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Radiotherapy and chemotherapy for elderly patients with stage I–II unresected lung cancer

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ABSTRACT: Radiotherapy (RT) is the standard therapy for unresected stage I–II nonsmall cell lung cancer (NSCLC). Using population-based data, we compared survival and toxicity among unresected elderly patients treated with combined chemoradiotherapy (CRT) or RT alone.

Using the Surveillance, Epidemiology and End Results (SEER) registry (National Cancer Institute, Bethesda, MD, USA) we identified 3,006 cases of unresected stage I–II NSCLC. We used propensity score methods to compare survival and rates of toxicity of patients treated with RT *versus* CRT.

Overall, 844 (28%) patients received CRT. Adjusted analyses showed that CRT was associated with improved survival (hazard ratio 0.85, 95% CI 0.78–0.94). Combination therapy was also associated with better survival among stage I patients treated with intermediate complexity RT (HR 0.80, 95% CI 0.70–0.90); however, no difference in survival was observed among patients treated with complex RT. In stage II patients, CRT was associated with improved survival regardless of the RT technique (HR 0.61–0.72). CRT was associated with increased odds of toxicity.

Despite increased toxicity, CRT may improve survival of elderly unresected patients with stage II disease as well as stage I NSCLC treated with intermediate RT complexity. Randomised trials are needed to clarify the balance of benefits and risk of CRT in unresected patients.

KEYWORDS: Chemotherapy, early stage, lung cancer, radiation, treatment, unresected

Nearly 20% of elderly patients with stage I–II nonsmall cell lung cancer (NSCLC) do not undergo resection due to poor lung function, frailty, comorbitidies or patient preferences [1, 2]. The current standard of care for these patients is radiotherapy (RT) alone [3, 4]. However, the long-term outcomes of these patients remain extremely poor, with only 50% surviving at 1 yr and ⩽35% beyond 2 yrs from diagnosis [5, 6]. Thus, there is a need to assess the potential role of other treatment modalities that could lead to improved survival of unresected patients with clinically localised disease.

Studies focused on patients with locally advanced, inoperable NSCLC (stage IIIA–IIIB) have shown that chemotherapy used concurrently with RT improves survival as well as local control rates [7, 8]. ~30% of patients with pathological stage I NSCLCs and up to 60% of patients with pathological stage II disease experience a relapse and/or die from lung cancer progression despite surgical removal of the primary tumour. These data suggests that, by the time of diagnosis, a considerable proportion of cancers classified as stage I–II disease had already disseminated either regionally or systemically. As these are pathologically staged tumours, the percentage of clinically staged, unresected cancers with lymph node or distant metastasis is probably higher. These data provide a rationale for evaluating the effectiveness of combined chemotherapy and RT (CRT) among unresected patients with clinical stage I–II disease. However, the few studies that specifically assessed the efficacy of CRT among these patients were conducted more than two decades ago, included small numbers of highly selected patients and had inconclusive results [9, 10]. Despite this lack of effectiveness data, CRT is frequently used to treat these patients in clinical practice [2, 11].

In this study, we used population-based data to assess whether CRT compared with RT alone is associated with improved survival among elderly patients with unresected stage I–II NSCLC. We also compared rates of severe toxicity in these treatment groups.

METHODS

The study was conducted using data from the Surveillance, Epidemiology and End Results (SEER) registry (National Cancer Institute, Bethesda, MD,

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USA) linked to Medicare claims. The SEER registry integrates cancer data from 17 regional registries in the USA [12]. SEER has been linked to Medicare enrolment and claims data using unique patient identifiers [13]. The study was approved by the Mount Sinai School of Medicine's Institutional Review Board (GCO 06-0130).

Using SEER linked to Medicare claims, we identified all elderly patients (aged >65 yrs) with primary cases of histologically confirmed, unresected NSCLC. All cases had clinical stage I–II disease and were diagnosed between 1992 and 2005. We further limited the cohort to patients who underwent primary treatment with external beam radiation. We excluded lung cancer cases diagnosed at autopsy or from death certificates as well as patients covered by a health maintenance organisation or who lacked Part B Medicare coverage at the time of diagnosis [1, 14]. We also excluded patients treated with simple (one-dimensional) RT planning (often used for palliation) or with missing information regarding the level of RT planning complexity [15]. Individuals residing in a long-term care facility or receiving hospice care were also excluded, as these patients would not be likely candidates for CRT. Finally, we excluded cases that did not undergo a chest computed tomography (CT) as part of the diagnostic work-up to evaluate the extent of disease.

Sociodemographic information was obtained from SEER. Socioeconomic status was estimated based on the median income for the census tract or ZIP code of the patient's residence using information provided by Medicare. We evaluated the burden of comorbidities among study patients using the Deyo adaptation of the Charlson comorbidity index, applying lung cancer-specific condition weights [16, 17].

Cancer cases were classified as adenocarcinoma, squamous cell carcinoma, large cell carcinoma or other histological type based on data provided by SEER. Stage of disease was categorised according to the seventh edition of the Tumour, Node, and Metastasis classification using SEER data on tumour size, extension and lymph node involvement [18].

We used Medicare data to ascertain the staging work-up of study subjects including use of computed tomography of the chest (ICD-9 code 87.41 and CPT-4 codes 71250, 71260 and 71270) or abdomen (ICD-9 code 88.01 and CPT-4 codes 74150, 74160 and 74170), abdominal ultrasound (ICD-9 code 88.76 and CPT-4 codes 76700 and 76705), bone scan (ICD-9 code 92.14 and CPT-4 codes 78300, 78305, 78306 and 78315), positron emission tomography (PET; CPT-4 codes 78814–78816) and mediastinoscopy (ICD-9 codes 34.22 and 34.29 and CPT-4 code 39400) [19]. Use of RT was determined from SEER and Medicare claims as combined data from these sources provides the most complete ascertainment of RT use [20]. Patients were categorised as RT treated if they were coded by SEER as having received primary treatment with external beam radiation or if Medicare in-patient, outpatient or physician claims indicated RT use [21]. Patients were classified into simple, intermediate and complex RT simulation, and planning groups based on Medicare codes from physician claims [15, 22]. Use of chemotherapy (platinum-based or other regimens) within 4 months of diagnosis was identified from Medicare in-patient, outpatient and physician claims [23].

We also used Medicare claims to identify lung cancer patients who received home health services [24]. To be eligible for Medicare home services, beneficiaries must be homebound; thus, we used these variables as a proxy for poor performance status.

The primary study outcome was overall (all cause) mortality. Survival was determined as the interval from the date of diagnosis to the date of death provided by Medicare; those alive on December 31, 2007 were classified as censored. We also evaluated, in secondary analyses, the rates of serious toxicity among elderly patients treated with CRT *versus* RT alone. Consistent with prior literature, severe toxicity was defined as a hospitalisation within 2 to 6 months of diagnosis for any of the following conditions: infection, fever, neutropenia, anaemia, thrombocytopenia, dehydration, nausea or emesis, renal dysfunction and unspecified adverse events of systemic therapy [25].

Statistical analysis

The distribution of baseline characteristics among patients treated with CRT *versus* RT alone was compared with the Chi-squared test. We used the Kaplan–Meier method to estimate unadjusted survival rates of patients in the two treatment groups.

We estimated each patient's propensity score for receiving CRT using logistic regression [26]. The model included variables indicating the patients' sociodemographic characteristics, comorbidities, diagnostic work-up (CT of chest or abdomen, abdominal ultrasound, bone scan, positron emission tomography and mediastinoscopy), cancer-related factors (histology, grade, tumour size, T status, location, histology and lymph node status) and use of home health services. We used multiple regression analyses to evaluate whether these characteristics were balanced across study groups after adjusting for propensity scores.

Cox regression analysis was used to compare survival of patients treated with RT alone *versus* CRT, adjusting for propensity scores in three ways. Initially, we fitted a Cox model comparing survival among patients in the two study groups after controlling for propensity scores as a continuous covariate. Then, we classified patients into quintiles based on their propensity scores and assessed the association between CRT use and survival with a stratified Cox model. Finally, patients treated with either RT alone or CRT were matched by their propensity scores. Survival among the two study groups was then compared using a marginal Cox model for correlated data [27].

The complexity of RT planning has evolved in the last decade from intermediate (two-dimensional) planning to complex (three-dimensional and intensity modulated RT). Recent data suggest that higher planning complexity is associated with improved survival of unresected patients with stage I–II NSCLC [15]. Thus, we performed secondary analyses to assess the potential benefit of CRT among elderly patients treated with intermediate or complex RT planning. We also conducted analyses stratifying the sample by stage at diagnosis (I *versus* II). Finally, we performed analyses adjusting for year of diagnosis to control for potential time trends in use of diagnostic tests or other lung cancer treatments.

The unadjusted odds ratios for severe toxicity, with 95% confidence intervals, were calculated for patients receiving CRT *versus* RT alone. We used logistic regression to estimate the odds ratio of severe toxicity requiring hospitalisation among

patients treated with CRT *versus* RT alone after adjusting for propensity scores. Analyses were performed using SAS statistical software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Of the 3,006 unresected stage I and II patients in the study, 844 (28%, 95% CI 26–30%) received CRT. Complex RT simulation and planning was used in 945 (31%) patients. The baseline characteristics of study patients treated with CRT *versus* RT alone are shown in table 1. Patients who received CRT were younger ($p<0.0001$), more likely to be male ($p=0.008$) and married ($p<0.0001$). Similarly, CRT use was more common among patients with lower comorbidity burden ($p<0.0001$). Larger tumour size ($p<0.0001$) and stage II disease ($p<0.0001$)

TABLE 1 Characteristics of unresected stage I and II nonsmall cell lung cancer treated with radiotherapy (RT) alone or combined chemoradiotherapy (CRT)

Characteristic	RT alone	CRT	p-value	
			Unadjusted	Adjusted#
Subjects n	2222	784		
Age yrs				
66–70	363 (17)	248 (29)	<0.0001	0.68
71–75	594 (27)	279 (33)		
>75	1205 (56)	317 (38)		
Female	1071 (50)	373 (44)	0.008	0.96
Race				
White	1861 (87)	729 (86)	0.40	0.99
African-American	184 (8)	71 (8)		
Hispanic	16 (1)	11 (1)		
Other	101 (5)	33 (4)		
Marital status				
Married	1037 (48)	492 (58)	<0.0001	0.93
Median income in ZIP code of residence				
Lowest quartile	634 (29)	252 (30)	0.46	0.99
Second quartile	555 (26)	231 (27)		
Third quartile	532 (25)	210 (25)		
Highest quartile	439 (20)	151 (18)		
Charlson comorbidity score				
⩽1	599 (28)	290 (34)	<0.0001	0.97
1–2	721 (33)	311 (37)		
>2	842 (39)	243 (29)		
Histology				
Adenocarcinoma	682 (32)	266 (32)	0.19	0.99
Squamous cell carcinoma	1015 (47)	413 (49)		
Large cell carcinoma	188 (9)	80 (9)		
Other	277 (13)	85 (10)		
Tumour location				
Upper lobe	1243 (57)	488 (58)	0.001	0.73
Middle lobe	107 (5)	27 (3)		
Lower lobe	714 (33)	262 (31)		
Main bronchus	81 (4)	54 (6)		
Other	17 (1)	13 (2)		
Tumour size mm				
⩽20	329 (20)	73 (12)	<0.0001	0.99
20–30	427 (29)	149 (24)		
30–50	578 (35)	222 (36)		
50–70	201 (12)	122 (20)		
>70	60 (4)	53 (9)		
Stage				
I	1781 (82)	584 (69)	<0.0001	0.79
II	381 (18)	260 (31)		

Data are presented as n (%), unless otherwise stated. #: p-values adjusting for propensity scores.

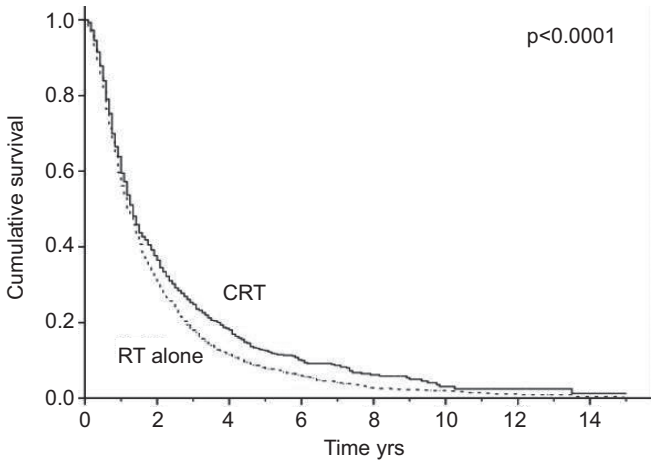

FIGURE 1. Survival of unresected stage I–II nonsmall cell lung cancer patients treated with combined chemoradiotherapy (CRT) or radiotherapy (RT) alone. Overall survival was significantly better among patients treated with combined CRT ($p<0.001$).

were also associated with increased use of CRT. All covariates were well balanced among study groups after adjusting for propensity scores (table 1).

Unadjusted Kaplan–Meier analysis showed that CRT was associated with improved survival ($p=0.004$; fig. 1). Similarly, CRT was associated with longer survival when analyses were restricted to patients who underwent intermediate RT planning ($p<0.0001$); however, no differences in survival were observed among patients treated with CRT or RT alone in analyses limited to patients who received complex RT ($p=0.96$). Among patients with stage I disease, chemotherapy was associated with improved survival when used in combination with intermediate ($p=0.001$) but not with high complexity RT ($p=0.65$; fig. 2a and b). CRT was associated with improved survival of stage II patients treated with both intermediate ($p=0.0001$) and high complexity ($p=0.003$) RT (fig. 2c and d).

Cox regression analysis adjusting for propensity score showed that CRT was associated with improved survival (hazard ratio 0.85, 95% CI 0.78–0.94; table 2). Analyses stratifying (HR 0.85,

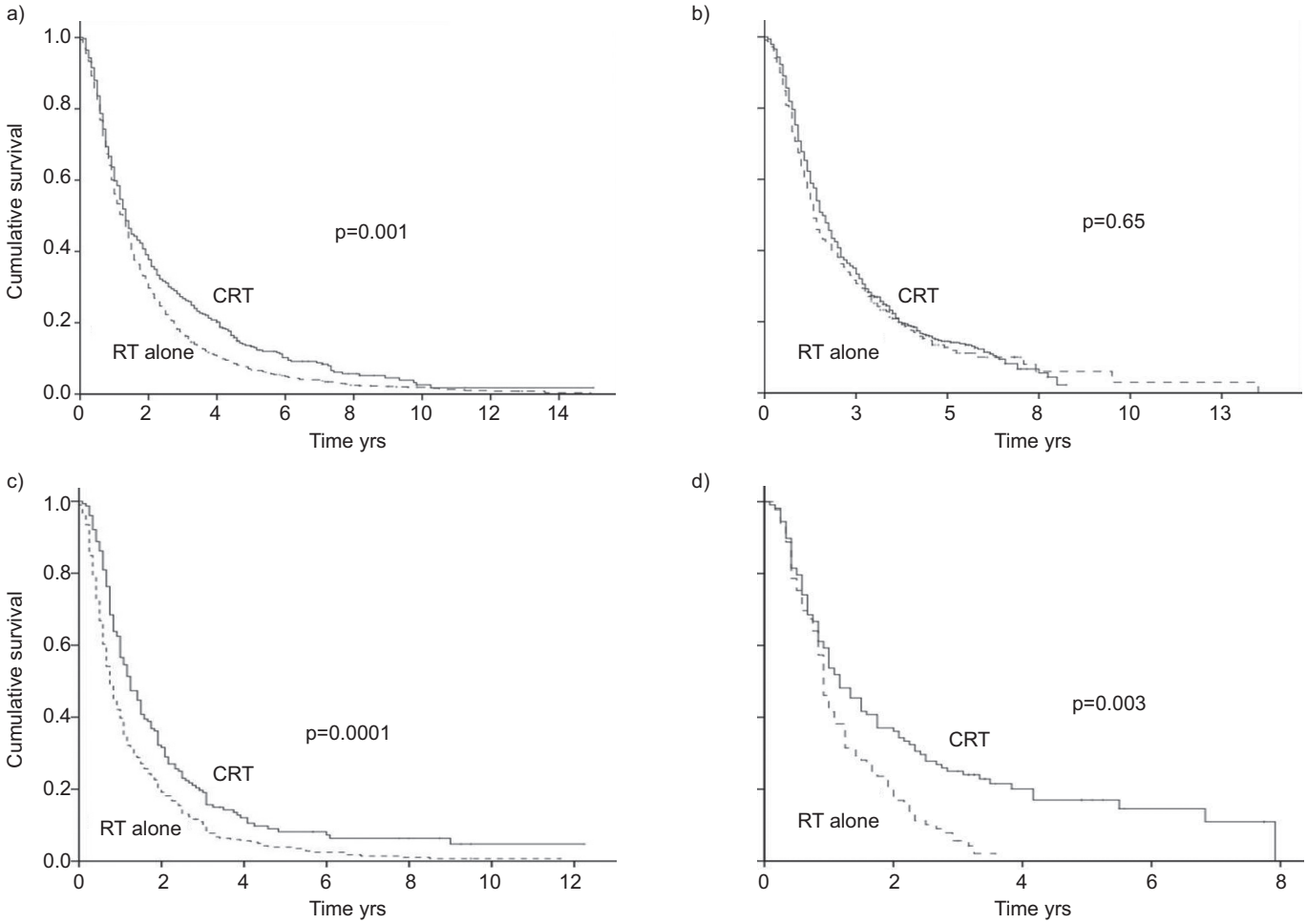

FIGURE 2. Overall survival of unresected stage I–II nonsmall cell lung cancer patients treated with combined chemoradiotherapy (CRT) or radiotherapy (RT) alone according to stage and RT complexity. a) Stage I patients treated with intermediate complexity radiotherapy: use of combined CRT was associated with improved overall survival ($p=0.0001$). b) Stage I patients treated with high complexity RT: no significant difference in survival was observed among patients treated with CRT or RT alone ($p=0.65$). c) Stage II patients treated with intermediate complexity RT: patients treated with combined CRT had improved survival ($p=0.0001$). d) Stage II patients treated with high complexity RT: CRT was associated with significantly improved survival rates ($p=0.003$).

TABLE 2 Propensity score analysis: comparison of survival of unresected stage I and II elderly lung cancer patients treated with combined chemoradiotherapy and radiation therapy (RT) alone

Model	HR# (95% CI)
Primary analysis	
Adjusting for propensity scores	0.85 (0.78–0.94)
Stratified by propensity score quintiles	0.85 (0.78–0.93)
Matched analysis	0.86 (0.79–0.94)
Secondary analyses	
Limited to intermediate complexity radiation therapy planning¶	
Adjusting for propensity scores	0.77 (0.69–0.86)
Stratified by propensity score quintiles	0.77 (0.69–0.86)
Matched analysis	0.78 (0.70–0.87)
Limited to complex radiation therapy planning	
Adjusting for propensity scores	1.03 (0.88–1.12)
Stratified by propensity score quintiles	1.00 (0.87–1.14)
Matched analysis	1.04 (0.89–1.22)
Adjusting for time trends	
Adjusting for propensity scores	0.88 (0.80–0.96)
Stratified by propensity score quintiles	0.87 (0.80–0.95)
Matched analysis	0.88 (0.81–0.96)
Stage I disease treated with intermediate complexity radiation therapy planning	
Adjusting for propensity scores	0.80 (0.70–0.90)
Stratified by propensity score quintiles	0.80 (0.70–0.91)
Matched analysis	0.78 (0.70–0.89)
Stage I disease treated with complex radiation therapy planning	
Adjusting for propensity scores	1.14 (0.95–1.34)
Stratified by propensity score quintiles	1.13 (0.94–1.35)
Matched analysis	1.08 (0.90–1.29)
Stage II disease treated with intermediate complexity radiation therapy planning	
Adjusting for propensity scores	0.72 (0.58–0.89)
Stratified by propensity score quintiles	0.70 (0.57–0.87)
Matched analysis	0.66 (0.53–0.82)
Stage II disease treated with complex radiation therapy planning	
Adjusting for propensity scores	0.64 (0.45–0.90)
Stratified by propensity score quintiles	0.61 (0.44–0.86)
Matched analysis	0.70 (0.48–0.98)

#: the hazard ratio (HR) represents the risk of death of a patient treated with combined chemoradiotherapy and radiotherapy compared with a patient treated with RT alone; ¶: the analyses were restricted to patients treated with intermediate complexity (two-dimensional) RT planning.

95% CI 0.78–0.94) or matching (HR 0.86, 95% CI 0.79–0.94) by propensity scores showed similar results. Similar results were obtained in analyses adjusting for year of diagnosis (HR 0.88, 95% CI 0.80–0.96). Secondary analyses, showed that CRT was associated with increased survival rates among patients who underwent intermediate (HR 0.77, 95% CI 0.69–0.86) but not complex (HR 1.03, 95% CI 0.88–1.12) RT planning. In analyses stratifying by stage, CRT was associated with increased survival among stage I patients treated with intermediate (HR 0.80, 95% CI 0.70–0.90) but not high complexity (HR 1.14, 95% CI 0.95–1.34) RT. Stage II patients treated with chemotherapy in combination with intermediate (HR 0.72, 95% CI 0.58–0.89) and complex (HR 0.64, 95% CI 0.45–0.90) RT had better survival.

~26% of patients treated with CRT were admitted to the hospital for at least one severe toxicity compared with 13% of patients treated with RT alone (OR 2.4, 95% CI 1.9–2.9; table 3). The most common severe toxicities among CRT-treated patients were hospitalisations for dehydration (10.9%), infection (8.7%) and neutropenia (>5.5%). The odds of hospitalisation for severe toxicity were significantly increased among patients treated with CRT for most of the conditions evaluated in the study including infection (OR 1.9, 95% CI 1.4–2.6), neutropenia (OR 24.6, 95% CI 10.5–57.3), fever (OR 2.6, 95% CI 1.2–5.8), dehydration (OR 1.9, 95% CI 1.4–2.5), nausea/emesis (OR 3.4, 95% CI 1.9–6.3), anaemia (OR 2.9, 95% CI 2.2–3.8), thrombocytopenia (OR 6.9, 95% CI 1.8–26.0) and unspecified adverse events of systemic therapy (OR 36.5, 95% CI 4.8–2.77.6). Similar results were obtained in analyses adjusting for propensity scores (table 3).

DISCUSSION

The long-term outcomes of unresected patients with early stage NSCLC treated with RT alone remain extremely poor [3, 6, 28]. In this study, we showed that CRT is associated with improved survival in a large cohort of unresected elderly patients with clinical stage I–II NSCLC. However, coupling chemotherapy and RT does not appear to provide a survival benefit to stage I patients who undergo complex RT planning. Additionally, CRT was associated with increased risk of severe toxicity requiring hospitalisation. These findings suggest that CRT should be considered for unresected stage II elderly patients or stage I cases treated in settings without access to high complexity RT.

Surgical resection is the treatment of choice for patients diagnosed with NSCLC at an early stage. Definitive thoracic RT is the conventional alternative to surgical resection for patients with significant comorbid conditions that preclude safe resection and for those who have preferences against surgery [3, 5, 29, 30]. More recently, stereotactic body RT and radiofrequency ablation have been proposed as potential treatments in this setting [31, 32]. Although initial results are promising, current data on the efficacy of these newer techniques is limited to small case series and, at present, no data is available from large randomised controlled trials (RCTs). Given the overall poor outcomes of unresected early stage lung cancer patients, even for those treated with RT, there is a need for exploring new management strategies.

CRT is considered the standard of care for NSCLC patients with inoperable, locally advanced (stage III) disease. Results of meta-analyses of RCTs primarily conducted among younger patients show that the addition of chemotherapy to RT improves survival in locally advanced disease [7]. Despite an increased risk of acute oesophageal toxicity, rates of locoregional control and survival appear to improve following concomitant compared with sequential CRT [8]. Little data is available concerning the role of CRT for the treatment of elderly patients with inoperable stage III NSCLC. The only elderly-specific phase III RCT was terminated early due to high rates of

TABLE 3 Hospitalisations for adverse events related to combined chemoradiotherapy (CRT) and radiation therapy (RT) among unresected stage I and II lung cancer patients in the study

Toxicity	Patients hospitalised with toxicity-related diagnoses		OR (95% CI)#	OR (95% CI) adjusted for propensity scores
	RT alone	CRT		
Infection	104 (4.8)	73 (8.7)	1.9 (1.4–2.6)	2.0 (1.4–2.8)
Neutropenia	⩽11(<0.5)¶	>50 (>5.5)	24.6 (10.5–57.3)	21.5 (9.0–51.4)
Fever	12 (0.6)	12 (1.4)	2.6 (1.2–5.8)	2.1 (0.9–5.2)
Dehydration	132 (6.1)	92 (10.9)	1.9 (1.4–2.5)	1.8 (1.4–2.5)
Nausea/emesis	19 (0.9)	25 (3.0)	3.4 (1.9–6.3)	3.1 (1.6–5.8)
Anaemia	105 (4.8)	108 (12.8)	2.9 (2.2–3.8)	2.8 (2.1–3.9)
Thrombocytopenia	⩽11 (<0.5)	⩽11 (<1.0)	6.9 (1.8–26.0)	11.5 (2.9–45.7)
Renal dysfunction	22 (1.0)	13 (1.5)	1.5 (0.7–3.0)	1.6 (0.8–3.4)
Unspecified adverse events of systemic therapy	⩽11 (<0.5)	<15 (<2.0)	36.5 (4.8–277.6)	30.8 (3.9–243.4)

Data are presented as n (%), unless otherwise stated. #: odds ratio for toxicity-related hospitalisation among patients treated with CRT compared with those treated with RT alone; ¶: because of Surveillance, Epidemiology and End Results registry linked to Medicare claims privacy rules, exact numbers are not reported for small subgroups, which might risk loss of confidentiality.

treatment-related toxicity [33]. Results of secondary analyses comparing elderly with younger patients enrolled in RCTs assessing the role of CRT in stage III NSCLC are inconsistent. While some studies showed increased toxicity and a lack of survival benefit [34, 35], others showed that elderly patients treated with CRT achieved survival rates that were equivalent to those of their younger counterparts [36]. However, very few patients with unresected stage I and II NSCLC were included in these studies.

As shown in this study, CRT is frequently used to treat elderly patients with unresected early-stage lung cancer, despite limited evidence from the literature. A single-centre, phase II study conducted >20 yrs ago showed an overall response rate of 65% in patients treated with CRT [9]. GREGOR *et al.* [10] conducted a three-arm trial in the 1980s comparing RT, CRT and a control arm among 83 patients with inoperable, non-metastatic NSCLC [10]. Response rates and overall survival were better for patients treated with RT or CRT compared with the control arm; no significant differences in survival were observed among the two active arms. However, these studies were not sufficiently powered to detect clinically relevant differences in survival with CRT and did not use modern RT techniques and/or chemotherapy regimens.

Our data extends these results by showing that CRT may be effective for the treatment of unresected elderly patients with stage I NSCLC that underwent intermediate complexity RT. Although complex RT is the most common technique used in developed countries, these data are relevant to the large number of patients who are treated in settings without access to more recent RT technology. Additionally, we found that CRT is associated with improved survival of unresected stage II elderly patients regardless of the type of RT planning used. These results are consistent with prior RCTs showing the benefit of CRT among unresectable patients with more advanced (stage III) disease. There are several potential mechanisms for the observed benefit of CRT among unresected patients. First, approximately one-third of patients with clinical stage I–II NSCLC have undetected involvement of regional lymph nodes. CRT has been shown to improve survival of unresectable patients with stage III NSCLC, most of whom also have positive regional lymph nodes [37, 38]. Thus, it is expected that CRT would also benefit patients with clinical early-stage NSCLC who have undetected regional or systemic metastasis. Secondly, it is also plausible that chemotherapy is beneficial for the subset of stage I patients who have local residual disease following intermediate complexity RT. Finally, chemotherapy and RT may act synergistically, improving rates of local control and thus, prolonging survival despite the lack of long-term benefit. Conversely, our data suggest that stage I patients treated with complex RT planning do not benefit from the addition of chemotherapy. Prior data suggested that high complexity RT is superior to intermediate complexity techniques for the treatment of unresected patients with clinical stage I disease [15]. Thus, chemotherapy may not provide additional benefits to complex RT-treated stage I patients who may have improved rates of local control.

The benefits of CRT need to be weighed in the context of its risks. Elderly patients with limited functional status or multiple comorbidities have a reduced survival and may not benefit from aggressive cancer treatment [39, 40]. Moreover, ageing is associated with changes in organ function and comorbidities that may lead to lower chemotherapy and RT tolerance. Despite almost universal concerns regarding the potential risks of therapy in the elderly, there is limited data on the rates of severe toxicity related to CRT, particularly among elders in the community with unresected NSCLC. A phase II trial of combined modality therapy in elderly patients with NSCLC reported acceptable rates of grade 3 and 4 toxicity suggesting that CRT was feasible in this age group [41]. Conversely, two retrospective analyses of patients included in phase II–III trials reported that patients >70 yrs of age were at an increased risk of toxic reactions, concluding that elderly patients do not benefit from CRT [35, 42]. More than one in four (26%) patients

who received CRT in our study experienced toxicity serious enough to merit hospitalisation, and CRT doubled the risk of severe toxicity. Stage II patients and stage I cases treated with intermediate complexity RT experienced a net survival benefit despite this increased risk of toxicity. Additional studies are needed in order to assess the impact of CRT on quality-adjusted life expectancy. Conversely, stage I NSCLC lung cancer patients who undergo complex RT are likely to be at risk of early morbidity, but will not experience a survival gain. Thus, potential risks and benefits of CRT should be discussed in detail with these patients before treatment's initiation.

Our study has some strengths and limitations worth noting. In contrast to randomised trials, use of CRT was not determined by chance in our study, but rather influenced by patients' characteristics (including their likelihood of response) and physicians' preferences. This treatment allocation process may generate systematic differences in the distribution of baseline characteristics among patients who received CRT *versus* RT alone. Therefore, survival differences among patients in these treatment groups may represent confounding by indication. However, we used propensity score methods to balance the study groups effectively controlling for all measured covariates, including detailed clinical and tumour characteristics, which are the most important prognostic factors for unresected early-stage NSCLC. Additionally, the differential effect of CRT among stage I and II patients, as well as those who underwent intermediate *versus* complex RT planning, suggest that our findings are not due to more frequent use of CRT among patients with good performance status or other favourable prognostic characteristics. In the absence of contemporary RCTs evaluating the role of CRT, our results provide useful information for physicians making decisions concerning the management of elderly NSCLC patients in routine clinical practice.

The SEER-Medicare linked database is a population-based registry and is, therefore, less affected by referral patterns and other sources of selection bias that might be present in single-centre studies. Ascertainment of cancer patients within participating areas is very high and the registry captures >90% of SEER patients ⩾65 yrs of age in SEER [23]. Thus, we anticipate that the generalisability results of the study will be substantial. However, the database does not include elderly patients without Medicare coverage or lung cancer patients aged <65 yrs; thus, our results may not be applicable to these groups.

In summary, our findings suggest that use of CRT may lead to improved outcomes for unresected elderly patients with clinical stage II disease or stage I NSCLC who underwent intermediate complexity RT. However, CRT-treated patients are more likely to experience early morbidity due to severe treatment-related toxicity. Conversely, stage I patients who undergo complex RT planning do not appear to benefit from the addition of chemotherapy. Randomised trials are needed to clarify the balance of benefits and risk of CRT in stage I–II patients unable to undergo resection. Newer therapies are necessary to improve the outcomes of these patients who have very poor long-term survival despite being diagnosed at an early stage.

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STATEMENT OF INTEREST

A statement of interest for J.P. Wisnivesky can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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