Adjuvant Treatment for Elderly Patients with Early-Stage Lung Cancer Treated with Limited Resection

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Abstract

Objectives: Limited resection is commonly used for treating older patients with early-stage non-small cell lung cancer (NSCLC) who cannot tolerate lobectomy. However, parenchymal-sparing procedures leave patients at increased risk of recurrence. The role of postoperative radiotherapy (PORT) and chemotherapy after limited resection is not established.

Methods: We identified 1,929 patients with stage I–II (≤ 5 cm in size) NSCLC who underwent limited resection (wedge or segmentectomy) from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. Using propensity score methods, we compared toxicity and survival of patients treated with limited resection alone, PORT, adjuvant chemotherapy, or PORT and chemotherapy. We conducted secondary analysis stratifying the sample by size (>2 – 5 cm), stage (IA vs. IB/IIA), and type of limited resection (wedge resection vs. segmentectomy).

Measurements and Main Results: Overall, 1,656 (85.8%), 159 (8.3%), 74 (3.8%), and 40 (2.1%) patients were treated with limited

resection alone, PORT, adjuvant chemotherapy, or PORT and chemotherapy, respectively. Adjusted analysis using inverse probability weighting showed that PORT (hazard ratio [HR], 1.57; 95% confidence interval [CI], 1.45–1.69), adjuvant chemotherapy (HR, 1.48; 95% CI, 1.36–1.61), and PORT and chemotherapy (HR, 1.73; 95% CI, 1.61–1.86) were associated with worse survival compared with limited resection alone. Similar results were obtained in secondary analyses. Compared with limited resection alone, the adjusted odds ratios for toxicity were 1.97 (95% CI, 1.6–2.4), 3.15 (95% CI, 2.58–3.85), 2.59 (95% CI, 2.0–3.4) for PORT, chemotherapy, and PORT and chemotherapy, respectively.

Conclusions: PORT and adjuvant chemotherapy are not beneficial and appear to be associated with increased toxicity and worse survival after limited resection in elderly patients with early-stage NSCLC. Alternative strategies should be explored to improve local control.

Keywords: lung cancer; early stage; treatment; chemotherapy; radiation

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Approximately 25 to 30% of all non-small cell lung cancers (NSCLC) are currently diagnosed at an early (I–II) stage (1). With the growing use of computed tomography (CT) for both diagnostic and screening purposes, it is expected that the incidence

of early cancers will increase (2). Surgical removal of lung cancer at this early stage represents the only opportunity for meaningful long-term survival in a disease that otherwise carries very poor prognosis (3, 4).

The standard surgical approach for stage I–II NSCLC is lobectomy with systematic lymph node sampling or mediastinal node dissection (5). This recommendation is based on the results of a single randomized clinical trial (RCT)

conducted by the Lung Cancer Study Group in the 1980s (6). This trial showed that lobectomy should be preferred over more limited surgical approaches (such as wedge resection or segmentectomy) because of a significantly lower risk of locoregional recurrence. However, lobectomy is frequently contraindicated in patients with early-stage lung cancer who have limited pulmonary reserve or multiple comorbidities related to older age or long smoking histories; these patients are, in general, treated with limited resection (7, 8). Postoperative radiotherapy (PORT) and adjuvant chemotherapy may improve the long-term outcomes of patients undergoing limited resection by reducing the risk of recurrence. However, there are limited data regarding the potential effectiveness and toxicity of these adjuvant treatments, particularly among the elderly (8).

In this study, we used population-based data from the Surveillance, Epidemiology, and End Results (SEER)-Medicare registry to compare the outcomes of elderly patients aged 65 years and older with NSCLC who underwent limited resection followed by observation, PORT, adjuvant chemotherapy, or combined PORT and chemotherapy.

Methods

Study Population

The study cohort was identified from SEER registry linked to Medicare claims, a large national database that allows for longitudinal surveillance of diagnosis, treatment, and outcomes of patients 65 years of age or older with cancer within representative areas of the United States (currently approximately 26% of the population) (9). Study subjects were older than 65 years of age, diagnosed between 1992 and 2007 with primary stage I–II NSCLC less than or equal to 5 cm in size, and treated with wedge resection or segmentectomy. Tumors greater than 5 cm and/or those that are centrally located are not generally amenable to limited resection and therefore were excluded from the study. Additionally, patients discharged to a nursing home after surgery were excluded, as they would be unlikely to receive PORT or chemotherapy due to poor functional status. Patients with NSCLC enrolled in health maintenance organizations or without Part B

(outpatient) Medicare coverage were also excluded due to lack of complete claims data.

From SEER, we obtained each patient's demographic information, including age, sex, race, ethnicity, and marital status. Medicare data were used to group patients into quartiles based on the median incomes of the census tract or zip code in which they resided. Comorbidities were assessed from Medicare claims by applying a modified version of the Charlson comorbidity index using lung cancer–specific weights (10, 11). Cancer characteristics, such as tumor location, histology, size, extension, and lymph node status, were obtained from SEER. Using this information, we determined the cancer stage based on the latest classification of the American Joint Commission on Cancer (12).

Medicare claims were used to assess the patient's diagnostic, staging, and preoperative evaluation. Using International Classification of Diseases (ICD-9) procedure codes and Current Procedural Terminology (CPT-4) codes, we identified patients who underwent fine-needle aspiration, fiberoptic bronchoscopy, a positron emission tomography scan, a preoperative ventilation/perfusion scan, cardiac or cardiopulmonary stress testing, and/or mediastinoscopy.

Treatment modalities were examined using a combination of SEER and Medicare data. Limited surgical procedures included wedge resection (SEER surgical code 21 and ICD-9 procedure code 32.29) or segmentectomy (SEER surgical code 22 and ICD-9 procedure code 32.3). We used Medicare claims to identify patients treated with video-assisted thoracoscopic surgery (ICD-9 procedure code 34.21 and CPT-4 code 32657) or open resection.

PORT use within 4 months of diagnosis was ascertained from a combination of SEER and Medicare information (9, 13). Medicare claims for PORT use included ICD-9 procedure codes 92.21 to 92.29. Radiotherapy planning and simulation were classified into simple, intermediate, and complex using Medicare physician claims (14). Adjuvant chemotherapy (platinum or nonplatinum) use is not reported in SEER and, therefore, was ascertained using a validated algorithm from Medicare inpatient, outpatient, physician, and durable medical equipment files (15).

Patients who develop complications after surgery or who have poor postoperative performance status are less likely to receive PORT or chemotherapy. Thus, we assessed for the presence or absence of postoperative complications (respiratory, cardiovascular, blood transfusions, extrapulmonary infections, and extended length of stay) using Medicare claims. We also identified patients with an extended length of stay (>15 d) during the index surgical hospitalization (16). Postoperative home health services claims, limited to homebound patients, were used as a proxy for poor postoperative performance status.

The primary study outcome, postoperative survival, was calculated using Medicare data that stay current as of the date of linkage with the SEER registry (17). Patients alive as of December 31, 2009 were censored at the date of the last follow-up. As in prior studies, treatment-related toxicity (secondary outcome) was defined as serious adverse events after treatment that required hospitalization (18). These adverse events were assessed from Medicare inpatient files and included radiation pneumonitis/esophagitis, infection, fever, neutropenia, anemia or requiring transfusion, thrombocytopenia, dehydration, nausea or emesis, acute renal dysfunction, and unspecified adverse events.

Statistical Analysis

Baseline sociodemographic data and disease characteristics of patients who received limited resection alone, PORT, adjuvant chemotherapy, or PORT and chemotherapy were compared using analysis of variance or the χ^2 test, as appropriate. As treatment allocation was not random, we used propensity score methods to control for potential selection bias. Propensity scores indicating the probability of patients being assigned to each treatment group, conditional on pretreatment characteristics (sociodemographic, diagnostic, staging, and operative work-up, tumor factors [size, location and stage], type of surgical approach [wedge resection or segmentectomy], postoperative complications, extended index hospitalization, and functional status), were generated using nominal regression. Probability weights were calculated for each patient as the inverse of the estimated propensity for undergoing the type of

treatment (limited resection alone, PORT, adjuvant chemotherapy, or PORT and chemotherapy) they actually received (19).

We used Cox regression to compare overall survival of patients treated with PORT, adjuvant chemotherapy, or PORT and chemotherapy versus limited resection alone while adjusting for selection bias using inverse probability weighting. We repeated these analyses limiting the cohort to patients 70 years of age or older. Several observational studies strongly suggest that limited resection and lobectomy are associated with similar oncologic outcomes in patients with stage I NSCLC less than or equal to 2 cm in size. As PORT after lobectomy is associated with worse outcomes in patients with stage I disease, we conducted secondary analyses limiting the sample to cases greater than 2 and less than or equal to 5 cm in size. We also evaluated in separate analyses the effectiveness of more modern, complex radiation planning techniques (three-dimensional planning and intensity-modulated radiotherapy) as well as platinum-based chemotherapy regimens. We conducted analysis adjusting for year of diagnosis to control for potential changes in staging procedures and other lung cancer treatments. Finally, we conducted stratified analysis by disease stage (IA vs. IB/IIA) and resection type (wedge resection vs. segmentectomy) to assess the effectiveness of adjuvant therapy among these key patient subgroups.

The SEER registry does not report on the presence of positive surgical margins, a negative prognostic factor and potential determinant of postoperative treatment. To evaluate the potential impact of this possible confounder, we performed a sensitivity analysis testing whether differences in the rate of positive margins across treatment groups could explain the observed association of postoperative treatments with survival (20). To conduct this analysis, we used published data on the prevalence of positive margins in patients with early-stage disease treated with limited resection and the relative increase in the hazard of death among patients with positive margins, to assess the robustness of our findings across different scenarios (21–23).

We calculated the unadjusted odds (with 95% confidence interval [CI]) of serious adverse events after each treatment. Logistic regression analysis using inverse probability weights was conducted to

estimate the adjusted odds of serious treatment-related adverse events affecting patients in the different treatment groups.

All analyses were conducted with SAS statistical software (SAS, Cary, NC) using two-sided *P* values. The Icahn School of Medicine at Mount Sinai Institutional Review Board considered the study exempt.

Results

A total of 1,929 patients diagnosed with stage I–II NSCLC less than or equal to 5 cm in size who underwent limited resection were identified from the SEER-Medicare database. Of these, 1,656 (85.8%) underwent limited resection alone, 159 (8.3%) received PORT, 74 (3.8%) underwent adjuvant chemotherapy, and 40 (2.1%) patients were treated with PORT and chemotherapy. The median follow-up time for the entire cohort was 50 months.

The baseline characteristics of patients in each treatment group are reported in Table 1. Patients who received some type of postoperative therapy were younger ($P < 0.0001$); however, there were no significant differences in the distribution of sex, race/ethnicity, marital status, estimated income, and comorbidity score among groups ($P > 0.05$ for all comparisons). Larger tumor size ($P < 0.0001$), N1 involvement ($P < 0.0001$), and advanced-stage tumors ($P < 0.0001$) were more common among patients who received postoperative therapies. No difference in histology or tumor location was observed across treatment groups ($P > 0.05$ for both comparisons). Type of surgery (wedge resection vs. segmentectomy, $P = 0.06$) and video-assisted thoracoscopic surgery versus open resection ($P = 0.31$) was not statistically different across groups.

Cox regression analysis using inverse probability weighting showed that PORT (hazard ratio [HR], 1.57; 95% CI, 1.45–1.69), adjuvant chemotherapy (HR, 1.48; 95% CI, 1.36–1.61), and PORT and chemotherapy (HR, 1.73; 95% CI, 1.61–1.86) were associated with worse survival as compared with surgery alone (Table 2). Analyses restricted to patients treated with platinum-based chemotherapy (HR, 1.14; 95% CI, 1.04–1.25) showed similar results. No benefit from PORT (HR, 1.48; 95% CI, 1.35–1.61), adjuvant chemotherapy (HR, 1.67; 95% CI, 1.52–1.82), and PORT and chemotherapy (HR, 2.44; 95% CI,

2.25–2.65) was observed among patients 70 years of age or older. Similarly, analyses limited to complex PORT showed no improvement either alone (HR, 1.36; 95% CI, 1.20–1.54) or in combination with chemotherapy (HR, 1.07; 95% CI, 0.93–1.22). PORT (HR, 1.51; 95% CI, 1.36–1.68), adjuvant chemotherapy (HR, 1.36; 95% CI, 1.22–1.54), and PORT and chemotherapy (HR, 1.15; 95% CI, 1.02–1.30) were also associated with worse survival in patients with tumors greater than 2 and less than or equal to 5 cm in size. Analyses adjusting for year of diagnosis showed consistent results.

Analyses stratified by stage showed that PORT (HR, 1.76; 95% CI, 1.59–1.93), adjuvant chemotherapy (HR, 2.75; 95% CI, 2.48–3.05), and PORT and chemotherapy (HR, 1.94; 95% CI, 1.78–2.11) were not associated with a survival benefit in patients with stage IA disease. Similar results were observed among patient with stage IB/IIA disease, except for the point estimate for adjuvant chemotherapy alone (HR, 0.88) that suggested a potential benefit despite a nonsignificant association (95% CI, 0.76–1.01). None of the postoperative treatments evaluated were associated with improved survival in analyses limited to patients treated with wedge resection or to patients treated with segmentectomy.

Sensitivity analyses showed that potential differences in the rates of positive surgical margins across treatment groups are unlikely to explain the lack of effectiveness of postoperative treatments observed in our study. As seen in Table 3, PORT was not associated with a survival benefit even when positive margins were six times more likely among PORT-treated patients, and the HR for death among patients having a positive margin was 1.5 (HR, 1.29; 95% CI, 1.20–1.40) or 3 (HR, 1.01; 95% CI, 0.93–1.09). Similar results were obtained in analyses evaluating the adjusted HR for adjuvant chemotherapy and PORT and chemotherapy.

Overall, the number of patients who experienced treatment-related toxicity was 133 (8%), 21 (14%), 16 (21%), and 13 (30%) among those who underwent limited resection alone, PORT, adjuvant chemotherapy, and PORT and chemotherapy, respectively. The most common serious adverse events collectively among groups were infection, dehydration, and anemia. Unadjusted analysis showed that the odds ratio (OR) for severe toxicity was 1.79 (95% CI, 1.09–2.93), 3.05 (95% CI, 1.71–5.44), and

Table 1. Characteristics of patients with Stage I–II non–small cell lung cancer treated with limited resection alone, postoperative radiotherapy, adjuvant chemotherapy, or postoperative radiotherapy and chemotherapy

Characteristic	Surgery Alone (n = 1,656)	PORT (n = 159)	Adjuvant Chemotherapy (n = 74)	PORT and Chemotherapy (n = 40)	P Value
Age, mean ± SD, yr	74.8 ± 5.5	74.3 ± 5.2	72.2 ± 4.4	72.5 ± 4.7	<0.0001
Female, n (%)	926 (56)	84 (53)	46 (62)	19 (48)	0.41
Race/ethnicity, n (%)					
White	1,488 (90)	142 (89)	>11 (>15)	>11 (>28)	0.14
Black/Hispanic	98 (6)	≤11 (≤7)	≤11 (≤15)	≤11 (≤28)	
Other	70 (4)	≤11 (≤7)	≤11 (≤15)	≤11 (≤28)	
Married, n (%)	899 (54)	93 (59)	40 (54)	22 (55)	0.79
Median Income in ZIP code of residence, n (%)					
Lowest quartile	370 (22)	37 (23)	14 (19)	>11 (>28)	0.32
Second quartile	388 (24)	39 (25)	16 (22)	≤11 (≤28)	
Third quartile	418 (25)	35 (22)	24 (32)	≤11 (≤28)	
Highest quartile	480 (29)	48 (30)	20 (27)	≤11 (≤28)	
Comorbidity score, n (%)					
≤1	373 (22)	43 (28)	14 (19)	≤11 (≤28)	0.49
1–2	672 (41)	58 (36)	26 (35)	>11 (>28)	
>2	611 (37)	58 (36)	34 (46)	18 (45)	
Histology, n (%)					
Adenocarcinoma	973 (59)	94 (59)	40 (54)	>11 (>28)	0.48
Squamous cell	513 (31)	>11 (>7)	20 (27)	>11 (>28)	
Large cell	62 (4)	≤11 (≤7)	≤11 (≤15)	≤11 (≤28)	
Other	108 (6)	>11 (>7)	≤11 (≤15)	≤11 (≤28)	
Tumor Location, n (%)					
Upper/middle lobe	1,093 (66)	113 (71)	54 (73)	>11 (>28)	0.12
Lower lobe	563 (34)	46 (29)	20 (27)	≤11 (≤28)	
Tumor size, mm	20.4 ± 8.9	23 ± 9.2	24.9 ± 10.0	24.4 ± 11.5	<0.0001
N0 disease	1,637 (99)	144 (91)	>11 (>15)	>11 (>28)	<0.0001
Stage, n (%)					
IA	1,163 (70)	94 (59)	32 (43)	18 (45)	<0.0001
IB	438 (27)	50 (32)	>11 (>15)	>11 (>28)	
IIA	55 (3)	15 (9)	≤11 (≤15)	≤11 (≤28)	
Surgical technique, n (%)					
Wedge resection	1,202 (73)	127 (80)	51 (69)	>11 (>28)	0.06
Segmentectomy	454 (27)	32 (20)	23 (31)	≤11 (≤28)	
VATS, n (%)	509 (31)	46 (29)	30 (41)	>11 (>28)	0.31
No. of lymph nodes removed, n (%)					
≤5	1,494 (90)	142 (89)	>11 (>15)	>11 (>28)	0.93
>5	162 (10)	17 (11)	≤11 (≤15)	≤11 (≤28)	

Definition of abbreviations: PORT = postoperative radiotherapy; VATS = video-assisted thoracoscopic surgery. Exact number of patients not reported in cells with fewer than 11 individuals to maintain patients' confidentiality.

4.79 (95% CI, 2.45–9.38) for patients treated with PORT, adjuvant chemotherapy, and PORT and chemotherapy versus limited resection alone, respectively. Similarly, adjusted analysis showed increased odds of toxicity among patients treated with PORT (OR, 1.97; 95% CI, 1.6–2.4), adjuvant chemotherapy (OR, 3.1; 95% CI, 2.58–3.85), and PORT and chemotherapy (OR, 2.59; 95% CI, 2.0–3.4).

Discussion

A considerable number of elderly patients with newly diagnosed early-stage NSCLC have reduced pulmonary reserve (24). In these patients, limited resections are usually

indicated owing to the lower risk of postoperative respiratory failure, perioperative mortality, and long-term disability (24–26). Given the higher risk of recurrence associated with limited resection, we investigated whether PORT or adjuvant chemotherapy, individually or in combination, are associated with improved patient outcomes. Our findings suggest that these treatments do not improve survival of patients 65 years and older undergoing limited resection for NSCLC less than or equal to 5 cm in size. Although this was an observational study, our results suggest that other approaches are needed to improve locoregional control in patients with early-stage NSCLC who are not candidates for lobectomy.

The role of PORT after lobectomy in stage I–III NSCLC has been extensively evaluated. The PORT Meta-analysis Trialists Group performed a systematic review and meta-analysis of 10 RCTs conducted between 1966 and 2004 that included more than 2,000 patients (27, 28). The analysis concluded that PORT was either noneffective or detrimental after lobectomy in stage I–III NSCLC. However, the conclusions of the PORT meta-analysis are subject to several limitations. Many of the studies analyzed were older RCTs that used radiation techniques not consistent with current standards (e.g., cobalt machines or single radiation fields). Additionally, there was considerable heterogeneity across studies that, when

Table 2. Propensity score analysis: comparison of survival of elderly patients with Stage I and II lung cancer treated with limited resection alone, postoperative radiotherapy, adjuvant chemotherapy, or postoperative radiotherapy and chemotherapy

Analysis	Treatment		
	PORT, HR (95% CI)	Adjuvant Chemotherapy, HR (95% CI)	PORT and Chemotherapy, HR (95% CI)
Full cohort (tumors ≤ 5 cm in size)	1.57 (1.45–1.69)	1.48 (1.36–1.61)	1.73 (1.61–1.86)
Full cohort limited to platinum-based chemotherapy	—	1.14 (1.04–1.25)	1.26 (1.15–1.38)
Limited to tumors > 2–5 cm in size	1.51 (1.36–1.68)	1.36 (1.22–1.54)	1.15 (1.02–1.30)
Limited to patients ≥ 70 yr of age	1.47 (1.35–1.61)	1.67 (1.52–1.82)	2.44 (2.21–2.64)
Limited to complex PORT	1.45 (1.32–1.59)	—	1.07 (0.98–1.18)
Limited to complex PORT and tumors > 2–5 cm in size	1.36 (1.20–1.54)	—	1.07 (0.93–1.22)
Limited to patients with stage IA disease	1.76 (1.59–1.93)	2.75 (2.48–3.05)	1.94 (1.78–2.11)
Limited to patients with stage IB/IIA disease	1.28 (1.12–1.48)	0.88 (0.76–1.01)	1.46 (1.26–1.69)
Limited to patients treated with wedge resection	1.40 (1.28–1.54)	1.67 (1.52–1.84)	1.40 (1.28–1.54)
Limited to patients treated with segmentectomy	2.31 (1.97–2.71)	1.28 (1.09–1.50)	2.26 (1.97–2.59)

Definition of abbreviations: CI = confidence interval; HR = hazard ratio; PORT = postoperative radiotherapy. HR represents HR for death for adjuvant-treated patients compared with patients who underwent limited resection alone.

analyzed individually, produced inconsistent results. Despite these limitations, current guidelines recommend against PORT for patients with stage I–III NSCLC who underwent lobectomy (8).

Although not beneficial after lobectomy, PORT may have a role in patients treated with limited surgical approaches. However, this potential indication for PORT has not been evaluated

in a RCT. A previous study using the SEER database (not linked to Medicare records) examined the effects of PORT after limited resection in localized tumors less than or equal to 7 cm in size (i.e., T1–2, N0, M0 disease) (29). The study found a detrimental effect on overall survival with PORT compared with surgery alone (median survival 32 vs. 44 mo, respectively). However, these results were

limited by a lack of information in the SEER registry regarding the staging and diagnostic work-up of these patients, comorbidities, type of surgery, postoperative complications, and functional status, all factors associated with PORT use and survival. Additionally, SEER does not report data on chemotherapy use that, in our study, was more common among PORT-treated patients. Moreover,

Table 3. Sensitivity analysis of the potential impact of positive surgical margin status on the effectiveness of postoperative treatments

Probability of Positive Margins According to Treatment (%)		Increased Hazard of Death for Patients with Positive Margins	HR for Postoperative Treatment Adjusted for Positive Margins (95% CI)
PORT	Limited resection alone		
	10	1.5	1.52 (1.40–1.63)
	10	1.5	1.41 (1.30–1.52)
	10	1.5	1.29 (1.20–1.40)
	10	3	1.46 (1.35–1.57)
	10	3	1.23 (1.14–1.33)
Adjuvant chemotherapy	Limited resection alone		
	10	1.5	1.43 (1.31–1.55)
	10	1.5	1.33 (1.22–1.44)
	10	1.5	1.22 (1.13–1.33)
	10	3	1.37 (1.26–1.49)
	10	3	1.16 (1.07–1.27)
PORT and chemotherapy	Limited resection alone		
	10	1.5	1.67 (1.56–1.79)
	10	1.5	1.55 (1.44–1.67)
	10	1.5	1.43 (1.33–1.54)
	10	3	1.61 (1.49–1.73)
	10	3	1.36 (1.27–1.46)

Definition of abbreviations: CI = confidence interval; HR = hazard ratio; PORT = postoperative radiotherapy.

the study included patients treated from 1988 to 2003 but did not have access to information about PORT complexity. However, planning and simulation techniques considerably evolved during the study period. Our study extends these results by showing the lack of effectiveness of PORT and chemotherapy among a large cohort of elderly patients aged 65 years and older treated with wedge resection or segmentectomy. These data are consistent with the outcomes of patients with stage I–II disease treated with PORT after lobectomy and suggest that the increased risk of toxicity observed in our study outweighs the potential improvement of locoregional control, particularly in older patients who may have a more limited life expectancy. Brachytherapy applied at the time of resection could be a promising alternative to external beam radiation, having been shown in observational studies to decrease local recurrence while limiting toxicity risk in high-risk patients (30). However, additional studies are needed to evaluate the effectiveness of this treatment.

The role of adjuvant chemotherapy after limited resection of early-stage NSCLC is also uncertain. Chemotherapy, specifically platinum-based regimens, have been proven beneficial to survival after lobectomy in patients with more advanced stage NSCLC, especially those with lymph node spread. The Lung Adjuvant Cisplatin Evaluation meta-analysis analyzed data from the five largest RCTs investigating cisplatin-based regimens after complete resection and found a 5-year absolute survival benefit of 5.4% with adjuvant chemotherapy (31). However, this benefit varied considerably with stage; the meta-analysis showed that the majority of the survival benefit came from treating stage II (HR, 0.83; 95% CI, 0.73–0.95) and stage III (HR, 0.83; 95% CI, 0.72–0.94) NSCLCs, whereas patients with stage IA tumors (≤ 3 cm in size; HR, 1.40; 95% CI, 0.95–2.06) had worse outcomes when treated with adjuvant chemotherapy. Observational studies suggest these results may be extrapolated to elderly patients (32). The role of adjuvant chemotherapy in stage IB tumors remains controversial; the only RCT focused exclusively on these patients reported no significant survival advantage with the addition of chemotherapy (33). However, subgroup analyses suggested that adjuvant therapy may have a role in patients with tumors

greater than or equal to 4 cm in size. Consistent with the results of studies conducted in patients treated with lobectomy, the results of stratified analysis suggest that adjuvant chemotherapy is not associated with improved survival after limited resection of stage IA disease but may be effective in patients with more advanced IB and IIA disease. However, our study was limited to patients older than 65 years; thus, these results should not be generalized to younger patients with NSCLC who may tolerate chemotherapy better and, due to a more extended life expectancy, may be at higher risk of recurrence.

The study has strengths and limitations that should be noted. A major strength of the SEER-Medicare registry is that it includes a large, population-based sample of elderly patients with lung cancer. Thus, our results should be highly representative of older patients with NSCLC encountered in routine practice. The information contained in Medicare claims allowed us to concomitantly evaluate the comparative effectiveness of PORT and chemotherapy and to control for multiple confounders. However, use of the different therapies evaluated in the study was not randomly allocated but rather determined by physician decisions, patients' preferences, and practice patterns. Consequently, lack of randomization likely generated systematic differences in the distribution of prognostic factors among patients in the four treatment groups. Although we used propensity score methods to minimize the impact of treatment selection, residual confounding due to unmeasured covariates may remain. In particular, we did not have information regarding surgical margins. Patients with positive margins have increased risk of recurrence and, therefore, may be more likely to receive PORT or adjuvant chemotherapy, a factor that may partially explain the study results. However, extensive sensitivity analyses showed that the potential confounding effect of positive margins is unlikely to explain the lack of effectiveness of PORT and adjuvant chemotherapy observed in the study. Of note, these analyses showed, under certain scenarios, similar survival with PORT and adjuvant chemotherapy compared with limited resection alone.

Although the possibility of selection bias is a limitation of the analyses, there are no prior or planned RCTs evaluating the

effectiveness of these postoperative treatments after limited resection. Our results suggest that PORT and adjuvant chemotherapy are unlikely to be beneficial in this setting; thus, these findings should help guide decisions in clinical practice. Ideally, these results should be validated in prospective clinical trials.

The large number of patients in SEER allowed us to restrict the study to a relatively homogenous population of patients with NSCLC in terms of tumor size and stage. However, the study had limited power to assess the potential role of postoperative treatments in specific patient subgroups. In particular, prior RCTs showed that adjuvant chemotherapy improves survival among younger patients with stage II disease treated with lobectomy. Our study did not include sufficiently large number of patients with N1 involvement to allow us to replicate these findings. Similarly, SEER does not report information on recurrence rates or disease-free survival; thus, we could not assess if PORT or adjuvant chemotherapy improves these outcomes. However, even if recurrence rates are reduced, the negative impact on overall survival will preclude use of these treatments.

In summary, our observational data suggest that PORT and chemotherapy are not associated with improved outcomes and may actually worsen survival of elderly patients aged 65 years and older who underwent limited resection for stage I–II NSCLC. Although these results should be validated in prospective trials, our findings provide important comparative effectiveness data regarding the potential usefulness of these treatments. Physicians should discuss with their elderly patients with NSCLC the potential risks and benefits of PORT and adjuvant chemotherapy. ■

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