient will be assigned to a certain treatment (i.e. PORT vs. no PORT), on the basis of his or her pretreatment characteristics. To perform the propensity score analyses, we estimated the probability that each patient would receive PORT using logistic regression.[32] The model included variables for the patients' sociodemographic characteristics, comorbidities, cancer-related factors (histology, grade, tumor size, T status, location, histology, number of lymph nodes evaluated, and number of positive lymph nodes), type of resection, postoperative complications, and use of home health services during the postoperative period. Once the model was fitted, we used regression analyses to evaluate whether the baseline covariates were balanced across study groups after adjusting for propensity scores.

Cox regression analysis was used to compare survival of patients treated with and without PORT, adjusting for propensity scores in three ways. First, we included the propensity score as a continuous covariate in a Cox model comparing survival of patients who receive PORT

and those who did not. Ina second approach, we classified patients into quintiles based on their propensity for PORT and then fitted a stratified Cox model. Finally, we matched patients treated with and without PORT by their propensity scores and compared survival among study groups using a marginal Cox model with a robust sandwich variance estimator.[33]

In order to assess the potential effectiveness of PORT with and without chemotherapy, we conducted secondary analyses adjusting as well as stratifying for chemotherapy use. Additionally, we conducted stratified analyses to assess the effectiveness of intermediate and high complexity RT planning. Finally, we performed propensity score analyses adjusting for year of diagnosis to control for possible time trends in the use of other lung cancer treatments.

We performed an instrumental variable (IV) analysis to control for unmeasured confounders. IV analysisis a technique that attempts to simulate a randomized controlled trial using observational data. We used geographic variability in the use of PORT for the IV analysis.[34–36] Different geographic regions (Health Care Service Areas; HCSAs) in SEER were classified as high- or low- utilization areas based on the proportion of patients in the HCSAs that received PORT (excluding areas with ≤5 patients). Areas where the proportion of patients treated with PORT was above the median were classified as high-utilization areas. The IV was calculated as the difference between the adjusted 1-and 3-year survival in the high- and low-utilization areas, divided by the probability of undergoing PORT in those regions [34]. Thus, the IV estimate represents the absolute difference in 1- and 3-year survival among patients treated with and without PORT. Adjusted survival was estimated using a Cox model controlling for age, sex, race, and use of chemotherapy. The confidence interval (CI) of the IV estimate was obtained using bootstrap.[34]

Based on the number of deaths observed among patients in the cohort, we estimated that the study had >80% power to detect a 15 to 20% decreased hazard of death with PORT at a 0.05 significance level. Analyses were performed using SAS (SAS, Cary, NC) software. The study was reviewed by the Institutional Review Board and classified as exempt.

Results

Overall, 710 (54%; 95% CI: 51 to 57%) patients with N2 disease received PORT. The baseline characteristics of the study cohort are shown in Table 1. Patients who received PORT were more likely to be younger ($p<0.0001$) and have a higher income ($p=0.03$) but there were no significant differences among groups in the distribution of sex, race/ethnicity, income, or comorbidities ($p >0.05$ for all comparisons). Similarly, the tumor status and histology of cancers treated with and without RT were similar. However, the number of positive N2 lymph nodes varied among patients who received and did not receive RT ($p=0.05$). Rates of lobectomy and pneumonectomy were similar in the two groups ($p=0.11$); patients treated with RT were more likely to receive adjuvant chemotherapy ($p <0.0001$). Except for postoperative use of chemotherapy (not included in the model), all covariates were well balanced among groups after adjusting for propensity scores (Table 1).

On unadjusted analysis, survival of patients treated with and without PORT was not significantly different ($p=0.30$). Similarly, propensity score analyses did not show an improved survival with use of PORT (Table 2). A Cox model adjusting for propensity scores showed that postoperative survival was not improved with PORT (HR: 1.11; 95% CI: 0.97–1.27). Analyses stratifying (HR: 1.12; 95% CI: 0.98–1.28) or matching (HR: 1.10; 95% CI: 0.95–1.27) by propensity score showed similar findings. Secondary analyses adjusting for use of adjuvant chemotherapy or limiting the sample to patients treated with or without

postoperative chemotherapy, or with intermediate and high complexity RT planning also showed that PORT was not associated with improved survival (HR range 1.06 to 1.25). Finally, the association between PORT use and survival remained unchanged, when analyses were repeated adjusting for potential time trends in the use of other lung cancer treatments.

Assessment of PORT use in the HCSAs in SEER showed that approximately 34.1% of the patients in the low-use areas received PORT in comparison to 66.7% in the high utilization areas. The IV estimate showed that PORT was associated with a 0.04 decrease in 1-year cumulative survival (95% CI: −0.15 to 0.08). Similarly, 3-year survival among patients treated with and without PORT was not significantly different (absolute difference in cumulative survival −0.08; 95% CI: −0.24 to 0.15).

Discussion

The role of PORT in patients with completely resected stage III NSCLC with involvement of N2 lymph nodes remains uncertain. However, despite lack of conclusive evidence from randomized trials, PORT is frequently used to treat elderly patients with N2 disease.[37] Using a population-based registry, we found that PORT is not associated with improved survival of elderly patients with resected NSCLC who were found to have N2 disease on pathologic staging. These data suggests that PORT should not be routinely used to treat these patients outside research trials.

Prognosis of patients who undergo lung cancer resection is highly dependent on the extent of lymph node involvement. While long-term survival may be achieved by approximately 70% of patients without lymph node metastasis, it decreases to 20 to 35% for those with microscopic N2 disease.[5, 6] Given that 20 to 40% of patients with N2 disease experience treatment failure due to local-regional relapse, PORT is frequently used to reduce to risk of local recurrence. Several small randomized controlled trials conducted from 1965 to the 1990s assessing the role of PORT following NSCLC resection showed discordant results.[8–12] Enthusiasm for PORT diminished after the 1998 PORT Meta-Analysis Trialists Group reported a 7% absolute greater mortality associated with PORT, particularly for patients with N0 or N1 disease.[13, 14, 38] The meta-analyses also showed a non-significant survival benefit in patients with N2 lymph node involvement, suggesting that PORT may be beneficial for patients with more advanced disease.

More recent data has renewed the interest in PORT. A number of recent studies have suggested that PORT may be of benefit for patients with completely resected N2 NSCLC.[37, 39–41] A subgroup analysis of the Adjuvant Navelbine International Trialist Association trial, showed that PORT led to longer overall survival in patients with resected N2 NSCLC.[41] Analysis of the SEER database (not linked to Medicare) of patients with resected NSCLC between 1998 and 2002 showed that PORT was associated with longer survival for patients with N2 disease.[37] However, SEER data does not contain information about comorbidities, complications of surgery, or use of adjuvant chemotherapy.[28] As lower number of comorbidities and chemotherapy use are associated with PORT treatment, lack of adjustment for these covariates may explain the discordant results among studies. Additionally, this previous study used standard regression analysis to compare the outcomes of patients treated with and without PORT and did not perform more advanced statistical techniques to control for selection bias. Our findings are consistent with the conclusions of the PORT Meta-Analysis Trialists Group suggesting that, until definitive data is available, use of PORT should we limited to patients enrolled in clinical trials.

The Lung Adjuvant Radiotherapy Trial (LungArt) is an ongoing multicenter phase III randomized controlled trial evaluating the effectiveness of PORT in patients with resected NSCLC with N2 lymph node involvement. The study, sponsored by a French cooperative group, will recruit a total of 700 patients randomized to PORT vs. a control arm. Our results highlights the importance of enrolling patients into this study, should provide useful data to assess assumptions regarding the potential effect of PORT on survival and to determine the appropriate duration of follow-up so that the study will be adequately powered.

Several strengths and limitations regarding our study are worth noting. Because this was a retrospective study, the use of PORT was not random but rather influenced by patients' and physicians' preferences, baseline characteristics, and practice patterns. Consequently, differences in outcomes among patients treated with and without PORT may be explained by confounding by indication. However, we used propensity score methods to balance the study groups and control for all measured covariates including detailed clinical and tumor characteristics which are the most important prognostic factors for stage III NSCLC. Additionally, IV analyses provide a consistent estimate of the effect of PORT even in the presence of unmeasured confounders. Thus, until data from contemporary RCTs is available, these results are a valuable source of information about the potential benefit of PORT.

The SEER-Medicare database is a population-based registry and, is therefore less affected by referral patterns and other sources of bias. Thus, the generalizability of our results should be excellent. The large number of patients with N2 disease in the registry and the extended follow-up time ensured that the study was powered to detect relatively small benefits of PORT. However, SEER does not provide data regarding disease recurrence; thus, we were not able to assess whether PORT is associated with other important secondary outcomes such as increase disease free survival and/or lower rates of local recurrence. Additionally, no data regarding the total radiation dose or fractionation schedule used to treat each patient is provided in the SEER-Medicare database. Thus, we were not able to assess the impact of these factors on lung cancer survival. We excluded patients treated with neoadjuvant chemotherapy and did not assess whether the extent of lymph node dissection influences the potential effect of PORT; these issues should be explored in future studies.

In summary, our findings suggest that PORT is not associated with improved survival of elderly stage III NSCLC with N2 disease that underwent surgical resection. Thus, our results are consistent with the conclusion of prior meta-analyses that also found no benefit for PORT in this clinical setting. These data should be important given that the SEER-Medicare trends shows that a large proportion of elderly patients with N2 disease are currently being treated with PORT despite the lack of definitive evidence from RCTs.

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The sponsors of the study had no role in the study design, data collection, analysis, and interpretation, or writing of the report.

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Table 1

Baseline Characteristics of Patients with N2 Non-small Cell Lung Cancer According to Postoperative Radiation Therapy Treatment

Characteristic	PORT[1] N=710	No PORT N=597	P-value	
			Unadjusted	Adjusted[2]
Age, years, n (%)			<0.0001	0.96
≤70	297 (42)	177 (30)		
71–75	241 (34)	196 (33)		
>75	172 (24)	224 (38)		
Female, n (%)	371 (52)	279 (47)	0.04	0.99
Race, n (%)				
White	612 (85)	518 (87)	0.77	0.89
African-American	46 (7)	37 (6)		
Hispanic	18 (3)	15 (3)		
Other	34 (5)	27 (4)		
Median Income in ZIP Code of Residence, n (%)				
Lowest quartile	134 (19)	145 (24)	0.03	0.94
Second quartile	182 (26)	155 (26)		
Third quartile	187 (26)	124 (21)		
Highest quartile	204 (29)	172 (29)		
Charlson Comorbidity Score, n (%)				
≤1	324 (46)	245 (41)	0.14	0.98
1–2	223 (31)	190 (31)		
>2	163 (23)	162 (27)		
Tumor Status, n (%)				
T1	172 (24)	148 (25)	0.98	0.99
T2	419 (59)	348 (58)		
T3	119 (17)	101 (17)		
Number of Lymph Nodes Evaluated, n (%)				
≤5	170 (24)	126 (21)	0.19	0.70
6–9	163 (23)	124 (21)		
≥10	377 (53)	347 (58)		
Number of Positive Lymph Nodes, n (%)				
≤2	311 (44)	300 (50)	0.05	0.89
3–4	156 (22)	108 (18)		
≥5	243 (34)	189 (32)		
Histology, n (%)				
Adenocarcinoma	455 (64)	379 (63)	0.71	0.98
Squamous cell carcinoma	199 (28)	167 (28)		
Large cell carcinoma	38 (5)	31 (5)		

Characteristic	PORT[1] N=710	No PORT N=597	P-value	
			Unadjusted	Adjusted[2]
Other	18 (3)	20 (3)		
Type of Surgery, n (%)			0.11	0.98
Lobectomy	623 (88)	506 (85)		
Pneumonectomy	87 (12)	91 (15)		
Adjuvant Chemotherapy, n (%)				
None	455 (64)	461 (77)	<0.0001	0.002[3]
Platinum-based	223 (31)	118 (20)		
Other Chemotherapy	32 (5)	18 (3)		

[1] PORT denotes postoperative radiotherapy.

[2] P-values adjusting for propensity scores.

[3] Variable not included in the propensity score model as chemotherapy is used in most cases concomitantly with radiation.

Table 2

Propensity Score Analysis: Comparison of Survival of Resected N2 Patients Treated with and without Postoperative Radiation Therapy

Model	Hazard Ratio (95% CI[1])	
	Without Adjustment for Chemotherapy Use	Adjusting for Chemotherapy Use
Primary Analysis: Entire Cohort		
Adjusting for Propensity Scores	1.11 (0.97–1.27)	1.13 (0.99–1.30)
Stratified by Propensity Score Quintiles	1.12 (0.98–1.28)	1.14 (1.00–1.30)
Matched Analysis	1.10 (0.95–1.27)	1.12 (0.97–1.29)
Stratified Analyses		
Limited to Chemotherapy Treated Patients[2]		
Adjusting for Propensity Scores	1.17 (0.88–1.56)	-
Stratified by Propensity Score Quintiles	1.18 (0.89–1.58)	-
Matched Analysis	1.22 (0.88–1.67)	-
Limited to Non-Chemotherapy Treated Patients		
Adjusting for Propensity Scores	1.13 (0.97–1.32)	-
Stratified by Propensity Score Quintiles	1.14 (0.98–1.33)	-
Matched Analysis	1.25 (0.96–1.32)	-
Limited to Patients Treated with Intermediate Complexity RT Planning		
Adjusting for Propensity Scores	1.09 (0.94–1.26)	1.10 (0.94–1.27)
Stratified by Propensity Score Quintiles	1.09 (0.94–1.27)	1.10 (0.95–1.28)
Matched Analysis	1.05 (0.91–1.21)	1.06 (0.91–1.22)
Limited to Patients Treated with High Complexity RT Planning		
Adjusting for Propensity Scores	1.09 (0.87–1.38)	1.17 (0.92–1.48)
Stratified by Propensity Score Quintiles	1.13 (0.89–1.43)	1.20 (0.95–1.54)
Matched Analysis	1.09 (0.95–1.27)	1.12 (0.97–1.29)
Adjusting for Time Trends		
Adjusting for Propensity Scores	1.06 (0.92–1.22)	1.07 (0.93–1.24)
Stratified by Propensity Score Quintiles	1.07 (0.93–1.22)	1.10 (0.95–1.25)
Matched Analysis	1.05 (0.91–1.21)	1.07 (0.93–1.24)

[1] CI denotes confidence interval. The hazard ratio represents the risk of death of a patient treated with postoperative radiotherapy compared with a patient who did not received postoperative radiotherapy.

[2] The analyses were restricted to patients treated with adjuvant chemotherapy.