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Study of The Predictors for Radiation Pneumonitis in Patient With Non-Small Cell Lung Cancer Received Radiotherapy After Pneumonectomy

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Research

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Abstract

Background: To identify the valuable predictors of grade≥2 radiation pneumonitis (RP) in patient treated with radiotherapy after pneumonectomy for non-small cell lung cancer (NSCLC); and to construct a nomogram predicting the incidence of grade≥2 RP in such patients.

Methods: We reviewed 74 patients with NSCLC received radiotherapy after pneumonectomy from 2008 to 2018. The endpoint was grade≥2 RP. Univariate and multivariate regression analysis were conducted to evaluate significant factors of grade ≥2 RP. Receiver operating characteristic (ROC) curve was used to establish optimal cutoff values and the nomogram was built to make the predictive model visualized. Descriptive analysis was performed on 5 patients with grade 3 RP.

Results: A total of 25(33.8%) patients developed grade≥2 RP and 5(6.8%) patients were grade 3 RP. V5, V10, V20, V30, MLD, PTV, and PTV/TLV were associated with the occurrence of grade≥2 RP in univariate analysis, while none of the clinical factors was significant; V5(OR,1.195;95%CI,1.082-1.319; P<0.001) and V20(OR,1.412;

95%CI,1.161-1.717; P=0.001) were the independent significant predictors by multivariate analysis and were included in the nomogram. The ROC analysis for the cutoff values for predicting grade≥2 RP were V5>22%(AUC=0.816, sensitivity:0.712, specificity:0.837) and V20>8%(AUC=0.822, sensitivity:0.681, specificity:0.828). Additionally, grade≥3 RP did not occur when V5<30%, V20<13% and MLD<751.2cGy, respectively.

Conclusions: Our study showed that V5 and V20 were independent predictors for grade≥2 RP in NSCLC patients receiving radiotherapy after pneumonectomy. Grade 3 RP did not occur whenV5<30%, V20<13% and MLD<751.2cGy, respectively. In addition, patient underwent right pneumonectomy may have a lower tolerance to radiation compared to left pneumonectomy.

Background

Radiotherapy given after surgery is an effective treatment for patients with non-small cell lung cancer (NSCLC) to improve local control and survival of the disease. It is not only applied for patients with positive surgical margins or N2 nodal involvement, but also for recurrence and second tumor in NSCLC after surgical resection[1–4]. However, patient receiving radiotherapy following previous surgery has a higher risk of developing radiation pneumonitis (RP) [5, 6]. RP as one of the most common dose-limited toxicities following thoracic radiotherapy can severely affect life quality and uncommonly result in death [7]. Inoue et al. reported the 3-year survival rates of patients, who experienced no, mild, and severe RP, were33.4%, 38.2%, and0%, respectively(P = 0.0028)[8].

Previous studies have tried to correlate the incidence of RP following lung cancer surgery with several clinical and dosimetric variables[9, 10].However, most of them were conducted on the effect of RP after pulmonary lobectomy and rarely covered pneumonectomy. Although pneumonectomy is a high-risk

procedure associated with greater morbidity and mortality, it is still necessary for a tumor located near the center of the lung invading the large vascular or main bronchus when lobectomy cannot achieve safe margin[11–13]. Compared to receive radiotherapy after lobectomy, patients underwent pneumonectomy suffered a significant decrease in overall survival[14, 15]. To date, still very few related investigations have been reported, so that the specific independent factors for RP in patients with NSCLC after pneumonectomy were unclear.

In this study, we collected data of baseline patient factors, dose-related variables and rates of RP, aiming to identify the valuable predictors of grade ≥ 2 RP in NSCLC patient received radiotherapy after pneumonectomy, and to construct a nomogram predicting the incidence of grade ≥ 2 RP in such patients.

Methods

Patients

From December 2008 to September 2018, patients with NSCLC received radiotherapy after pneumonectomy in Shanghai Chest Hospital were retrospectively reviewed. Clinical, dose–volume histogram (DVH) factors, and radiographic findings were collected from 92 patients who met the following criteria: (1) Pathologically confirmed non-small cell lung cancer. (2) Underwent pneumonectomy (left or right lung). (3) Received thoracic radiotherapy after pneumonectomy with or without chemotherapy. (4) Having available dosimetric data for radiotherapy and clinical records for at least 6 months of follow-up. The exclusion criteria included receiving stereotactic body radiotherapy (SBRT), neoadjuvant chemotherapy or radiotherapy before surgery. Finally, 74 patients were selected as the study sample.

Treatment

All patients received pneumonectomy and thoracic radiotherapy with or without chemotherapy. Radiotherapy was delivered by 3D-conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT) once a day through Monday to Friday. The median total radiation dose was 56Gy ranging from 50 to 64Gy, receiving 1.8 to 2.5Gy per fraction. Gross tumor volume (GTV) was defined as the visible recurrence tumor or lymph node and positive resection margins confirmed by postoperative pathology; Clinical tumor volume (CTV) was included the GTV plus an 0.5-0.8cm margin, or the involved mediastinal lymphatic drainage regions for multiple N2 with R0 resection. Considering respiratory movement and setup uncertainty, planning target volume (PTV) was the GTV and CTV plus 0.5-1cm margins to generate PTV-G and PTV-C, respectively. The dose-volume constraints for normal tissues were set as follows: to the spinal cord <50Gy; to the heart, V40<50%, to the esophagus, V55<50%. The chemotherapy regimens were chosen by the attending medical oncologists.

Clinical and dosimetric factors definition

Clinical factors included gender, age, smoking status, performance status, surgical laterality, tumor pathology, nodal status, tumor status, TNM stage, surgical margin, radiation dose, radiation technique, chemotherapy and the interval between chemotherapy and radiotherapy. Dosimetric factors evaluated were total lung V5/10/20/30(Vx was referred to the percentage of contralateral lung volume receiving xGy), mean lung dose (MLD), planning target volume (PTV), total lung volume (TLV) (defined as the total lung volume minus the GTV of lung tumor) and PTV/TLV (referred to the ratio of PTV to TLV).

Endpoint and Statistics

The endpoint of this study was grade≥2 RP defined in the Common Terminology Criteria for Adverse Events Version 5.0(CTCAE)[16].A diagnosis of RP was confirmed by at least two experienced radiation oncologists on the basis of clinical symptoms with radiographic infiltration within the radiation field during the first 6 months after completion of radiotherapy. This information was retrospectively extracted from the medical records by carefully reviewing all available chest radiographic images and clinical records until the last follow-up or death of the patient. All patients included in this study had follow-up CTs for at least 6 months.

Data analyses were performed using SPSS (version 23.0) and R software (version3.4.3). Univariate analysis was conducted to evaluate the influence of both clinical and dosimetric factors on grade≥2 RP risk. Due to the close correlation among dosimetric variables, we chose to generate a set multivariate model that included factors with $P<0.25$ on univariate analysis, for consistent comparisons of endpoints by dosimetric parameters being reviewed. Receiver operating characteristic (ROC) curve was used to establish optimal cutoffs which was identified its influence of RP in multivariate models, and the nomogram was built to make the predictive model visualized. To evaluate the usability of the nomogram, ROC curve and calibration plot of predictive model were performed. Descriptive analysis was performed on 5 patients with grade 3 RP. Welch's t-test was applied to analyze the subgroup stratified by surgical laterality in grade≥2 RP patients. All statistical tests were 2-sided and $P<0.05$ was considered statistical significance.

Result

A total of 74 patients receiving radiotherapy after pneumonectomy were included in the study. The indications of radiotherapy after pneumonectomy were positive multiple N2 lymph nodes in 20 cases (27.0%), positive surgical margin 12 cases (16.2%), both positive multiple N2 lymph nodes and surgical margin 11 cases (14.9%), and local chest recurrence 31 cases (41.9%). Patient characteristics were summarized in Table 1. Of all the 74 patients, 25(33.8%) developed grade ≥ 2 RP, 5 (6.8%) suffered grade 3 RP. Grade 4 and 5 RP was not occurred in these patients. The median radiation dose was 56 Gy (range 50-64Gy by 1.8–2.5 Gy per fraction) delivered by IMRT (54.1%) and 3D-CRT (45.9%). A total of 54 (73.0%) patients were treated with 2–6 cycles of sequential chemotherapy. The chemotherapy regimens consisted of vinorelbine, docetaxel, gemcitabine, pemetrexed combined with carboplatin or cisplatin. No

patient received concurrent chemotherapy during radiotherapy. The median interval between chemotherapy and radiotherapy was 3 months (1–6 months).

Table 1
Distribution of the clinical and treatment factors and their association with grade ≥ 2 radiation pneumonitis

Characteristic	No. of patients (%)	OR (95%CI)	*P*
Age		0.971(0.346–2.721)	0.955
60	50(67.6)		
≥ 60	24(32.4)		
Gender		0.250(0.029–2.156)	0.207
Male	66(89.2)		
Female	8(10.8)		
Smoking status		0.509(0.187–1.389)	0.187
Smoker	49(66.2)		
Non-smoker	25(33.8)		
ECOG PS		1.562(0.588–4.150)	0.370
0	35(47.3)		
1	39(52.7)		
Surgical laterality		0.732(0.255–2.098)	0.561
Left	50(67.6)		
Right	24(32.4)		
Nodal status		2.789(0.823–9.451)	0.099
N0-1	21(28.4)		
N2	53(71.6)		
Tumor status		1.562(0.592–4.120)	0.367
T1-2	38(51.4)		
T3-4	36(48.6)		
TNM stage		2.123(0.534–8.441)	0.285
-	14(18.6)		
-	60(82.4)		

Abbreviations: PS, performance status; RT, Radiotherapy; 3D-CRT,3D-conformal radiotherapy; IMRT, intensity-modulated radiotherapy; CMT, Chemotherapy; CT-RT time, the interval between chemotherapy and radiotherapy.

Characteristic	No. of patients (%)	OR (95%CI)	*P*
Pathology			
Adenocarcinoma	47(63.5)	1	
Squamous	16(21.6)	1.135 (0.336–3.835)	0.838
Other	11(14.9)	1.257(0.249–6.357)	0.782
RT dose, Gy		2.175(0.814–5.808)	0.121
60	39(52.7)		
≥ 60	35(47.3)		
Fraction dose, Gy		0.976(0.263–3.619)	0.971
≤ 2	62(83.8)		
2	12(16.2)		
RT technique		0.910(0.564–1.471)	0.702
3D-CRT	34(45.9)		
IMRT	40(54.1)		
CMT schedule			
Pre-RT	26(35.2)	2.200(0.614–7.886)	0.226
Post-RT	20(27.0)	1.615(0.412–6.338)	0.492
Combination	8(10.8)	1.000(0.151–6.643)	1.000
None	20(27.0)	1	
CMT with gemcitabine		0.771(0.238-2.500)	0.665
Yes	17(23.0)		
No	57(77.0)		
CMT with docetaxel		2.824(0.885–9.010)	0.080
Yes	15(20.3)		
No	57(79.7)		
CMT with vinorelbine		0.476(0.138–1.639)	0.269
Yes	18(24.3)		

Abbreviations: PS, performance status; RT, Radiotherapy; 3D-CRT,3D-conformal radiotherapy; IMRT, intensity-modulated radiotherapy; CMT, Chemotherapy; CT-RT time, the interval between chemotherapy and radiotherapy.

Characteristic	No. of patients (%)	OR (95%CI)	*P*
No	56(75.7)		
CMT course		0.972(0.291–3.253)	0.964
4	16(21.6)		
≥ 4	38(51.4)		
CMT-RT time, months		1.466(0.468–4.590)	0.511
≤ 2	22(29.7)		
2	32(43.2)		

Abbreviations: PS, performance status; RT, Radiotherapy; 3D-CRT,3D-conformal radiotherapy; IMRT, intensity-modulated radiotherapy; CMT, Chemotherapy; CT-RT time, the interval between chemotherapy and radiotherapy.

In the univariate analysis, dosimetric factors including V5, V10, V20, V30, MLD, PTV and PTV/TLV were associated with the incidence of grade ≥ 2 RP, while none of the clinical factors was significant (Tables 1 and 2). In addition, a trend was observed for nodal status (P = 0.099) and chemotherapy with docetaxel (P = 0.080). Patient gender, smoking status, nodal status, radiation dose, chemotherapy schedule and chemotherapy with docetaxel with P < 0.25 in the univariate analysis were thus included in the multivariate analysis. To avoid multicollinearity, dosimetric factors were not included in the multivariate analysis simultaneously. ROC curves were displayed for the optimal thresholds and found V5 and V20 had the better area under the ROC curve (AUC) value (Fig. 1 AUC = 0.816 and 0.822, respectively). In multivariate models, V5(OR,1.195; 95%CI,1.082–1.319; P < 0.001) and V20(OR,1.412;95%CI,1.161–1.717;

Table 2
Univariate analysis of the DVH parameters in predicting grade ≥ 2 radiation pneumonitis.

	Total patient n = 74 Median (IQR)	Patients with RP(≥2) n = 25 Median (IQR)	Patients with RP (≤ 1) n = 49 Median (IQR)	OR	(95%CI)	*p* value
V5(%)	17.0(10.0–25.0)	25.0(18.0–40.0)	12.0(8.0–20.0)	1.155	(1.075–1.240)	0.001
V10(%)	10.0(5.0–15.0)	15.5(11.5–22.0)	7.0(3.0–12.0)	1.237	(1.114–1.372)	0.001
V20(%)	3.0(1.5-7.0)	8.0(4.0–12.0)	2.0(1.0–5.0)	1.390	(1.175–1.644)	0.001
V30(%)	2.0(0.5-4.0)	4.0(1.3–6.8)	1.0(0.0–2.0)	1.579	(1.232–2.023)	0.001
MLD (cGy)	344.2(221.8-476.7)	560.5(394.2-751.8)	265.6(167.9-383.8)	1.009	(1.004–1.013)	0.001
PTV (cc)	184.3(129.5-273.9)	246.9(169.4-335.1)	174.0(115.5-238.9)	1.005	(1.001–1.009)	0.011
TLV (cc)	2042.9(1688.3-2492.8)	2209.3(1938.2-2484.9)	1986.6(1654.8-2506.7)	1.001	(1.001–1.002)	0.315
PTV/TLV (%)	9.2(5.9–14.3)	10.7(6.7–19.7)	8.3(5.0-12.8)	1.070	(1.006–1.138)	0.031

Abbreviations: DVH, dose–volume histogram; IQR, interquartile range; V5/10/20/30, Vx the percentage of the lung volume that received more than xGy, respectively; MLD, mean lung dose; PTV, planning target volume; TLV, total lung volume; PTV/TLV, the ratio of PTV to TLV.

P = 0.001) were statistically significantly associated with the risk of grade ≥ 2 RP (Table 3). The optimal cutoffs for V5 and V20 in ROC analysis revealed that V5 > 22% (sensitivity:0.712, specificity:0.837) andV20 > 8% (sensitivity:0.681, specificity:0.828) were the reasonable predictors. Then, a nomogram was built to make the predictive model of grade ≥ 2 RP visualized (Fig. 2a). It showed a satisfying AUC value was 0.862 in this patient prediction cohort (Fig. 2b). Also, the calibration curve illustrated favorable consistency between the predicted RP and the actual observation (Fig. 2c). Table 4 showed the domestic values of the 5 patients who developed grade 3 RP.

Table 3
Multivariate models including either V5 or V20 for predicting grade ≥ 2 radiation pneumonitis.

Variable	Model including V5		Model including V20	
	OR (95%CI)	*P*	OR (95%CI)	*P*
V5	1.195(1.082–1.319)	0.001	-	-
V20	-	-	1.412(1.161–1.717)	0.001
Gender	0.178(0.011–2.990)	0.231	0.234(0.018–3.111)	0.234
Male vs Female				
Smoking status	0.516(0.105–2.525)	0.414	0.485(0.110–2.147)	0.340
Smoker vs Non-smoker				
Nodal status	1.478(0.306–7.141)	0.627	1.169(0.234–5.854)	0.849
N0-1 vs N2				
RT dose, Gy	3.671(0.824–16.356)	0.088	1.962(0.512–7.521)	0.326
60 vs ≥ 60				
CMT schedule				
Pre-RT	1.450(0.215–9.773)	0.702	1.898(0.331–10.887)	0.472
Post-RT	0.312(0.036–2.703)	0.290	0.559(0.069–4.501)	0.584
Combination	0.333(0.024–4.574)	0.411	0.681(0.056–8.329)	0.764
None	1		1	
CMT with docetaxel	4.449(0.751–26.362)	0.100	2.171(0.388–12.151)	0.378
Yes vs No				

Abbreviations: V5/20, Vx the percentage of the lung volume that received more than xGy, respectively; RT, Radiotherapy; CMT, Chemotherapy.

Table 4
DVH values of the 5 patients developed grade 3 radiation pneumonitis.

Patient No.	Total dose/Gy	MLD/cGy	V5(%)	V10(%)	V20(%)	V30(%)	PTV/cc	PTV/TLV (%)
1	50	804.9	42	36	22	4	168.2	6.5
2	50	751.9	40	20	15	12	1139.3	45.7
3	60	887.0	30	24	20	10	300.1	15.1
4	60.2	751.2	32	25	13	7	310.5	19.9
5	60	1190.0	52	23	19	6	244.9	12.5

Abbreviations: V5/10/20/30, Vx the percentage of the lung volume that received more than xGy, respectively; MLD, mean lung dose; PTV, planning target volume; TLV, total lung volume; PTV/TLV, the ratio of PTV to TLV.

Since the different surgical laterality affected received radiation dose of the residual lung and heart, we carried out the subgroup analysis stratified by surgical side (Table 5). Our results showed that while there was no difference in the incidence of RP between two groups, the mean values of DVH thresholds (V5, V20, V30, MLD) in right pneumonectomy were significantly lower than left pneumonectomy in grade ≥ 2 RP patients.

Table 5
Comparison of the dosimetric parameters of grade ≥ 2 RP in patients receiving pneumonectomy between left-sided and right-sided group.

Variable	Left pneumonectomy (n = 18)	Right pneumonectomy (n = 7)	*p* value
RP incidence	36.0% (18/50)	29.2 (7/25)	0.610
MLD (cGy)	640.9 ± 219.3	375.2 ± 198.6	0.014
V5(%)	29.8 ± 11.7	19.7 ± 10.7	0.042
V10(%)	18.1 ± 6.9	11.9 ± 7.2	0.050
V20(%)	10.1 ± 5.1	5.1 ± 4.3	0.037
V30(%)	5.4 ± 3.3	2.0 ± 2.4	0.024
Radiation dose (Gy)	55.6 ± 5.1	56.0 ± 5.5	0.549
PTV (cc)	331.5 ± 240.2	309.8 ± 290.2	0.850
PTV/TLV (%)	14.6 ± 9.9	15.6 ± 13.2	0.839

Abbreviations: RP, radiation pneumonitis; V5/10/20/30, Vx the percentage of the lung volume that received more than xGy, respectively; MLD, mean lung dose; PTV, planning target volume; PTV/TLV, the ratio of PTV to TLV.

Data were presented as mean ± standard deviation (SD).

Discussion

RP is the most common complication in radiation therapy for lung cancer [5–7]. Compared to lobectomy, it could be more threatening for patient underwent pneumonectomy[14]. However, there are (to our knowledge) no published studies expressly investigating the correlation between clinical or dosimetric factors and RP in patients underwent pneumonectomy. It is clinically important to explore possible predictors to mitigate the RP incidence in this special population who had already been in high risks. Hence, we conducted a retrospective study and verified V5 and V20 as predictors for grade ≥ 2 RP. To our knowledge, this is the first study to explore the predictors of RP in patients who once received pneumonectomy.

The dosimetric limitations of radiotherapy for NSCLC patients underwent pneumonectomy mainly drew on the experience of adjuvant hemithoracic radiotherapy for patients with malignant pleural mesothelioma (MPM) following extrapleural pneumonectomy (EPP) for a long time. While considering the difference in radiation volumes between the two malignancies, the experience directly exported to NSCLC patients seemed not conformable[17]. Interestingly, the conclusions drawn from our study were consistent with published literatures on mesothelioma patients. In a cohort of 63 patients treated with IMRT after EPP at the MD Anderson Cancer Center, Rice et al. found that V20 was the sole significant factor related to pulmonary-related deaths (PRDs). Strikingly, the results showed that patient with V20 > 7% increased a 42-fold risk of PRDs and V5 was almost more than 80%[18]. Similarly, Bece et al. described 55 patients receiving hemithoracic radiotherapy, none of whom developed RP under restriction on lung V20 < 10% and V5 < 60%[19].In a review of the literature, Chi et al. reported that high incidence of severe RP was observed when V20 and V5 were higher than 7% and 60%, respectively[20]. Moreover, our findings were also correlated with several studies exploring the predictors of RP in NSCLC patients underwent surgery. For instance, in a cohort of 109 patients with NSCLC received postoperative radiotherapy (PORT), Xin Tang et al.[21]reported that ipsilateral lung V5 (iIV5 > 64.9%) was significantly associated with severe acute radiation pneumonitis (SARP, grade ≥ 3) incidence. In another retrospective report of 199 NSCLC patients treated with PORT, including 23 patients who underwent pneumonectomy, V20 > 20% was identified as one of cutoff levels for predicting grade ≥ 2 RP [22]. Analogously, Gong Y and co-workers[23] found that both ipsilateral lung V5(iV5 > 71.2%) and total lung V20(V20 > 21.4%) showed a strong statistically association with acute severe RP in lung cancer patients after surgery.

In general, our findings suggested that V5 and V20 could keep as predictors of RP for patients with NSCLC following pneumonectomy. However, the cutoff values of our study seemed lower than the above researches, and we reasoned this discrepancy on two aspects as follows. On one hand, we discreetly set lung V5 < 30% and V20 < 10% in more than 85% of radiotherapy treatment plans in consideration of the high mortality and morbidity rate of pneumonectomy. Such strict dose limits have rarely been seen in previous studies that almost excluded patients received pneumonectomy. On the other hand, prior reports mainly set grade ≥ 3 RP as the endpoint leading to a much stricter limitation. Additionally, compared to grade 2 RP, grade ≥ 3 RP with more severe clinical symptoms and poorer survival needed to be treated with steroids and oxygen. In a study of 99 patients, the grade 3 pneumonitis was in 8% patients, and all

of them died within 8 months after treatment[24]. Ascribed to the smaller case number and lower incidence, we had difficulty obtaining effective thresholds of grade 3 RP from ROC curve, therefore only descriptive results were showed. We found no incidence of grade ≥ 3 RP was observed when$V5 < 30\%$, $V20 < 13\%$ and $MLD < 751.2$ cGy, respectively. A recent publication, under restrictions on contralateral lung $V20 < 10\%$ in 32 patients with stage pIII-N2 NSCLC after pneumonectomy, there were only 2 patients developed RP[25]. This result was verified by our study with a larger population, and restrictions of V5 and V20 should be more strictly defined especially for patients with post-pneumonectomy.

In our research, 25(33.8%) patients developed grade ≥ 2 RP and 5(6.8%) patients were grade 3 RP, consistent with previously reported RP rate ranged from 15–40% in grade 2 and 2–9% in grade 3 RP[7, 26]. It seems reasonable to postulate that receiving chemotherapy could increase the risk of RP[27]. While neither chemotherapy agent nor timing was significantly associated with grade ≥ 2 RP, only a trend for chemotherapy with docetaxel ($P = 0.080$) was observed in the current study. That may be confounded by other factors related to the decision of whether using chemotherapy. Additionally, the heterogeneity of chemotherapy regimens also influenced the effect of timing and interval between chemotherapy and radiotherapy with respect to RP. In the researches by Boonyawan et al. and Kim et al., the same results were shown that chemotherapy did not increase RP risk[22, 28]. Like chemotherapy, poor pulmonary function tests (especially FEV1% predicted, DLCO) have also been classically described to increase risk of RP[29]. Because patients who undergoing pneumonectomy were routinely received pulmonary function tests before, they rarely had another test after surgery. We can almost ensure there was no significant heterogeneity in the basic lung function of these patients, as they can endure pneumonectomy after being evaluated by professional surgeons. In fact, the evaluation of pulmonary function was seldom considered in other published data if patients underwent surgery[5, 19, 20, 22, 23]. In a study involved 260 patients from two centers, poor pulmonary function at baseline was found to have no correlation with the risk of pneumonitis[30].

Right pneumonectomy was known to be associated with a higher mortality and morbidity compared with left pneumonectomy[31, 32]. Furthermore, Martin and co-workers observed that risks of perioperative death and complications were significantly higher for right pneumonectomy after preoperative radiation in patients with NSCLC[33]. Our results showed that mean DVH thresholds of developing grade ≥ 2 RP in right pneumonectomy group were significantly lower than that in left ones, but no difference in incidence between the two groups was observed. Consistent with the series of studies, it suggested that patient underwent right pneumonectomy not only suffered a worse prognosis but also had a lower tolerance to radiation. Therefore, receiving radiotherapy following right pneumonectomy should be performed only in selected patients.

As the nomogram quantifies risk by illustrating and combing the relative importance of various factors, it has been widely used in clinical assessment[34]. Thus, we developed a nomogram predicting the incidence of grade ≥ 2 RP and performed ROC curve and calibration plot to validate its prediction efficiency. The results showed that combing the values of V5 and V20 in our nomogram could be used in

practical work with less bias and better accuracy. While there may be other factors influencing the occurrence of RP, further research should be carried to improve the nomogram.

This study had several limitations. Firstly, it was limited by its retrospective nature, with inevitably uncontrolled and unobserved selection bias in patient enrollment. Secondly, there were only 5 patients with grade 3 RP due to the low incidence, leading to difficulties in making further analyses. Finally, as a single-center research, the number of cases in this study was relatively insufficient. However, to be precise, they were rare but precious. Even as one of the lung cancer centers with the largest surgery quantity in China, there were only a few dozen patients with this procedure each year, and less than 10% of them received radiotherapy afterward. Notwithstanding its limitation, this is the first study exploring the optimal predictors for RP in patient with NSCLC underwent pneumonectomy, making a certain contribution to reduce the risk of RP and improve patients' quality of life and survival.

Conclusion

Our study showed that V5 and V20 were independent risk factors for grade ≥ 2 RP in patient with NSCLC receiving radiotherapy after pneumonectomy. Grade 3 RP did not occur when$V5 < 30\%$, $V20 < 13\%$ and $MLD < 751.2$ cGy, respectively. In addition, patient underwent right pneumonectomy may have a lower tolerance to radiation compared to left pneumonectomy.

Abbreviations

RP: radiation pneumonitis; ROC: receiver operating characteristic; NSCLC: non-small cell lung cancer; DVH: dose–volume histogram; SBRT: stereotactic body radiotherapy; 3D-CRT: 3D-conformal radiotherapy; IMRT: intensity-modulated radiotherapy; GTV: gross tumor volume; CTV: clinical tumor volume; PTV: planning target volume; MLD: mean lung dose; TLV: total lung volume; MPM: malignant pleural mesothelioma; EPP: extrapleural pneumonectomy; PRDs: pulmonary-related deaths; PORT: postoperative radiotherapy; SARP: severe acute radiation pneumonitis.

Declarations

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Consent for publication: Not applicable.

Competing interests: The authors declare that they have no competing interest.

References

1. Mikell JL, Gillespie TW, Hall WA, et al. Postoperative radiotherapy is associated with better survival in non-small cell lung cancer with involved N2 lymph nodes: results of an analysis of the National Cancer Data Base. J Thorac Oncol 2015;10:462-71.
2. Liu T, Mu Y, Dang J, et al. The role of postoperative radiotherapy for completely resected pIIIA-N2 non-small cell lung cancer patients with different clinicopathological features: a systemic review and meta-analysis. J Cancer 2019;10:3941-9.
3. Feng W, Zhang Q, Fu XL, et al. The emerging outcome of postoperative radiotherapy for stage IIIA(N2) non-small cell lung cancer patients: based on the three-dimensional conformal radiotherapy technique and institutional standard clinical target volume. BMC Cancer 2015;15:348.
4. Testolin A, Favretto MS, Cora S, et al. Stereotactic body radiation therapy for a new lung cancer arising after pneumonectomy: dosimetric evaluation and pulmonary toxicity. Br J Radiol 2015;88:20150228.
5. Dang J, Li G, Zang S, et al. Comparison of risk and predictors for early radiation pneumonitis in patients with locally advanced non-small cell lung cancer treated with radiotherapy with or without surgery. Lung Cancer 2014;86:329-33.
6. Bledsoe TJ, Nath SK, Decker RH. Radiation Pneumonitis. Clin Chest Med 2017;38:201-8.
7. Jain V, Berman AT. Radiation Pneumonitis: Old Problem, New Tricks. Cancers 2018;10:222.
8. Inoue A, Kunitoh H, Sekine I, et al. Radiation pneumonitis in lung cancer patients: A retrospective study of risk factors and the long-term prognosis. Int J Radiat Oncol Biol Phys 2001;49:649-55.
9. Giuranno L, Ient J, De Ruysscher D, et al. Radiation-Induced Lung Injury (RILI). Front Oncol 2019;9:877.
10. Zhang X-J, Sun J-G, Sun J, et al. Prediction of radiation pneumonitis in lung cancer patients: a systematic review. J Cancer Res Clin Oncol 2012;138:2103-16.

11. Janet-Vendroux A, Loi M, Bobbio A, et al. Which is the Role of Pneumonectomy in the Era of Parenchymal-Sparing Procedures? Early/Long-Term Survival and Functional Results of a Single-Center Experience. Lung 2015;193:965-73.
12. Sugarbaker DJ, Haywood-Watson RJ, Wald O. Pneumonectomy for Non-Small Cell Lung Cancer. Surg Oncol Clin N Am 2016;25:533-51.
13. Skrzypczak PJ, Roszak M, Kasprzyk M, et al. Pneumonectomy - permanent injury or still effective method of treatment? Early and long-term results and quality of life after pneumonectomy due to non-small cell lung cancer. Kardiochir Torakochirurgia Pol 2019;16:7-12.
14. Kim H, Lussier YA, Noh OK, et al. Prognostic implication of pulmonary function at the beginning of postoperative radiotherapy in non-small cell lung cancer. Radiother Oncol 2014;113:374-8.
15. Albain KS, Swann RS, Rusch VR, et al. Phase III study of concurrent chemotherapy and radiotherapy (CT/RT) vs CT/RT followed by surgical resection for stage IIIA (pN2) non-small cell lung cancer (NSCLC): outcomes update of North American Intergroup 0139 (RTOG 9309). 2005 ASCO Annual Meeting Proceedings. *J Clin Oncol* 2005;23
16. Institute NC. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.Available at:https://ctepcancergov/protocolDevelopment/electronic_applications/ ctchtm#ctc_50 2017.
17. Perrot Md, Wu L, Wu M, et al. Radiotherapy for the treatment of malignant pleural mesothelioma. Lancet Oncol 2017;18:e532-e42.
18. Rice DC, Stevens CW, Correa AM, et al. Outcomes after extrapleural pneumonectomy and intensity-modulated radiation therapy for malignant pleural mesothelioma. Ann Thorac Surg 2007;84:1685-92; discussion 92-3.
19. Bece A, Tin MM, Martin D, et al. Hemithoracic radiation therapy after extrapleural pneumonectomy for malignant pleural mesothelioma: Toxicity and outcomes at an Australian institution. J Med Imaging Radiat Oncol 2015;59:355-62.
20. Alexander Chi, Zhongxing Liao, Nam P. Nguyen, et al. Intensity-Modulated Radiotherapy After Extrapleural Pneumonectomy in the Combined-Modality Treatment of Malignant Pleural Mesothelioma. J Thorac Oncol 2011;6:1132-41.
21. Tang X, Li Y, Tian X, et al. Predicting severe acute radiation pneumonitis in patients with non-small cell lung cancer receiving postoperative radiotherapy: Development and internal validation of a nomogram based on the clinical and dose-volume histogram parameters. Radiother Oncol 2019;132:197-203.
22. Boonyawan K, Gomez DR, Komaki R, et al. Clinical and Dosimetric Factors Predicting Grade ≥2 Radiation Pneumonitis After Postoperative Radiotherapy for Patients With Non-Small Cell Lung Carcinoma. Int J Radiat Oncol Biol Phys 2018;101:919-26.
23. Gong Y, Wang S, Xu Y, et al. 124P: Acute severe radiation pneumonitis in post-operation radiation therapy among patients with lung cancer: An analysis of dose-volume parameters. J Thorac Oncol 2016;11:S109-S10.

24. Graham M, Purdy J, Emami B, et al. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 1999;45:323-9.
25. Wang W, Men Y, Wang J, et al. Postoperative radiotherapy is effective in improving survival of patients with stage pIII-N2 non-small-cell lung Cancer after pneumonectomy. BMC Cancer 2019;19:478.
26. Verma V, Simone C, Werner-Wasik M. Acute and Late Toxicities of Concurrent Chemoradiotherapy for Locally-Advanced Non-Small Cell Lung Cancer. Cancers 2017;9:120.
27. Palma DA, Senan S, Tsujino K, et al. Predicting radiation pneumonitis after chemoradiation therapy for lung cancer: an international individual patient data meta-analysis. Int J Radiat Oncol Biol Phys 2013;85:444-50.
28. Tae Hyun Kim, Kwan Ho Cho, Hong Ryull Pyo, et al. Dose-volumetric Parameters for Predicting Severe Radiation Pneumonitis after Threedimensional Conformal Radiation Therapy for Lung Cancer. Radiology 2005;235:208-15.
29. Li C, Wu W, Chen N, et al. Clinical characteristics and outcomes of lung cancer patients with combined pulmonary fibrosis and emphysema: a systematic review and meta-analysis of 13 studies. J Thorac Dis 2017;9:5322-34.
30. Wang J, Cao J, Yuan S, et al. Poor baseline pulmonary function may not increase the risk of radiation-induced lung toxicity. Int J Radiat Oncol Biol Phys 2013;85:798-804.
31. Blanc K, Zaimi R, Dechartres A, et al. Early acute respiratory distress syndrome after pneumonectomy: Presentation, management, and short- and long-term outcomes. J Thorac Cardiovasc Surg 2018;156:1706-14.
32. Fernandez FG, Force SD, Pickens A, et al. Impact of laterality on early and late survival after pneumonectomy. Ann Thorac Surg 2011;92:244-9.
33. Martin J, Ginsberg RJ, Abolhoda A, et al. Morbidity and mortality after neoadjuvant therapy for lung cancer: The risks of right pneumonectomy. Ann Thorac Surg 2001;72:1149-54.
34. Wang C, Yang C, Wang W, et al. A Prognostic Nomogram for Cervical Cancer after Surgery from SEER Database. J Cancer 2018;9:3923-8.

Figures

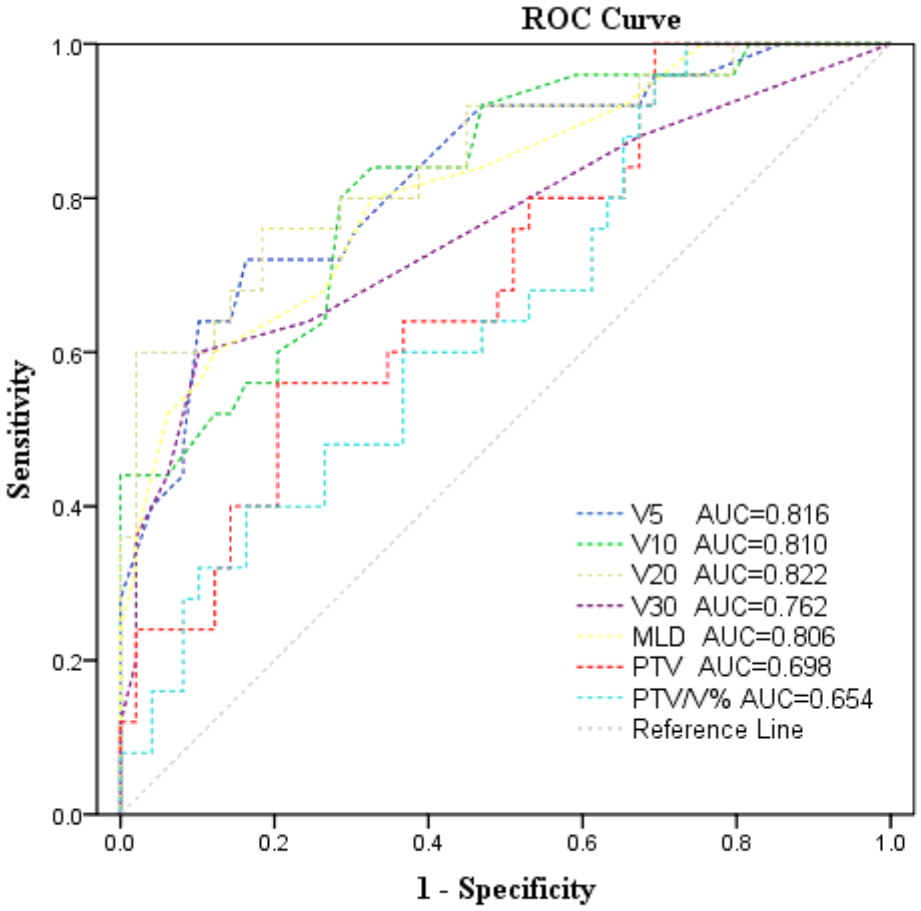

Figure 1

ROC curves of V5, V10, V20, V30, MLD, PTV, and PTV/TLV for predicting the incidence of grade≥2 radiation pneumonitis.

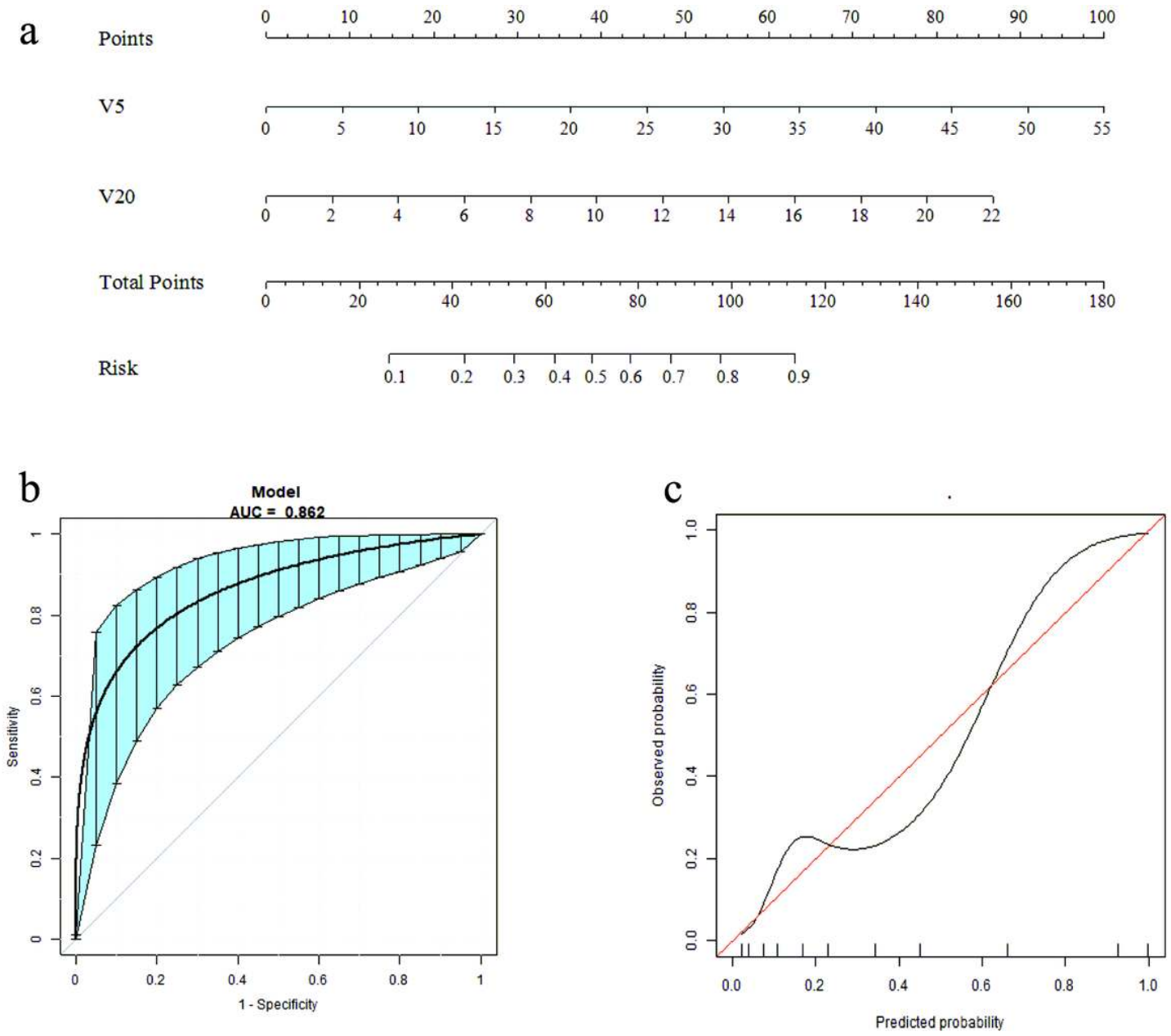

Figure 2

a. Nomogram predicting the occurrence of grade≥2 radiation pneumonitis. b. ROC curve performed to assess the performance of the radiation pneumonitis predictive nomogram. c. Calibration curves of the nomogram predicting the incidence of grade≥2 radiation pneumonitis. The x-axis and y-axis indicate the predicted and actual probabilities of developing ≥2 radiation pneumonitis, respectively. A perfect prediction would correspond the slope of diagonal 45-degree broken line.