Radiotherapy and Oncology 113 (2014) 374–378

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Lung cancer radiotherapy

Prognostic implication of pulmonary function at the beginning of postoperative radiotherapy in non-small cell lung cancer

Hwanik Kim [a], Yves A. Lussier [b,c,d], O Kyu Noh [a,b,c,d,*], Haiquan Li [b,c,d], Young-Taek Oh [a], Jaesung Heo [a]

[a] Department of Radiation Oncology, Ajou University School of Medicine, Suwon, Republic of Korea; [b] Department of Medicine; [c] BIO5 Institute; and [d] Leon Levy Cancer Center, The University of Arizona, Tucson, USA

ARTICLE INFO

Article history:
Received 20 August 2014
Received in revised form 4 November 2014
Accepted 4 November 2014
Available online 28 November 2014

Keywords:
Non-small cell lung cancer
Postoperative radiotherapy
Pulmonary function
Prognostic factor

ABSTRACT

Purpose: The purpose of this study was to investigate the prognostic effect of pulmonary function at the beginning of postoperative radiotherapy (PORT) in non-small cell lung cancer (NSCLC).
Materials and methods: From January 2002 to December 2012, 115 patients with NSCLC who underwent PORT and took the forced expiratory volume in 1 second (FEV1) at the beginning of PORT were analysed. PORT began within 4–6 weeks following surgery, and the 3-dimensional conformal technique was used with conventional fractionation. The high and low FEV1 groups were divided by the median absolute value of FEV1 at the beginning of PORT, and we compared the clinical factors and survival between two groups.
Results: The median absolute value of FEV1 at the beginning of PORT was 1.68 L (range, 0.83–3.89), and patients were divided into low and high FEV1 groups (<1.68 L versus ⩾1.68 L). Patients in the low FEV1 group showed a lower preoperative FEV1 (mean, 1.94 L versus 2.73 L, $p < 0.001$) and received more pneumonectomy (36.8% versus 8.6%, $p < 0.001$) compared to the high FEV1 group. The overall median follow-up time was 31 months (range, 3–110), and 5-year locoregional recurrence-free survival (LRRFS), distant metastasis-free survival (DMFS) and overall survival (OS) were 52.4%, 48.9%, and 45.9%, respectively. Five-year OS of the low FEV1 group was significantly lower than that of the high FEV1 group (35.4% versus 56.9%, $p = 0.002$), and no significant differences were found in LRRFS and DMFS. In a multivariate analysis, the difference of OS between the low and high FEV1 groups remained significant (Hazard Ratio = 2.04, CI, 1.18–3.55, $p = 0.011$).
Conclusions: The FEV1 at the beginning of PORT was an independent significant prognostic factor in patients with NSCLC who received PORT. Considering this analysis was limited to only patients receiving PORT, further studies are warranted to compare the survival effect of postoperative pulmonary function between groups with/without PORT.

The adjuvant role of postoperative radiotherapy (PORT) remains controversial in the treatment of non-small cell lung cancer (NSCLC). Meta-analysis of nine randomised trials evaluating the role of PORT showed its detrimental effect on survival despite a significant decrease in the local control rate [1]. In this analysis, the detrimental effect was prominent in patients with N0 and N1 stages and was less prominent in N2 disease. These stage-dependent detrimental effects on survival suggest that PORT-induced inter-current mortality is due to the old-fashioned technique of radiotherapy with a high daily and total dose [2]. However, since modern radiotherapy techniques have been implemented, radiation-induced morbidity and mortality have lessened [3] and the beneficial effect of PORT for N2 patients has been shown in a large-scale retrospective analysis using the SEER database [4]. This beneficial effect for N2 disease was also demonstrated in the Adjuvant Navelbine International Trialist Association (ANITA) trial [5]. Several recent retrospective studies evaluating the role of PORT showed favourable results in patients with N2 involvement [6–8]. These trends of a beneficial effect of PORT may be a result of the improvement of the therapeutic ratio using modern techniques of radiotherapy, which minimise the irradiated dose to levels found in normal tissues. Moreover, several studies have shown that there is no excessive increase in the risk of death from intercurrent disease (DID) [3], cardiopulmonary morbidity and quality of life [9], and mortality from heart disease [10] in patients treated with PORT using modern techniques. However, although

* Corresponding author at: 164 Worldcup-ro, Yeongtong-gu, Suwon 443-380, Republic of Korea.
E-mail address: okyu.noh@gmail.com (O Kyu Noh).

http://dx.doi.org/10.1016/j.radonc.2014.11.007
0167-8140/

radiation-induced cardiopulmonary problems may not increase the risk of death in the era of modern radiotherapy, it can have a negative effect on long-term clinical outcomes in patients with compromised cardiopulmonary function.

In our institution, we performed spirometry at the beginning of PORT to assess the baseline level of pulmonary function after surgery and excluded patients with compromised pulmonary function who might have the potential risk of DID from PORT. Using this PORT cohort, we aimed to investigate the prognostic significance of pulmonary function at the beginning of PORT on survival in patients treated with PORT.

Methods and materials

From the tumour registry database of our institution, we identified 151 patients with NSCLC who received PORT after surgical resection between January 2002 and December 2012. Of these 151 patients, we selected 115 patients who underwent spirometry at the beginning of PORT for this study.

Lobectomy or pneumonectomy with mediastinal lymph node dissection was performed, and PORT was delivered to patients with a positive node (primarily N2) or positive resection margin on the pathological specimen. PORT began within 4–6 weeks following surgical resection. Three-dimensional conformal radiotherapy (3-D CRT) was used, and radiotherapy was planned using a mega-voltage photon beam ($\geqslant$6 MV). The clinical target volume (CTV) included a bronchial stump, involved nodal stations and subsequent draining of the involved nodal stations. The planning target volume (PTV) was expanded from the CTV by a margin of 1–1.5 cm. Conventional fractionation (1.8–2.0 Gy/day) was used with total dose of a 50.4–66 Gy according to the risk of loco-regional recurrence. The electively irradiated nodal stations were excluded from the boost field at a dose of 44–45 Gy. In the planning of PORT, dose-volume was constrained to a mean lung dose of 20–25 Gy, and less than 25–30% of the lung volume that received over 20 Gy (V20 < 25–30%). We did not modify these constraints for those with lower FEV1. If adjuvant chemotherapy was decided, then four to six cycles of platinum-based chemotherapy were administered 3–4 weeks after the completion of PORT. For the first year after completion of PORT, patients were followed-up every 3 months. For next 2 years, we followed-up every 6 months and then we performed an annual check-up. At each visit of follow-up, we checked chest X-ray or chest CT scan. Annual PET–CT was performed optionally.

Forced expiratory volume in 1 second (FEV1) was performed just prior to computed tomography (CT) simulation for the assessment of reserved lung function after surgical resection. To investigate the prognostic value of FEV1, we divided the two groups according to the median value of FEV1 and compared the clinical parameters and survivals (locoregional-free survival, distant metastasis-free survival and overall survival) between these two groups. We did not perform survival analysis according to specific causes of death due to retrospective data collection. Comparison between the two groups was analysed using a chi-square test or Fisher's Exact Test for categorical variables and Student's *t*-test or Mann–Whitney *U* test for continuous variables.

The survival time was defined by the duration between the date of the surgical resection and the date of the last follow-up evaluation or events and was calculated using the Kaplan–Meier method. The log-rank test and Cox proportional hazards regression model were used for univariate and multivariate analysis, respectively. Two-sided *p*-values less than 0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS statistics software, version 19.0 (IBM SPSS, New York, USA). This study was reviewed and approved by the institutional review board of Ajou University Hospital.

Results

From a total of 115 patients, 94 (81.7%) patients were males, and the age ranged from 30 to 77 years (median, 62). The types of surgical resection were lobectomy in 89 patients (77.4%) and pneumonectomy in 26 patients (22.6%). Pathological examination revealed that adenocarcinoma was observed in 45 patients (39.1%), and squamous cell carcinoma was found in 59 patients (51.3%). Preoperative FEV1 ranged from 1.01 to 4.81 L (median, 2.38). Forty-one patients (35.7%) exhibited pathological N1 stage, and 74 patients (64.3%) were pathological N2 stage. The total radiation dose of PORT ranged from 30.6 to 75.0 Gy (median, 54 Gy). Adjuvant chemotherapy was administered in 35 patients (30.4%), and the cycle of chemotherapy ranged from 1 to 6 (median, 4). The positive resection margin was shown in 10 patients (8.7%).

The absolute value of FEV1 at the beginning of PORT ranged from 0.83 to 3.89 L (median, 1.68), and percentage value ranged from 34 to 104% (median, 61). At the median absolute value of FEV1, we classified the two groups as high FEV1 versus low FEV1 and patient characteristics between the two groups are summarised in Table 1. Between the two groups, there were no significant differences in tumour histology, T-stage, N-stage, and resection margin status. The age of patients in the high FEV1 group was significantly older than the low FEV1 group (mean age, 63.5 versus 55.8, $p < 0.001$). The proportion of females was higher in the low FEV1 group (7.9% versus 29.8%, $p = 0.002$), but the proportion of smokers was higher in the high FEV1 group (84.5% versus 68.4%,

Table 1
Patient characteristics between low and high FEV1 groups.

	High FEV1 ($\geqslant$1.68 L) $n = 58$	Low FEV1 (<1.68 L) $n = 57$	*p*
Age (year)			<0.001
Median (range)	64 (38–77)	58 (30–72)	
Gender			0.002
Male	54	40	
Female	4	17	
Smoking history			0.043
Yes	49	39	
No	8	18	
*COPD history			0.742
Yes	4	6	
No	53	51	
Tumour histology			0.941
Adenocarcinoma	22	23	
Squamous	30	29	
Others	6	5	
Preoperative FEV1 (L)			<0.001
Median (range)	2.61 (1.57–4.81)	1.96 (1.01–2.90)	
Type of surgery			<0.001
Lobectomy	53	36	
Pneumonectomy	5	21	
T stage			0.376
T1	5	5	
T2	43	37	
T3	4	10	
T4	6	5	
N stage			0.422
N1	23	18	
N2	35	39	
Resection margin			0.528
Positive	4	6	
Negative	54	51	
Radiotherapy dose (Gy)			0.035
Median dose (range)	54.0 (30.6–65.0)	54.0 (45.0–75.0)	
Chemotherapy			0.010
Yes	24	11	
No	34	46	

* COPD = chronic obstructive pulmonary disorder.

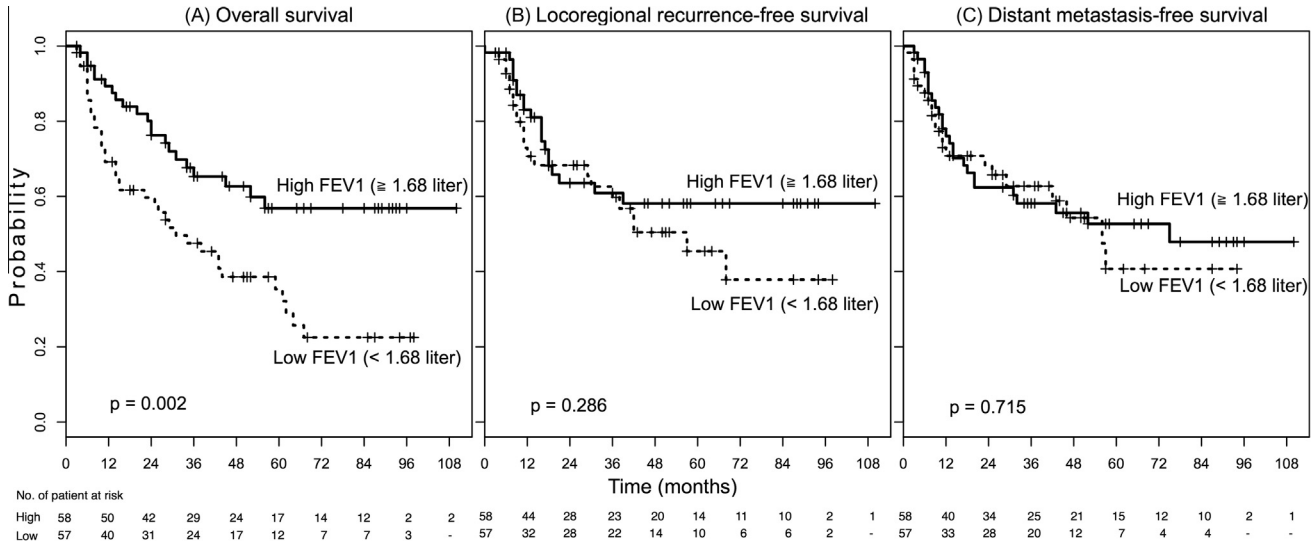

Fig. 1. Kaplan–Meier survival curves. (A) Overall survival. (B) Locoregional recurrence-free survival. (C) Distant metastasis-free survival between high and low FEV1 groups.

$p = 0.043$). Preoperative FEV1 was significantly higher in the high FEV1 group compared to the low FEV1 group (mean FEV1, 2.73 L versus 1.94 L, $p < 0.001$). Pneumonectomy was performed more often in the low FEV1 group compared to the high FEV1 group (8.6% versus 36.8%, $p < 0.001$). Radiation dose was significantly different between the two groups (mean total dose, 55.7 Gy versus 53.4 Gy, $p = 0.035$), but the median of the total dose was 54.0 Gy in both groups. Adjuvant chemotherapy was administered more in the high FEV1 group compared to the low FEV1 group (41.4% versus 19.3%, $p = 0.010$). Nine patients (7.8%) treated with steroids due to symptomatic radiation pneumonitis (SRP) and there was no statistical difference in the rate of SRP between two groups (7.5% versus 8.6%, $p = 1$).

The median follow-up time of the 115 patients was 31 months (range, 3–110), and the overall survival (OS) was 45.9% at 5 years. All patients were followed-up at least once and subject to systemic examination after PORT completion. The 5-year locoregional recurrence-free survival (LRRFS) and distant metastasis-free survival (DMFS) were 52.4% and 48.9%, respectively. The overall survival of the high FEV1 group was significantly higher than that of the low FEV1 group (5-year survival, 56.9% versus 35.4%, $p = 0.002$) (Fig. 1A). There were no significant differences in LRRFS and DMFS between the high and low FEV1 groups (5-year LRRFS, 58.1% versus 45.4%, $p = 0.286$; 5-year DMFS, 52.7% versus 40.7%, $p = 0.715$) (Fig. 1B and C).

Univariate analysis for other clinical factors demonstrated that patients with pneumonectomy showed a significant decrease in overall survival compared to patients with lobectomy ($p = 0.013$). Increased nodal stage (N2 disease) was a significant adverse factor affecting overall survival ($p < 0.001$), and administration of adjuvant chemotherapy showed a trend of favourable overall survival ($p = 0.102$). Gender, history of smoking, chronic obstructive pulmonary disease, preoperative FEV1 (<2.38 L versus ⩾2.38 L), tumour histology, T-stage, positivity of resection margin and irradiated total dose (<54.0 Gy versus ⩾54.0 Gy) were not significant factors affecting overall survival. Multivariable analysis revealed that FEV1 at the beginning of PORT (FEV1 < 1.68 L) remained a significant prognostic factor for overall survival (HR = 2.04, $p = 0.011$) (Table 2).

We further analysed the 5-year OS of patients with low FEV1 according to different cut-offs (Fig. 2). There was a trend of decreasing 5-year OS at the range below the cut-off FEV1 of 2.10 L.

Discussion

We hypothesised that pulmonary function at the beginning of PORT can affect the outcomes in patients treated with PORT, and our result showed that low values of FEV1 were an independent negative prognostic factor on overall survival (<1.68 L versus ⩾1.68 L, HR = 2.04, $p = 0.011$). In addition, we calculated the 5-year overall survival in patients with FEV1 less than the specific cut-off value, and there was a trend of decreasing survival at the range below the cut-off value of 2.1 L (Fig. 2). These results suggest that pre-PORT pulmonary function below a specific level can be detrimental to overall survival in patients treated with PORT. Radiation oncologists tend to exclude patients with poor pulmonary function before the beginning of PORT because it is assumed that they would be susceptible to subtle lung toxicity induced by thoracic irradiation. Generally, FEV1 lower than approximately 1.0 L after surgery was adopted as an exclusion criterion [9]. In this study, patients with an FEV1 lower than 0.8–1.0 L after surgery were excluded from performing PORT. However, even after excluding the patients with poor FEV1, our results showed that the value of FEV1 remained a prognostic factor. Between the high and low FEV1 groups, there were no significant differences in LRRFS and DMFS, but a significant difference in OS (Fig. 1). These results suggest that the value of FEV1 may be associated with the risk of death from intercurrent disease (DID). Our results are limited to discussion about whether PORT

Table 2
Multivariable analysis of parameters affecting on overall survival.

Variable		HR	95% confidence interval	*p*
FEV1 (L)	<1.68/⩾1.68	2.04	1.18–3.55	0.011
Type of surgery	Pneumonectomy/lobectomy	1.66	0.93–2.94	0.084
N stage	N2/N1	1.75	0.95–3.20	0.071
Chemotherapy	Yes/no	0.65	0.32–1.31	0.226

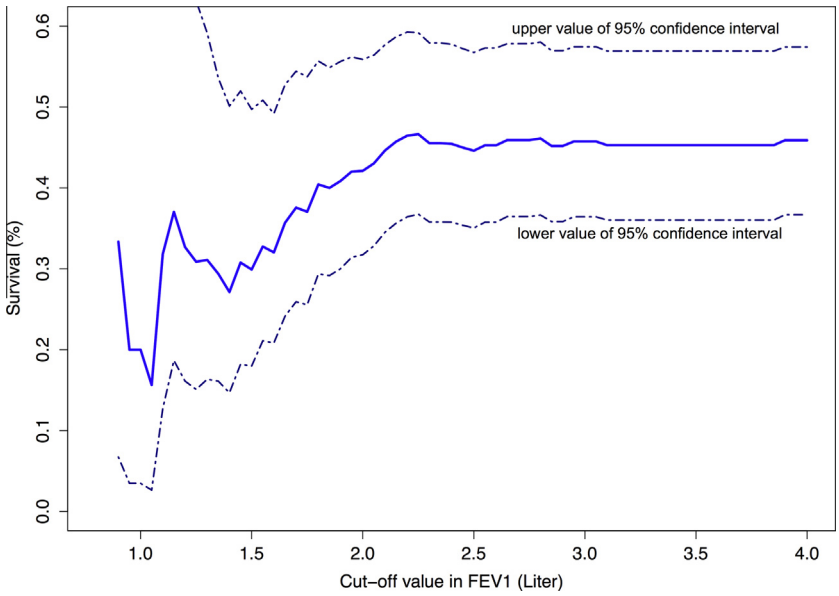

Fig. 2. Five-year overall survival in the patients showing FEV1 less than specific cut-off value.

itself could increase the risk of DID in the low FEV1 group because the study population was restricted to patients treated with PORT. Pulmonary function itself is known as a long-term predictor of mortality in the general population [11]. Moreover, several studies have reported that there is no PORT-induced worsening of pulmonary function [9,12], which is different from that of patients treated with definitive chemoradiotherapy, which demonstrated a decrease of approximately 10% of pulmonary function [13]. These minimal or lack of changes in pulmonary function after PORT may result from the lower dose and smaller field limited to mediastinum compared to that of the definitive setting as well as the advanced techniques of radiotherapy, which enable the minimisation of the irradiated dose and volume of normal lung tissue. In these contexts, PORT can be administered safely without compromising the pulmonary function under the use of 3-dimensional conformal radiotherapy techniques at doses of adjuvant setting (50–60 Gy). However, although PORT can be feasible without a decrease in FEV1 [9] and the risk of DID related to PORT was not excessively increased by the modern radiotherapy technique [3], we should be cautious about the minimal but substantial risk of DID, that may exist in patients treated with PORT. Miles et al. suggested that RT-induced mortality is strongly dependent on the size of the radiation field and at least partly offsets the benefit of PORT using their simple model based on clinical data [14]. In their study, the increase in OS was assumed to be equal to the increase in cancer-specific survival minus the rate of mortality from PORT. This model suggested that the tailored small field-size targeting the areas most at risk of recurrence might provide the highest therapeutic ratio, which can result in an increase in OS by minimising the risk of RT-induced toxicities. This relationship between the increase in OS and the tailored small field-size also supports the minimal risk of RT-induced mortality in the era of modern techniques. However, it also suggests that the substantial risk of mortality from PORT exists even in a small field size, although it may be very small. Our hypothesis was that the potential risk of DID can affect the OS in the patient group with a relatively low FEV1 at the beginning of PORT, and our results suggested that the substantial risk of DID might exist. Thus, the effect of low FEV1 at the beginning of PORT should be carefully assessed with regard to the risk and benefit of PORT in further studies.

We analysed the prognostic effect of FEV1 at the beginning of PORT because this timing is more proper to assess the functional reserve than the FEV1 value prior to surgery. Initial pulmonary function has been known as a prognostic factor in patients that underwent surgery [15,16] and in advanced-stage patients treated with chemotherapy or radiotherapy [17]. However, to the best of our knowledge, previous studies investigating the effect of pulmonary function at the beginning of PORT are rare. This may be due to the unreliable or underestimated values related to the early postoperative injury of the chest wall, which does not fully recover within 4–6 weeks in most cases. However, although the result of the postoperative pulmonary function test may not reflect the real functional reserve, it can provide crude information about the general postoperative condition and pulmonary function. Our results suggest that the postoperative FEV1 could provide prognostic information, and additional investigations should be performed to elucidate the clinical importance of pulmonary function at the beginning of PORT.

We compared the clinical variables between the low and high FEV1 groups, which revealed the factors related to the level of postoperative FEV1 (Table 1). The value of preoperative FEV1 was higher in the high FEV1 group compared to the low FEV1 group, and the proportion of patients that underwent a pneumonectomy was significantly higher in the low FEV1 group compared to the high FEV1 group. This finding clearly showed that the initial pulmonary function and the extent of surgical resection were closely related to the level of postoperative pulmonary function. Poor preoperative pulmonary function and the extent of resection are known as poor prognostic factors in NSCLC patients treated with surgery [16]. In this study, preoperative FEV1 was not significant factor affecting overall survival (log-rank, $p = 0.479$), and the extent of resection was a significant factor in univariate analysis (log-rank, $p = 0.013$). The extent of resection also did not sustain its significance in multivariate analysis ($p = 0.084$). The only significant prognostic factor was the value of FEV1 at the beginning of PORT. These findings suggest that postoperative FEV1, which is closely related to the initial FEV1 and the extent of resection, is the major determining factor for overall survival. For other variables, patients in the low FEV1 group were predominantly female, younger and mostly non-smokers compared to the high FEV1

group. Patients with NSCLC diagnosed at a young age tend to be non-smoking females, and an aggressive treatment approach, such as pneumonectomy, may be considered in such cases more often than in older patients with similar clinical stages and conditions. Patients in the low FEV1 group had good prognostic factors, such as female and younger age [18], but the OS of the low FEV1 group was significantly lower compared to the high FEV1 group (Fig. 1A). Although the proportion of administration of adjuvant chemotherapy was higher in the high FEV1 group compared to the low FEV1 group (high FEV1 versus low FEV1, 41.4% versus 19.3%, $p = 0.010$), adjuvant chemotherapy was not prognostic in multivariate analysis (yes versus no, HR = 0.65, $p = 0.226$).

Our results suggest that the level of pulmonary function at the beginning of PORT can be one of the important factors to be monitored in the setting of randomised clinical trials. Recently published meta-analyses reported that Linac-based modern PORT was associated with significantly lower risk of death and local recurrence in stage IIIA-N2 NSCLC patients [19,20]. Furthermore, these analyses suggest that the role of modern PORT should be re-evaluated in stage III patients even after receiving (neo)-adjuvant chemotherapy. For proper evaluation of the role of PORT in randomised trials, several clinical factors should be monitored because they may impact the results [21,22]. In this context, randomised trials for modern PORT can be enhanced by stratification with postoperative pulmonary function.

The results of this study are limited by the single institutional retrospective analysis, and the other pulmonary function parameters could not be evaluated due to insufficient data, particularly with regard to the carbon monoxide diffusing capacity (DLCO). We cannot exclude the possibility that disease relapses are underestimated in this study. Moreover, since extensive surgery may lead to poor pulmonary function due to advanced disease, our results may be biased by the fact that there might be more cancer deaths in patients with poor pulmonary function. Nonetheless, this study suggests that the postoperative pulmonary function (at the beginning of PORT) can be a significant prognostic factor affecting OS in patients treated with PORT. The prognostic significance of postoperative pulmonary function should be investigated in large clinical studies with more detailed parameters of pulmonary function, and it would be helpful to more precisely determine the vulnerability of patients from PORT and to minimise the risk of PORT in these patients.

In conclusion, the FEV1 at the beginning of PORT was an independent significant prognostic factor in patients with NSCLC who received PORT. Since our study was limited to those with PORT, additional studies comparing two groups with/without PORT will be helpful to understand the prognostic value of poor pulmonary function after surgery.

Conflicts of interest

None declared.

Acknowledgement

We greatly appreciate the support of Colleen Kenost and A. Grant Schissler in editing of the manuscript.

References

[1] PORT meta-analysis trialists group. Postoperative radiotherapy in non-small-cell lung cancer. Systematic review and meta-analysis of individual patient data from nine randomised controlled trials. Lancet 1998;352:257–63.
[2] Munro AJ. What now for postoperative radiotherapy for lung cancer? Lancet 1998;352:250–1.
[3] Machtay M, Lee JH, Shrager JB, Kaiser LR, Glatstein E. Risk of death from intercurrent disease is not excessively increased by modern postoperative radiotherapy for high-risk resected non-small-cell lung carcinoma. J Clin Oncol 2001;19:3912–7.
[4] Lally BE, Zelterman D, Colasanto JM, Haffty BG, Detterbeck FC, Wilson LD. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. J Clin Oncol 2006;24:2998–3006.
[5] Douillard JY, Rosell R, De Lena M, Riggi M, Hurteloup P, Mahe MA, et al. Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non-small-cell lung cancer treated with adjuvant chemotherapy: the adjuvant Navelbine International Trialist Association (ANITA) randomized trial. Int J Radiat Oncol Biol Phys 2008;72:695–701.
[6] Scotti V, Meattini I, Saieva C, Agresti B, de Luca Cardillo C, Bastiani P. Postoperative radiotherapy in N2 non-small cell lung cancer: a retrospective analysis of 175 patients. Radiother Oncol 2010;96:84–8.
[7] Zou B, Xu Y, Li T, Li W, Tang B, Zhou L, et al. A multicenter retrospective analysis of survival outcome following postoperative chemoradiotherapy in non-small-cell lung cancer patients with N2 nodal disease. Int J Radiat Oncol Biol Phys 2010;77:321–8.
[8] Dai H, Hui Z, Ji W, Liang J, Lu J, Ou G, et al. Postoperative radiotherapy for resected pathological stage IIIA-N2 non-small cell lung cancer: a retrospective study of 221 cases from a single institution. Oncologist 2011;16:641–50.
[9] Kepka L, Bujko K, Orlowski TM, Jagiello R, Salata A, Matecka-Nowak M, et al. Cardiopulmonary morbidity and quality of life in non-small cell lung cancer patients treated with or without postoperative radiotherapy. Radiother Oncol 2011;98:238–43.
[10] Lally BE, Detterbeck FC, Geiger AM, Thomas Jr CR, Machtay M, Miller AA, et al. The risk of death from heart disease in patients with non small cell lung cancer who receive postoperative radiotherapy: analysis of the surveillance, epidemiology, and end results database. Cancer 2007;110:911–7.
[11] Schunemann HJ, Dorn J, Grant BJ, Winkelstein Jr W, Trevisan M. Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the Buffalo Health Study. Chest 2000;118:656–64.
[12] Choi NC, Kanarek DJ, Grillo HC. Effect of postoperative radiotherapy on changes in pulmonary function in patients with stage II and IIIA lung carcinoma. Int J Radiat Oncol Biol Phys 1990;18:95–9.
[13] Borst GR, De Jaeger K, Belderbos JS, Burgers SA, Lebesque JV. Pulmonary function changes after radiotherapy in non-small-cell lung cancer patients with long-term disease-free survival. Int J Radiat Oncol Biol Phys 2005;62:639–44.
[14] Miles EF, Kelsey CR, Kirkpatrick JP, Marks LB. Estimating the magnitude and field-size dependence of radiotherapy-induced mortality and tumor control after postoperative radiotherapy for non-small-cell lung cancer: calculations from clinical trials. Int J Radiat Oncol Biol Phys 2007;68:1047–52.
[15] Win T, Jackson A, Sharples L, Groves AM, Wells FC, Ritchie AJ, et al. Relationship between pulmonary function and lung cancer surgical outcome. Eur Respir J 2005;25:594–9.
[16] Birim O, Kappetein AP, van Klaveren RJ, Bogers AJ. Prognostic factors in non-small cell lung cancer surgery. Eur J Surg Oncol 2006;32:12–23.
[17] Lee JH, Song EM, Sim YS, Ryu YJ, Chang JH. Forced expiratory volume in one second as a prognostic factor in advanced non-small cell lung cancer. J Thorac Oncol 2011;6:305–9.
[18] Lee JH, Machtay M, Kaiser LR, Friedberg JS, Hahn SM, McKenna MG, et al. Non-small cell lung cancer: prognostic factors in patients treated with surgery and postoperative radiation therapy. Radiology 1999;213:845–52.
[19] Billiet C, Decaluwe H, Peeters S, Vansteenkiste J, Dooms C, Haustermans K, et al. Modern post-operative radiotherapy for stage III non-small cell lung cancer may improve local control and survival: a meta-analysis. Radiother Oncol 2014;110:3–8.
[20] Patel SH, Ma Y, Wernicke AG, Nori D, Chao KS, Parashar B. Evidence supporting contemporary post-operative radiation therapy (PORT) using linear accelerators in N2 lung cancer. Lung cancer 2014;84:156–60.
[21] Shen WY, Ji J, Zuo YS, Pu J, Xu YM, Zong CD, et al. Comparison of efficacy for postoperative chemotherapy and concurrent radiochemotherapy in patients with IIIA-pN2 non-small cell lung cancer: an early closed randomized controlled trial. Radiother Oncol 2014;110:120–5.
[22] Le Pechoux C, Arriagada R, Pignon JP. Need for new powered trials to assess the role of post-operative radiotherapy for stage III non-small cell lung cancer. Radiother Oncol 2014.