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ORIGINAL ARTICLE

Risk of Radiation Pneumonitis after Post-lobectomy Thoracic Radiotherapy for Non-small-cell Lung Cancer

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ABSTRACT

Introduction: *Patients who had lobectomy prior to thoracic radiotherapy may be more prone to developing radiation pneumonitis (RP) given their smaller remaining lung volume. There is no consensus on the normal lung dose constraints in this population. V20 ≤30% to 35% and mean lung dose (MLD) ≤20 Gy are common dose constraints used in definitive radiotherapy for lung cancer. We aimed to determine whether V20 ≤33% and mean MLD ≤20 Gy are safe constraints with an acceptable risk of RP in post-lobectomy patients.*

Methods: *The data of all patients who received post-lobectomy thoracic radiotherapy for non-small-cell lung cancer at a single centre in Hong Kong from 2011 to 2018 were analysed retrospectively. The endpoint was Common Terminology Criteria for Adverse Events (CTCAE) grade ≥3 RP. Statistical analysis was performed to investigate whether V10 and V20 of whole lung were predictive factors for RP.*

Results: *Fifty-five patients had been treated using the dose constraints of V20 ≤33% and MLD ≤20 Gy. Three patients developed grade 5 RP. No patients had grade 3 or 4 RP. There was no significant association between the V10, V20 and grade ≥3 RP.*

Conclusion: *Our data showed that the risk of grade ≥3 RP was 5.5% in post-lobectomy patients using dose constraints of V20 ≤33% and MLD ≤20 Gy. Further prospective studies are necessary to clarify the optimal dose constraints in this population.*

Key Words: *Carcinoma, non-small-cell lung; Radiation pneumonitis; Radiotherapy, adjuvant*

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中文摘要

肺葉切除術後接受胸部放療的非小細胞肺癌患者出現放射性肺炎的風險

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引言：在胸部放療前接受肺葉切除術的患者，由於其剩餘肺體積較小，可能更易出現放射性肺炎。對於正常肺部劑量限制尚未有共識。V20 ≤30%至35%及平均肺部劑量（MLD）≤20 Gy是用於肺癌最終放療的常見劑量限制。本研究旨在確定在肺葉切除術後患者中，V20 ≤33%和MLD ≤20 Gy是否安全及可接受放射性肺炎的風險範圍。

方法：回顧分析2011年至2018年在香港單中心進行肺葉切除術後接受胸部放療的非小細胞肺癌患者的數據。終點為根據毒性標準（CTCAE）定義的≥3級放射性肺炎。進行統計分析以檢視全肺中使用V10和V20是否放射性肺炎的預測因素。

結果：55名患者接受V20 ≤33%和MLD ≤20 Gy的劑量限制。3例患者出現5級放射性肺炎。沒有患者出現3或4級放射性肺炎。V10、V20和≥3級放射性肺炎間無顯著關聯。

結論：研究結果顯示使用劑量限制為V20 ≤33%和MLD ≤20 Gy的肺葉切除術後患者，其≥3級放射性肺炎的風險為5.5%。需要進一步前瞻性研究闡明最佳劑量限制。

BACKGROUND

External beam radiotherapy plays an important role in the treatment of thoracic malignancy. Radiation pneumonitis (RP) resulting from radiation-induced injury of normal lung tissue is an important concern for thoracic oncologists. Radiotherapy after tumour resection has been found to be detrimental to survival in some early-stage lung cancer.[1] It has been suggested that any improvement of local control by radiotherapy might be offset by fatal RP in these patients.[2] Predictive factors of RP in definitive radiotherapy with or without concurrent chemotherapy include V10 and V20 of whole lung (both ipsilateral and contralateral lungs),[3] higher daily dose,[4] concurrent chemotherapy,[4] old age,[5] pre-radiotherapy forced expiratory volume,[6] and female sex.[6]

The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) suggested limiting V20 (whole lung) to ≤30% to 35% and mean lung dose (MLD) to ≤20 Gy to 23 Gy in patients with non-small-cell lung cancer who are treated with definitive radiotherapy.[7] This dose constraint may not be applicable in patients who have reduced lung volume as a result of surgical lung resection. A retrospective study showed that mesothelioma patients undergoing radiotherapy after pneumonectomy had a significantly higher risk of RP.[8] This is not surprising, given their much smaller residual lung volume. The QUANTEC recommended more stringent dose constraints of V20 <4% to 10%, V5 <60%, and MLD <8 Gy for post-pneumonectomy patients.[7]

What remains unclear is whether patients who had lobectomy, with its associated reduced lung volume, also require more stringent dose constraints. Suggested dose constraints in the post-lobectomy setting include V20 ≤35% and MLD <20 Gy.[9] It is unknown whether post-lobectomy patients could be treated using the dose constraints employed for definitive radiotherapy (V20 to ≤30%-35% and MLD ≤20-23 Gy) with an acceptable risk of RP.

A recently published retrospective study by the MD Anderson Cancer Center (MDACC) has shown that in patients who received radiotherapy after lobectomy, pneumonectomy or wedge resection, V10 >30% and V20 >20% were predictive of grade ≥ 2 RP.[10] The predictive dosimetric parameters of RP specific to post-lobectomy patients receiving radiotherapy are less clear.[10]

We performed a retrospective study to investigate the incidence of grade ≥3 RP in post-lobectomy patients treated with the dose constraints of V20 ≤33% and MLD ≤20 Gy. We hypothesised that V10 and V20 of whole lung are predictive factors of grade ≥3 RP.

METHODS

We retrospectively reviewed the clinical records of all patients who underwent postoperative radiotherapy for non-small-cell lung cancer from January 2011 to January 2018 in Tuen Mun Hospital, Hong Kong. Only data from patients that had undergone lobectomy were included. These patients were identified using the MOSAIQ® Radiation Oncology information system and the Clinical Data Analysis and Reporting System of the Hong Kong Hospital Authority.

Clinical factors including age, disease stage, performance status, smoking status, specific lobe(s) resected, tumour histology, indications for radiotherapy, dose fractionation of radiotherapy, radiotherapy technique (three-dimensional [3D] conformal or intensity-modulated radiotherapy [IMRT]), and the use of concurrent chemotherapy were recorded. Dosimetric parameters including V5, V10 and V20 of whole lung, MLD, mean heart dose, and planning target volume (PTV) size were recorded as well.

The primary endpoint of the study was grade ≥3 RP according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.[11] The diagnosis of RP was made by two clinical oncologists either at the time of presentation or retrospectively upon reviewing the clinical record. Grade 2 RP was not included as the primary endpoint, because its retrospective diagnosis can be difficult. For instance, cough or shortness of breath after radiotherapy could be attributed to underlying co-morbidities such as chronic obstructive pulmonary disease (COPD).

Fisher's exact test was used to determine if V10 ≥30% and V20 ≥20% were predictive of grade ≥3 RP. The Mann-Whitney *U* test was used to determine whether V5, V10 and V20 of whole lung, mean heart dose, MLD, and PTV size were associated with the risk of grade ≥3 RP. Receiver operating characteristic curve analysis was used to establish the optimal cut-off points for dosimetric parameters identified to be associated with grade ≥3 RP.

This retrospective study was approved by the New Territories West Research Ethics Committee (Ref NTWC/CREC/18053).

RESULTS

A total of 58 patients were identified. Three patients were excluded from analysis because of the following reasons: declined further radiotherapy after only six fractions given (n = 1), only palliative lobectomy performed for obstructive pneumonia prior to radiotherapy (n = 1), and death from extrathoracic recurrence shortly after completion of radiotherapy (n = 1). The patient with disease recurrence was found to have extensive liver metastases 2 weeks after completion of radiotherapy. He developed liver failure and succumbed to it 2 weeks later.

Among the 55 patients available for analysis, the median age was 63 years. 69.1% had adenocarcinoma; 16.4% had squamous cell carcinoma; and 7.3% had lymphoepithelial-like carcinoma. Their demographics, stage, histology and the specific lobe(s) resected are listed in Table 1.

Most patients received radiotherapy for N2 disease (52.7%). Other indications included positive / close margin, gross residual tumour, and inoperable recurrence after initial curative surgery. The mean radiotherapy dose was 54 Gy (range, 50 Gy-66 Gy). The common

Table 1. Clinical characteristics.*

	n = 55
Age, median (range), years	63 (44-78)
Male:female	41:14
ECOG performance status	
0	4 (7.3%)
1	40 (72.7%)
2	11 (20%)
Smoking status	
Active	15 (27.3%)
Never	15 (27.3%)
Ex-smoker	25 (45.4%)
Stage	
I	3 (5.5%)
II	10 (18.2%)
IIIA	38 (69.1%)
IIIB	3 (5.5%)
IV (oligometastatic)	1 (1.8%)
Histology	
Adenocarcinoma	38 (69.1%)
Squamous	9 (16.4%)
LELC	4 (7.3%)
Others	4 (7.3%)
Lobe(s) resected†	
Right upper	27 (49.1%)
Right middle	7 (12.7%)
Right lower	8 (14.5%)
Left upper	14 (25.5%)
Left lower	3 (5.5%)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; LELC = lymphoepithelial-like carcinoma.
* Data are shown as No. (%), unless otherwise specified.
† Four patients had resection of two lobes in the right lung.

dose fractionations were 60 Gy/30 fr/6 weeks (40.0%), 54 Gy/27 fr/5.5 weeks (25.5%), and 50 Gy/25 fr/5 weeks (18.2%). Other dose fractionation used for patients with confirmed recurrence after lobectomy included 66 Gy/33 fr/6.5 weeks. The details of radiotherapy are listed in Table 2.

Table 2. Radiotherapy details.

	No. (%)
Indications	
N2	29 (52.7%)
Close margin	8 (14.5%)
Positive margin	7 (12.7%)
Gross residual	7 (12.7%)
Inoperable recurrence	3 (5.5%)
Pleural invasion	1 (1.8%)
Chemotherapy	
Sequential	34 (61.8%)
Concurrent	7 (12.7%)
Nil	14 (25.5%)
Planning technique	
Three-dimensional conformal	51 (92.7%)
IMRT	4 (7.3%)
Dose fractionation	
60 Gy/30 fr/6 wk	22 (40.0%)
54 Gy/27 fr/5.5 wk	14 (25.5%)
50 Gy/25 fr/5 wk	10 (18.2%)
Others	9 (16.3%)

Abbreviation: IMRT = intensity-modulated radiotherapy.

Table 3. Dosimetric parameters.

	Median (range)
V5 (whole lung)	60% (3.5%-90.6%)
V10 (whole lung)	40% (1.7%-60.2%)
V20 (whole lung)	21.7% (1%-33.3%)
Mean lung dose (Gy)	13.0 (1.1-20.0)
Mean heart dose (Gy)	6.8 (0.3-35.1)
Planning target volume (cc)	259.5 (101-951)

All but two patients were treated using the dose constraint of V20 ≤33% and MLD ≤20 Gy. One patient had a V20 of 33.2% and one patient had a V20 of 33.3%. The V5, V10, V20 of whole lung, MLD, mean heart dose, and PTV size of all patients are listed in Table 3.

The median follow-up duration was 25 months. Patients who had undergone post-lobectomy radiotherapy in our hospital had regular follow-up by both a cardiothoracic surgeon and a clinical oncologist. History taking, physical examination, and chest X-ray were done during these clinic visits. Computed tomography (CT) scan was performed only if there was clinical suspicion for any pathology. The follow-up interval was every 3 to 4 months during the first year.

Three patients developed grade 5 RP. All three of them had V10 ≥30% and V20 ≥20%. No patient with grade 3 or 4 RP was identified. The clinical information of these three patients are listed in Table 4. The dosimetric parameters of these three patients and the remaining patients in our study are listed in Table 5.

Among the 55 patients included in the analysis, 33 had V10 ≥30% and V20 ≥20%. The risk of grade ≥3 RP was 5.5% (95% confidence interval [CI] = 1.4%-16.1%). The mortality from RP among patients with V10 ≥30% and V20 ≥20% was 9.1% (95% CI = 2.4%-25.5%).

There was no significant association between V10 ≥30%, V20 ≥20% and the occurrence of grade ≥3 RP ($p = 0.267$). No statistically significant relationship was found between grade ≥3 RP and V5 ($p = 0.393$), V10 ($p = 0.128$), or V20 of whole lung ($p = 0.767$), MLD ($p = 0.541$), or PTV size ($p = 0.436$).

All three patients with grade 5 RP were hospitalised for acute shortness of breath within 15 days after completion

Table 4. Clinical information of patients with grade 5 radiation pneumonitis.

	Patient A	Patient B	Patient C
Sex / age (years)	Male / 70	Male / 73	Male / 78
Lung lobe resected	Left upper lobe	Right lower lobe	Left upper lobe
Indication of radiotherapy	N2	N2	N2
Chemotherapy	Sequential (VP for 4 cycles then RT)	Sequential (VP for 4 cycles then RT)	Nil
Dose fractionation	50 Gy/25 fr/5 wk	50 Gy/25 fr/5 wk	60 Gy/30 fr/6 wk
Radiotherapy technique	Conformal	Conformal	Conformal
Preoperative forced expiratory volume (L)	1.79	2.23	1.60
Preoperative forced expiratory volume (% of predicted)	76%	86%	79%

Abbreviations: RT = radiotherapy; VP = vinorelbine-cisplatin.

Table 5. Dosimetric parameters of patients with grade 5 radiation pneumonitis compared with patients without grade ≥3 radiation pneumonitis.

	Patient A	Patient B	Patient C	Patients without grade ≥3 radiation pneumonitis
V5 (whole lung)	54.3%	80.5%	55.9%	52.7%
V10 (whole lung)	42.7%	56.0%	44.3%	37.4%
V20 (whole lung)	25.7%	24.4%	22.2%	21.8%
MLD (Gy)	13.6	14.0	13.5	12.7
PTV size (cc)	249	266	630	299.3

Abbreviations: MLD = mean lung dose; PTV = planning target volume.

of radiotherapy (range, 7-15 days). Two patients received a short course of corticosteroid treatment for the presumed diagnosis of acute exacerbation of COPD in the first admission to the acute medical ward and were discharged. Both were re-admitted within 10 days after the last dose of prednisolone and eventually died during the second hospitalisation. The diagnosis of RP was made by two clinical oncologists after reviewing the clinical history, imaging, and laboratory findings. In the third patient, the diagnosis of RP was made in the first admission in the oncology ward. He was discharged with a tapering dose of steroid. This patient was re-admitted on tapering doses of steroid and died during the second hospitalisation.

In summary, all three patients had deterioration of symptoms shortly after steroids were stopped or tapered to a lower dose.

The median overall survival of the 55 patients was 40 months (Figure).

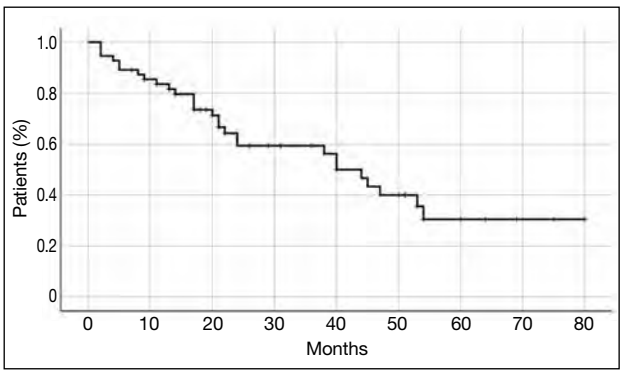

Figure. Overall survival of 55 patients who received post-lobectomy thoracic radiotherapy for non-small-cell lung cancer.

DISCUSSION

Our study demonstrated that even after restricting V20 to ≤33% and MLD to ≤20 Gy, there was still a notable risk of RP in post-lobectomy patients, with an overall mortality of 5.5%.

Consistent with the MDACC's results regarding the predictive role of V10 >30% and V20 >20%,[10] all three patients with grade 5 RP had V10 >30% and V20 >20%. However, because of the small sample size, we were not able to demonstrate the predictive value of any dosimetric parameters including V10 and V20 of whole lung.

It should be noted that 60% of our patients had V10 ≥30% and V20 ≥20%. It may not be practicable to regard V10 <30% and V20 <20% as dose constraints. Patients who have V10 ≥30% and V20 ≥20% may still be permitted to undergo thoracic radiotherapy, provided that the benefit in reducing recurrence would outweigh the higher than normal risk of RP. Nevertheless, efforts should be made to keep V10 <30% and V20 <20%. Possible strategies to reduce the risk of RP include the use of four-dimensional CT ventilation for functional avoidance and IMRT.[12]

The observation that all three patients had deterioration of symptoms and died after finishing or while tapering down steroid raised our concern. Two of our patients were initially managed by physicians as acute exacerbations of COPD with a short course of prednisolone 30 mg daily. Steroid prescribed for RP is usually of much higher dose and longer duration. Prednisone is commonly prescribed at a starting dose of at least 40 to 60 mg daily (or 1 mg/kg daily) and is slowly tapered over 8 to 12 weeks while monitoring patient symptoms.[13] We hypothesise that the prednisolone given in these two patients, for the presumed diagnosis of COPD, did suppress their pneumonitis and led to initial improvement of their symptoms. Following their discharge from hospital, the tapering or cessation of steroids might have led to rebound of RP, finally leading to repeat admission and death.

There were no patients with grade 3 or 4 RP. It can be argued that if some of the patients that ultimately developed grade 5 RP were correctly diagnosed earlier, death might not have ensued. However, this would unlikely alter the rate of grade ≥3 RP. These patients were all admitted for severe shortness of breath requiring oxygen. Their clinical conditions in their first admission already satisfied the criteria for diagnosing grade 3 RP, regardless of the subsequent treatment outcome. Nevertheless, better cooperation between physicians in the acute medical ward and oncologists may be beneficial. Earlier diagnosis of RP and the use of steroid with adequate dose and duration may potentially alter the outcome.

Our results compared less favourably with the MDACC study. In the MDACC study, only 3.3% of their patients had grade 3 RP, and no patients had grade 4 or 5 RP.[10] Their lower rate of RP may be explained by their more advanced radiotherapy technique. Only 34% of their patients were treated with 3D conformal technique. The remaining was treated with IMRT or proton therapy. In our study, 93% of patients were treated with 3D conformal technique. IMRT has been shown to carry a lower risk of RP compared with 3D conformal technique.[12] 17% of the patients in the MDACC study were treated with proton therapy, which has been shown to significantly reduce V10 and V20 compared with photon techniques.[14] Our study results are likely more applicable to patients treated with conformal radiotherapy, which is still commonly used worldwide.

In a Chinese study on RP in post-lobectomy patients, among 85 patients included for analysis, 25.9% developed grade ≥3 RP.[15] In a subsequent publication involving 177 patients from the same centre, multivariate analysis showed that total lung mean dose (>10.8 Gy), V5 to ipsilateral lung (>64.9%), and concurrent chemotherapy were significantly associated with grade ≥3 RP.[16] Based on these factors, a nomogram to predict the risk of grade ≥3 RP was generated. The incidence of grade ≥3 RP was not reported in the full paper of this subsequent publication.

A Japanese group published their finding in salvage radiotherapy in 21 patients with recurrence after surgery treated between 2000 and 2004.[17] All patients had undergone lobectomy and mediastinal lymph node dissection before developing recurrence. The mean salvage radiotherapy dose was 60 Gy (range, 46-60 Gy). Three patients developed grade ≥2 RP. Grade 3 RP developed in one patient only. The predominant beam arrangement was anteroposterior-posteroanterior followed by off-cord oblique fields. Their grade ≥3 RP risk was 4.8%. This slightly lower risk might be related to the lower dose received by normal lung. Their median V20 and MLD were 17% and 9.1 Gy, respectively. The median V20 and MLD in our study were 21.7% and 13 Gy, respectively. Our result is likely more relevant in the adjuvant setting where there is no documented disease recurrence.

Our study has some limitations. First, it was a retrospective study. Most of our patients did not have regular surveillance CT scans. A better-designed prospective study with regular CT scans would allow better reporting of RP of all grades. However, we believe that grade ≥3 RP is an objective and unequivocal outcome compared with RP of lower grades. For instance, CTCAE grade 3 pneumonitis is defined as either limiting self-care activities of daily living, causing severe symptoms, or requiring oxygen. Such clinically significant symptoms would usually prompt further investigation and lead to the diagnosis of RP even in the absence of regular follow-up cross-sectional imaging.

Second, due to the paucity of grade ≥3 RP in our study, we were not able to conduct a robust statistical analysis to identify any predictive factors. A multicentre study is likely required to have enough cases of severe RP for statistical analysis to identify the predictive factors and cut-off point.

Despite the limitations, our study has some strengths. First, our study adds to the scarce literature of RP in post-lobectomy patients receiving radiotherapy. There are few published data on the safety of post-lobectomy thoracic radiotherapy and the risk of RP using dose constraints of V20 ≤33% and MLD ≤20%.

Second, our patients had good follow-up and complete radiotherapy records. Most of our patients reside locally and all of them continued follow-up in our hospital. No patients were excluded from analysis due to incomplete radiotherapy records, likely because our patients were treated in recent years with easily accessible electronic records.

Most studies published so far about RP in post-lobectomy patients were retrospective in nature and had the inherent problems of underdiagnosis or incomplete data. The Lung ART study is an ongoing prospectively designed

multicentre study to evaluate the role of postoperative thoracic radiotherapy in completely resected N2 non-small-cell lung cancer.[18] The results will likely provide new insights in the risk of RP and the appropriate dose constraints in this group of patients.

CONCLUSION

In summary, we demonstrated that the risk of grade ≥3 RP in post-lobectomy patients was 5.5% despite fulfilling the dose-volume constraints of V20 ≤33% and MLD ≤20 Gy. The mortality from RP among patients with V10 ≥30% and V20 ≥20% was as high as 9.1%. This adds to the scarce literature on the appropriate dose constraint in post-lobectomy thoracic radiotherapy. A high index of suspicion and prompt diagnosis of RP is important for patients receiving post-lobectomy radiotherapy. Prospectively designed multicentre studies, such as the Lung ART study, can provide further information on the risk of RP and the appropriate dose-volume constraints.

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