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Do the "oldest old" non-small cell lung cancer patients experience the worst outcomes after radiotherapy?

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ABSTRACT

Background: Older patients with cancer tend to be denied curative treatment because of the perception that they may not be able to tolerate treatment, especially if they are aged ≥80 years.

Aim: We aimed to verify our hypothesis that patients aged ≥80 years who receive radiotherapy for non-small cell lung cancer fare better than their younger counterparts.

Methods and Materials: Medical records of all patients with non-small cell cancer who were referred to our institution for radiotherapy between January 1, 2006, and September 30, 2025, were reviewed. All eligible patients completed the planned curative radiotherapy. The patients were categorized into two age groups: <80 and ≥80 years. Toxicity and overall and progression-free survival were compared among age groups. Toxicity was divided into two groups: grades 0–2 or 3≤. Multivariate analysis was performed using age, Charlson Scale score, sex, use of concomitant chemotherapy with radiotherapy, and adjuvant use of durvalumab as variables.

Results: Of the 528 patients, 470 completed radiotherapy. The age distribution was as follows: <80 years, 84% (n=395); and ≥80 years, 16% (n=75). No statistically significant difference in grade 3≤ toxicity was observed in the older age group. The chemoradiotherapy group had statistically significantly higher incidence rates of neutropenia ($p<0.01$) and esophagitis ($p=0.02$) compared with the radiotherapy monotherapy group. Moreover, the incidence rate of pneumonia was higher in the chemoradiotherapy ($p=0.01$) and adjuvant durvalumab ($p=0.01$) groups. Although the differences were not statistically significant, we observed higher trends in the incidence rates of thrombocytopenia in the older age ($p=0.06$) and chemoradiotherapy ($p=0.10$) groups compared with their counterparts, and neutropenia in male patients ($p=0.07$) compared with female patients. In the multivariate survival analysis, no statistically significant difference in overall survival was observed. However, the lower disease stage showed higher progression-free survival than the higher disease stage. There was a trend toward longer progression-free survival in the older age and adjuvant durvalumab groups (both $p=0.08$).

Conclusion: Compared with their younger counterparts, patients with non-small cell cancer aged ≥80 years showed no statistically significant differences in terms of faring even better after receiving radiotherapy for non-small cell cancer. However, these older patients showed trends of higher rates of severe thrombocytopenia and longer progression-free survival than younger patients. We could not verify our hypothesis; however, curative lung radiotherapy can be an effective and safe treatment for patients aged ≥80 years.

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide and occurs primarily in the elderly. Approximately two-thirds of people diagnosed with lung cancer are aged ≥65 years. The mean age at diagnosis is approximately 70 years[1]. Globally, the number of people aged ≥80 years, the "oldest old," is growing even faster than the number of the elderly (people aged ≥60 years) overall. Projections indicate that in 2050, the "oldest old" will number 426 million, more than triple the number in 2020[2].

Therefore, there is a growing need to establish an effective treatment for elderly patients with lung cancer. Currently, the standard treatment for locally advanced non-small cell lung cancer (NSCLC) is concurrent chemoradiotherapy (CCRT) with adjuvant durvalumab[3]. However, regarding NSCLC treatment in the elderly, there are only a few clinical trials informing decision-making[4-8], and some observational studies have analyzed large datasets[9-20]. Moreover, there are almost no data comparing the treatment result of "oldest old" to younger age group.

While previous studies have confirmed the efficacy and safety of stereotactic body radiation in the oldest old population[21-23], these studies focused on early-stage lung cancer, which comprises only approximately 30% of NSCLC cases[24-25]. Consequently, evidence guiding the use of definitive radiotherapy or concurrent chemoradiotherapy in the oldest old with more advanced or heterogeneous disease remains limited. This lack of data contributes to uncertainty in clinical decision-making and may lead to the underuse of potentially curative radiotherapy based solely on chronological age.

In this context, as a "regional core" hospital, our university hospital attracts patients from a wide-ranging area. Consequently, many oldest-old patients with NSCLC who have declined invasive therapy at other institutions arrive at our radiotherapy (RT) clinic for consultations. Many of these patients are in good health, and we believe that declining RT because of their chronological age would be unethical; therefore, they have been treated with RT or CCRT. Our general impression treating the "oldest-old" patients with NSCLC was that not only were they just as likely to complete their entire treatment course as younger patients, but they also appeared to fare even better than their younger counterparts.

To address our relatively paradoxical hypothesis that the "oldest-old" fare better than the younger counterparts, we retrospectively analyzed the effects of age and comorbidity on RT treatment and outcomes in a population-based cohort of patients with NSCLC referred to our regional university hospital, where a single radiation oncologist is treating all the patients with lung cancer.

Materials and Methods

The medical records of all patients with NSCLC referred to our institution between January 1, 2006, and September 30, 2025, were retrospectively reviewed to obtain data regarding patient and treatment characteristics and clinical outcomes. This period was selected because in our institution the electric data base has started from January 2006. As a single institution study, we would like to collect as many patients as possible. And therefore, we used all the data that was available. During this period, 528 patients with NSCLC received RT with a curative intent at our clinic, and all of them were included in this study.

The patients were categorized into two age groups based on age at diagnosis—<80 and ≥80 years—according to guidelines established by the United Nations[2]. The pretreatment patient factors, including sex, Eastern Cooperative Oncology Group performance status (PS) (0–1 or 2–3), the use of concurrent chemotherapy, and American Joint Committee on Cancer stage (0, 1–2, or ≥3), were analyzed. Comorbidities were scored using the Charlson Comorbidity Scale (0–2 vs. ≥3). The Charlson Scale, developed in 1987[26], provides a weighted index of comorbidity based on the relative risks of death associated with 19 clinical conditions and is an indicator of the number and severity of comorbid conditions. Owing to advances in disease management, the Charlson Scale was updated using the 10th revision of the International Classification of Diseases codes[27], and we used this version. Although for predicting cancer prognosis the age-adjusted version would be more accurate[28], because we would like to compare the efficacy between the Charlson Scale and age, we intentionally used the raw data of the Charlson Scale; in other words, the Charlson Scale without adjustment for age.

PRETREATMENT STAGING

All patients had histologically confirmed NSCLC by bronchoscopy or computed tomography (CT)-guided transthoracic biopsy. Pretreatment staging was performed in all patients using thoracic and abdominal CT, brain magnetic resonance imaging, and bone scintigraphy and fludeoxyglucose (FDG)-positron emission tomography (PET)-CT in most patients.

TREATMENT

The entire cohort was treated by a single radiation oncologist. As the work of Japanese radiation oncologists also includes treatment planning, the RT plans delivered to the patients were relatively homogenous. Treatment recommendations were individualized based on the established Japanese lung cancer guidelines.

CHEMOTHERAPY

The most common treatment regimen used during the study period was carboplatin and paclitaxel (CBDCA+PAC). Individual regimens were altered depending on the patients' condition. Medically unfit patients were treated with oral titanium silicate-1 or no chemotherapy.

RADIOTHERAPY

The RT regimen was homogeneous across all patients. The treatment consisted of 10-MV photons with a two-field combination of 60 Gy in 30 fractions (after 40 Gy, a cone-down field was created). Patients who received stereotactic body RT or hypofractionated regimen were excluded. In addition, because the primary endpoint of this study was to determine the safety of RT, patients who could not complete the treatment were excluded from the analysis of survival and adverse effects.

PATIENT FOLLOW-UP

The patients were followed up by a pulmonologist once a month for 5 years after RT and were evaluated each time using chest radiography. Every 3 months, the patients were evaluated using CT imaging, FDG-PET-CT, or both. Chemotherapy and RT toxicities were graded according to the Common Terminology Criteria for Adverse Events version 6.0[29]. The radiation oncologist evaluated acute adverse effects once a week throughout the RT period. Radiation pneumonia was evaluated by a pulmonologist once a month using chest radiography and by a radiation oncologist after 6 months and 1 year. Progression-free survival and overall survival were calculated for all patients.

STATISTICAL ANALYSES

Patient factors, treatment characteristics, and survival were compared among the two age groups (<80 and ≥80 years) per the Charlson Comorbidity Scale of 0–2 and ≥3 using the chi-squared tests, use of concurrent chemotherapy, PS 0–1 or ≥2, sex, and disease stages 1–2 or 3–4. The association between adjuvant durvalumab use and pneumonitis was also analyzed. Multivariate analysis was performed with age, Charlson Scale score, use of concurrent chemotherapy, and sex as covariates. In the analysis of pneumonitis, adjuvant durvalumab was added as a covariate. Significance was defined as a p-value <0.05. Kaplan–Meier curves were generated for overall survival and progression-free survival using log-rank analysis. The Cox proportional hazards model was used to detect the association between the aforementioned covariates. Multivariate analysis was performed using age, Charlson Scale score, sex, stage, and adjuvant use of durvalumab as covariates, and Wald analysis was performed to analyze significance. All calculations were performed using the SAS version JMP 12.2.0 software (SAS Institute, Cary, NC, USA).

Results

The median age of the 528 patients with NSCLC was 70 (range, 36–92) years. The age distribution was as follows: <80 years, 84.1% (n=444); and ≥80 years, 15.9% (n=84). The Charlson Scale scores were ≤2 in 71.4% (n=377) and ≥3 in 28.6% (n=151) of the patients. The PS scores were 0–1 in 85.0% (n=449) and ≥2 in 15.0% (n=79) of the patients. The disease stages were I–II in 11.2% (n=59) and III–IV in 66.9% (n=353) of the patients, and in 22.0% (n=116) of the patients, it was RT associated with postoperative recurrence. Of these, 58 patients did not complete the treatment and were excluded from this study. The median dose for patients who could not complete treatment was 30 (range, 2–54) Gy. There was no statistically significant correlation between the termination and age (≥80 years), but PS score (≥2) showed a correlation (p<0.01), and Charlson Scale score (p=0.09) and stage (p=0.09) showed trend of the worse groups with higher termination rate.

PATIENT CHARACTERISTICS

Table 1 shows the patient and tumor characteristics across the two age groups of patients who completed RT. Statistically significantly lower

tumor stages (stage I or II) were observed in the older age group.

Older age was not associated with a worse PS. However, a higher Charlson Scale score correlated with worse PS (in the higher Charlson Scale group, 17% of the patients had higher PS; in the lower Charlson Scale group, 11% of the patients had higher PS score [p=0.05]). Moreover, significantly more patients in the older age group received RT monotherapy. However, when the number of patients with stage I disease was subtracted from each age group, the difference was no longer observed.

Table 1. Patients, tumor characteristics, and treatment according to age groups

Characteristic	Age group <80 years (n=395)	Age group ≥80 years (n=75)	p value
Age	69 (range, 36–79) years	82 (range, 80–92) years	**p<0.01**
Male vs Female	312 (79%) vs 83 (21%)	58 (77%) vs 17 (23%)	p=0.99
New case/recurrence			
New	303 (77%)	61 (81%)	p=0.37
Recurrence	92 (23%)	14 (19%)	
Charlson Scale score			
0–2	281 (71%)	49 (65%)	p=0.13
≥3	114 (29%)	26 (35%)	
Stage			
I-II	29 (10%)	27 (44%)	**p=<0.01**
III-IV	274 (90%)	34 (56%)	
PS*			
0-1	346 (88%)	64 (86%)	p=0.55
2-3	49 (13%)	11(15%)	
Treatment			
RT** alone	67 (17%)	30 (40%)	**p<0.01**
CCRT***	236 (60%)	35 (47%)	
CCRT**+durvalumab	92 (23%)	10 (13%)	

*PS: Eastern Cooperative Oncology Group performance status; **RT: radiotherapy; ***CCRT: concurrent chemoradiotherapy

TOXICITY

Tables 2 and 3 show the correlation between acute and subacute toxicities and several variables. Because of the subacute nature of pneumonitis, we also analyzed the correlation between the adjuvant use of durvalumab and pneumonitis. There were four grade 5 pneumonitis cases in the younger age group and one grade 5 pneumonitis case in the older age group. In the multivariate analysis, the CCRT group has significantly higher incidence rates of neutropenia (p<0.01) and esophagitis (p=0.02) than the other groups, and the CCRT (p=0.01) and adjuvant durvalumab (p=0.01) groups had significantly higher incidence rates of pneumonia than the other group. A trend of higher incidence rate of neutropenia was observed in males (p=0.06), and a trend of higher incidence rate of thrombocytopenia was observed in the older age (p=0.06) and CCRT (p=0.10) groups.

Table 2. Grade ≥3 adverse effects according to patient characteristics

Variable	Neutropenia	Anemia	Thrombocytopenia	Esophagitis	Pneumonia
Age					
<80 years	27%	9%	3%	3%	11%
≥80 years	29%	5%	9%	1%	17%
p-value	p=0.7	p=0.31	**p=0.03**	p=0.45	p=0.17
Charlson Scale score					
0 - 2	26%	7%	4%	2%	11%
≥3	29%	11%	5%	3%	13%
p-value	p=0.52	p=0.22	p=0.50	p=0.78	p=0.13
Sex					
Male	25%	9%	4%	2%	13%
Female	34%	7%	4%	3%	8%
p-value	p=0.06	p=0.57	p=0.97	p=0.74	p=0.19
Stage					
I or II	22%	4%	6%	2%	13%
III or IV	29%	10%	5%	3%	12%
p-value	p=0.30	p=0.11	p=0.68	p=0.56	p=0.81
PS*					
0 or 1	28%	7%	5%	2%	11%
2 or 3	20%	17%	0%	7%	19%
p-value	p=0.21	**p=0.01**	p=0.08	**p=0.02**	p=0.08

*PS: Eastern Cooperative Oncology Group performance status

Table 3. Grade ≥3 adverse effects according to treatment variables

Variable	Neutropenia	Anemia	Thrombocytopenia	Esophagitis	Pneumonia
CCRT* or RT** monotherapy					
CCRT*	30%	8%	5%	3%	11%
RT** only	12%	11%	2%	0%	16%
p-value	p<0.01	p=0.31	p=0.31	p=0.07	p=0.13
Adjuvant therapy of durvalumab					
Yes					19%
No					10%
p-value					p<0.01

*CCRT: concurrent chemoradiotherapy; **RT: radiotherapy

OVERALL SURVIVAL AND PROGRESSION-FREE SURVIVAL

At the time of analysis, 266 (60%) patients died. The median follow-up time for living patients was 20 (range, 1–190) months.

Table 4 and 5 compare survival according to several variables. Multivariate analysis showed no variable with statistically significant increase in overall survival. However, the group with a lower disease stage (stage 1 or 2) showed a trend toward longer survival (p=0.09). Regarding progression-free survival, lower disease stage showed statistically significant longer survival than higher disease stage (p<0.01), and higher age (≥80 years) and the adjuvant use of durvalumab showed a trend of longer progression-free survival (both p=0.08). If only the patients with stage III disease were compared, the median overall survival and progression-free survival of the younger age group (n=204) were 29 months and 11 months, respectively. The overall survival of the older age group (n=31) was 15 months, and the progression-free survival did not reach the median.

Table 4. Overall and progression-free survival according to patient characteristics

Variable	1-year OS*	2-year OS*	1-year PFS**	2-year PFS**
Age				
<80 years	72%	54%	46%	33%
≥80 years	76%	54%	73%	61%
p-value	p=0.39		p<0.01	
Charlson Scale score				
0 or 1 or 2	73%	54%	48%	35%
3 or higher	70%	54%	54%	41%
p-value	p=0.57		p=0.99	
Sex				
Male	79%	51%	49%	38%
Female	82%	66%	54%	35%
p-value	p=0.02		p=0.25	
Stage				
I or II	86%	63%	69%	60%
III or IV	67%	49%	43%	52%
p-value	p=0.02		p<0.01	
PS***				
0 or 1	76%	57%	51%	36%
2 or 3	49%	34%	43%	41%
p-value	p<0.01		p=0.08	

*OS: Overall survival; **PFS: Progression free survival; ***Eastern Cooperative Oncology Group performance status

Table 5. Overall and progression-free survival according to treatment variables

Variable	1-year OS*	2-year OS*	1-year PFS**	2-year PFS**
CCRT*** or RT**** monotherapy				
CCRT***	74%	57%	51%	36%
RT**** only	63%	40%	47%	43%
p-value	p<0.01		p=0.21	
Adjuvant therapy of durvalumab				
Yes	75%	59%	57%	39%
No	72%	52%	47%	53%
p-value	p=0.41		p=0.42	

*OS: Overall survival; **PFS: Progression free survival; ***CCRT: concurrent chemoradiotherapy; ****RT: radiotherapy

Discussion

In this study, we aimed to verify our unconventional hypothesis that the "oldest-old" fare better than their younger counterparts after treatment for NSCLC with RT or CCRT. We observed a tendency toward this finding by analyzing our community-based cohort of patients with NSCLC.

As expected, there was a statistically significant difference between stages. This was because before stereotactic RT was commonly used in our institution, we performed curative RT (60 Gy in 30 fractions) in patients with early-stage lung cancer who were not candidates for surgery. Moreover, with increasing age, more patients received RT alone than CCRT. However, this difference disappeared when patients with stage I disease were excluded. At our clinic, patients with stage I disease usually receive RT monotherapy. Therefore, in our institution, age-related downstaging of treatment is not usually performed. However, the chemotherapy regimen was changed from a platinum doublet to daily CBDCA[6] or daily S-1[8] in many patients with higher risk, such as those with older age or several comorbidities. Many retrospective studies[9-12], cancer registries[13-16], and systematic reviews[17-19] have reported that older patients are more prone to undertreatment than younger patients. Instead of CCRT, they tended to receive sequential chemoradiotherapy, monotherapy, or even palliative RT. At our institution, as a general rule, we prescribe CCRT, and if patients are at a higher risk of experiencing untolerable adverse effects, we first consider changing the chemotherapy regimen. RT monotherapy was administered only in patients with severe renal failure.

In the multivariate analysis, acute toxicities were not significantly different between the age groups. Only trend of more grade 3 or higher thrombocytopenia was observed in the older age group. However, because the numbers were relatively low (3% in the younger age group, 9% in the older age group), and all were grade 3, this would not justify stopping curative treatment for the oldest old. Regarding survival, multivariate analysis revealed no statistically significant difference between the age groups. However, the progression-free survival showed a trend toward longer survival in the older age group than in the younger age group.

Regarding radiation pneumonia, there were no significant differences between the age groups. There were four grade 5 pneumonitis cases in the younger age group and one grade 5 pneumonitis case in the older age group. The literature shows mixed reports; some report that older patients experience more grade 3 or higher toxicities[4,5,9,12,17,20], whereas others report no differences[6,10,16,18]. We believe that the lack of a difference in toxicities between the age groups in our study was due to two reasons. First, we started using involved field RT in 2009, which is a method that shrinks the field of radiation and therefore reduces the risk of adverse effects in both age groups. Second, we addressed the oldest olds, who may not be as sensitive to pain. With their retrospective study with 125 patients, Soni et al. reported that patients aged ≥70 years had lower incidence rate of esophagitis compared with their younger counterpart[10]. This study precisely measured the radiation dose to the esophagus of each patient. They concluded that this could be attributed to a decrease in the sensation of visceral pain in older patients. In our study, we could not show that toxicity was lower in the elderly, but as clinicians meeting patients during RT, we had the

same finding. The oldest olds are performing well during RT. As expected, adjuvant use of durvalumab was associated with a higher rate of pneumonitis. In addition, two studies that investigated the use of adjuvant durvalumab for the elderly showed more grade 3 or higher toxicities in the elderly[5, 20]. In our study, only 10 patients in the older age group received adjuvant durvalumab, and there were two grade 3 pneumonitis cases. There may be an association between a higher rate of pneumonitis and the adjuvant use of durvalumab. This must be considered when making treatment decisions for elderly patients.

Multivariate analysis showed no variable with statistically significant increase in overall survival. Regarding progression-free survival, the lower disease stage showed significantly longer survival ($p<0.01$) than the higher disease stage, which is an understandable difference. If a p-value of 0.05–0.1 is considered an acceptable trend, overall survival was higher in the lower disease stage group ($p=0.09$) and, and the higher age (≥80 years), and the adjuvant use of durvalumab showed a trend of longer progression-free survival (both $p=0.08$). If the analysis was narrowed to stage III patients only, the median progression-free survival of the younger age group (n=204) was 11 months but was not reached in the older age group (n=31). This is another factor that suggested to us as clinicians that the oldest olds fare better; however, it did not show a statistically significant difference in our study. One cancer registry search[11] with a cutoff age of 75 years and one systematic review[17] with a cutoff age of 70 years showed no difference in survival when adjusted for treatment method. One randomized study[6], two systematic reviews[18], and one cancer registry search[16] reported better survival with CCRT than with sequential chemotherapy RT and RT monotherapy. Notably, in all of these studies, the elderly were defined as those aged ≥70 years. Studies have also reported worse survival rates in elderly individuals. Driessen et al. performed a retrospective analysis of 216 elderly patients with unresectable stage III NSCLC[15]. The 1-year survival rates after CCRT, sequential RT, and RT monotherapy were 57%, 50%, and 49%, respectively. They concluded that there was no significant difference in survival among the three methods. In this study, the Adult Comorbidity Evaluation-27 was "severe" in 43% of the CCRT, 62% of sequential RT, and 65% of RT monotherapy. The reason CCRT did not seem beneficial could be because most of the patient population was in a higher-risk group. Zhang et al. conducted a retrospective study of 789 patients with stage III unresectable NSCLC. This was a comparative study between younger and older age groups (cutoff age, 65 years). They concluded that the overall survival was significantly longer in the younger patient group than in the older patient group. Moreover, they reported that pneumonitis was significantly more fatal in the older age group than in the younger age group. Grade 5 pneumonia was observed in 20 (3%) patients. Notably, this study was conducted before the era of durvalumab consolidation therapy. In our study, there were five (1%) patients with grade 5 pneumonitis, all of whom received adjuvant durvalumab. Worse survival could have been affected by high grade 5 pneumonitis in the total patient cohort. More recently, two studies have reported the benefits of durvalumab in elderly patients. In their post-hoc analysis of the PACIFIC study, Socinski et al. reported that durvalumab was associated with treatment benefits and manageable safety, even in patients aged ≥70 years[5]. Park et al. reported a retrospective study of 286 patients with unresectable stage III NSCLC and compared older and younger age groups (cutoff age, 70 years)[20]. Durvalumab demonstrated similar survival outcomes in both groups. However, grade 3 or higher adverse effects were more common in the older age group than in the younger age group.

In 2019, there was a consensus of the International Geriatric Radiotherapy Group that older patients with cancer face discrimination because of their chronological age, and despite the presence of multiple comorbidity factors, older patients with cancer tolerate RT very well because of modern RT techniques, through which a potential cure is attainable[30]. We agree with the consensus. The older age group should not be discriminated against solely because of their chronological age. Although the oldest old do not perform better, at least they did not fare worse as their younger counterpart.

Conclusion

Patients with NSCLC aged ≥80 years show no statistically significant difference in terms of faring

even better after receiving radiotherapy for NSCLC compared with their younger counterparts. However, older patients with NSCLC had a trend of higher rates of severe thrombocytopenia and longer progression-free survival than younger patients with NSCLC. We could not verify our hypothesis; however, curative lung radiotherapy can be an effective and safe treatment for patients aged ≥80 years.

Conflict of Interest Statement:

The authors have no conflicts of interest to declare.

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