Journal of Radiotherapy in Practice

Journal of Radiotherapy in Practice (2011)
10, 191–199

doi:10.1017/S146039691000035X

Original Article

Correlation of six-minute walk test, pulmonary function test and radiation pneumonitis in the management of carcinoma of oesophagus: A prospective pilot study

Sheh Rawat, Gaurav Kumar, Abhishek Puri, Manoj Kumar Sharma, Anjali Kakria, Pankaj Kumar

Department of Radiation Oncology, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India

Abstract

Purpose: To correlate six-minute walk test (6MWT) and pulmonary function test (PFT) with incidence of radiation pneumonitis (RP) while treating patients with oesophageal cancer with conformal radiotherapy.

Methods: Forty-five patients were selected to the study protocol. Pulmonary evaluation was done objectively by chest x-ray (CXR), 6MWT and PFT and subjectively by symptoms of cough, dyspnoea and fatigue. These tests were performed before radiation and then repeated at 1, 3, 6 and 9 months after treatment. The dose-volume histogram (DVH) was used to derive doses received by lung and organs at risk. χ^2-test was used for calculating the p value.

Results: The walk distance change (WDC) correlated with the changes in PFT values ($p = 0.001$) were done at 3 and 9 months after radiation, respectively. V30 values of $\geq$20% correlated with the incidence of acute pneumonitis ($p = 0.007$). 6MVT/vital capacity (VC) values of $\leq$4 ft/l had a correlation with the incidence of clinically symptomatic RP at 9 months.

Conclusion: 6MWT and PFT are supplementary to each other for assessing the lung function status; but their individual role in predicting RP is weak. However, they are complementary to each other in assessing the risk of radiation-induced lung dysfunction.

Keywords

Six-minute walk test; pulmonary function test; radiation pneumonitis; carcinoma of oesophagus; dosimetric parameters

INTRODUCTION

Radiation pneumonitis (RP) has always been a concern and a dose limiting factor in patients undergoing thoracic irradiation.[1–5] Various researchers have tried to formulate correlations between global lung function and treatment related to morbidities, especially RP.[6–11] It has been observed that there is an incidence of up to 30% of radiation-induced lung injury following thoracic irradiation.[12–15] Therefore, it has become essential to evaluate various predictors of radiation-induced lung injury in day to

Correspondence to: Gaurav Kumar, Rajiv Gandhi Cancer Institute and Research Centre, Sector 5, New Delhi, India. Tel: +91-11-47022222; Fax: +91-11-27051037; E-mail: dr_gauravkumar@yahoo.com

day practice of radiotherapy (RT) planning for thoracic malignancies.

Acute RP manifests as shortness of breath, cough and occasionally mild fever which usually develops 1 to 6 months after thoracic radiation. Late pulmonary toxicity presents several months to years after radiation with progressive chronic dyspnoea and is often associated with fibrosis of the irradiated lung.[16]

Researchers have correlated the risk of lung injury with various dosimetric parameters, for stratifying patients who are at greater risk of RP in the management lung and oesophageal carcinoma. Six-minute walk test (6MWT) has been an economical, reproducible and prognostic parameter for assessing the overall cardiopulmonary status of patients with parenchymal lung diseases, heart failure, sarcoidosis, chronic obstructive pulmonary diseases (COPDs) etc.[17–23] It has been seen that even small changes in the walk distance from baseline are evident in patients with a diseased lung.[17] Some have correlated pulmonary function tests (PFTs) as an assessment tool of lung status whereas others have combined PFT and 6MWT as predictor tool for RP in patients undergoing thoracic irradiation for lung carcinoma.[4,24–26]

These useful metrics lack their correlation with RT planning in predicting RP in the management of carcinoma of oesophagus. We herein conducted a prospective study by correlating the 6MWT and PFT with the incidence of acute and chronic pneumonitis while treating patients with conformal RT in oesophageal cancer.

METHODS AND MATERIALS

Patient selection

From February 2008 to April 2009, 45 patients with locally advanced oesophageal cancer were selected to the study protocol at Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India. The selection criteria for inclusion were: patients with age >18 years of either sex with properly staged histologically proven disease involving thoracic oesophagus only and with no distant metastasis. These patients should not have had prior radiation to thorax and gave an informed consent for their inclusion in the study.

Pre-treatment patient evaluation

Patient evaluation included a complete history and physical examination, performance status, history of co-morbidities like COPD, coronary artery disease, lung infection, previous lung disease/injury or any thoracic surgery, previous history of cancer, chemotherapy or radiation. Smoking habits were also recorded.

Pre-treatment pulmonary function evaluation

A baseline pulmonary function evaluation was done objectively by a chest x-ray (CXR), a 6MWT, PFT including vital capacity (VC), forced expiratory volume in 1 second (FEV1) and diffusion capacity of carbon monoxide (DLCO) and subjectively by symptoms of cough, dyspnoea and fatigue.

Walk test

6MWT was performed in accordance with the American Thoracic Society Guidelines.[27] It was performed on a flat surface with a respiratory therapist by the side of the patient. Pre- and post-test heart rate, blood pressure and oxygen saturation were recorded along with patient symptoms of cough, dyspnoea and fatigue in grades as per the common terminology criteria for adverse events version 3 (CTCAE v3).[28] This test was performed before radiation as a baseline record and then repeated at 1, 3, 6 and 9 months after treatment. The walk distance changes (WDC) from baseline were correlated with the incidence of RP and also with other patients' treatment-related parameters. The 6MWT with different PFT variable ratios were also computed as in the literature.[29]

Radiation therapy and dosimetric factors

Patients were treated with either fractionated computer-based three-dimensional non-IMRT radiation therapy planning (RTP) on Mevatron KD-2 dual energy linear accelerator (Seimens Medical Solutions) or intensity-modulated radiation therapy (IMRT) on Primus KXE-2 (Seimens Medical Solutions) to a total dose of

https://doi.org/10.1017/S146039691000035X Published online by Cambridge University Press

50 Gy at 2.0 Gy per fraction. Planning computer tomography (CT) images were taken on a CT simulator (Sensation Open Duo wide bore by Seimens Medical Solutions) after patient immobilization by a cast (Orfit Industries) in supine position with arms raised above head.

Contouring of the target volumes in oesophageal carcinoma and organs at risk (OARs) such as spinal cord, heart, lungs, liver and bilateral kidneys was done on either Oncentra Masterplan (Anatomy Modeling by Nucletron B. V.) or Coherence Oncologist (Seimens Medical Solutions). The inverse treatment planning system (TPS) of Plato Sunrise Fuel (Nucletron B. V.) was used for the purpose of beam designing and obtaining dose-volume histogram (DVH) parameters.

Treatment plan evaluation

IMRT plans usually included five coplanar beams for a total dose of 50 Gy and the RTP plan included an initial phase of 36 Gy with anterior and posterior beams and later by three oblique beams for the remaining 14 Gy treatment.

During treatment planning, besides the target volumes, the following OARs were included: lung parenchyma, heart, spinal cord, liver and bilateral kidneys. Dose constrains to the lung as well as other critical structures like spinal cord and heart were prescribed as in literature.[4,24,30]

The TPS was used to compute the DVH, which was used to determine the dose received by 5% and 95% of gross tumour volume, clinical target volume and planning target volume, the volume of lung receiving more that 5 Gy, 10 Gy, 20 Gy, 30 Gy and 50 Gy (V5, V10, V20, V30 and V50), the mean lung dose, doses received by heart, liver and kidneys.

The IMRT beams were kept to the minimum so as to increase the dose homogeneity to the target volumes and decreasing doses to the lung.[31–33]

Chemotherapy

All patients received cisplatin (CDDP)-based chemoradiotherapy. The chemotherapy protocol included either weekly CDDP only regimen or CDDP along with 5-flurouracil (5FU) as a continuous infusion over 5 days in the initial 5 days and the last 5 days of RT (phase I and phase II). The CDDP doses were 50 mg/m^2 for CDDP alone regimen and 30 mg/m^2 for CDDP along with 5FU-based regimen. The dose for 5FU was 600 mg/m^2 of continuous infusion for 96 hours on days 1–4 and days 29–34 plus cisplatin on days 1 and 29.

Surgery

Surgery was performed 4–6 weeks after completion of chemoradiotherapy in patients with resectable disease. The different techniques used were either three-field, Ivor-Lewis, or transhiatal esophagectomy.[34]

Post-treatment pulmonary function evaluation

Post-treatment pulmonary function evaluation was done objectively (CXR, PFT and 6MWT) and subjectively (symptoms of cough, dyspnoea and fatigue) at 1, 3, 6 and 9 months after treatment, as was done for pre-treatment baseline evaluations. The grading of the observed toxicity was done as per CTCAE v3.

Statistical analysis

Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) software version 16. χ^2-test was used for calculating the p value.

RESULTS

The patient and disease characteristics are shown in Table 1 and the treatment characteristics are shown in Table 2.

The baseline walk test values for different patients had a maximum of 163 m and minimum of 74 m. The mean value was 118.50 m.

The WDC characteristics from baseline to 3 and 9 months are shown in Table 3.

The WDC from baseline to 3 months was calculated. It was found that this change significantly correlated with the PFT values of VC

https://doi.org/10.1017/S146039691000035X Published online by Cambridge University Press

Table 1. *Patients and disease characteristics (n = 45)*

Patient characteristics	No. of patients
Age group	
<50 years	12
>50 years	33
Gender	
Male	29
Female	16
Performance status	
1	39
2	6
Smoking history	
Smokers	19
Non-smokers	26
Tumour location	
Upper thoracic	15
Mid thoracic	24
Lower thoracic	6
Length of disease	
1 to 5 cm	16
6 to 10 cm	26
>10 cm	3
Histopathology	
Squamous	40
Adenocarcinoma	5
Co-morbidity	
No Co-morbidity	29
DM	3
CAD/HTN	7
DM + CAD/HTN	3
COPD	3

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, hypertension.

Table 2. *Treatment-related characteristics*

Treatment characteristics	No. of patients
Technique	
IMRT	22
RTP	33
Protocol	
Radical RT+CCT	24
RTCT-Sx	21
Total Treatment Time	
<40 days	21
>41 days	24
Schedule of chemotherapy	
Weekly	35
Phases I and II	10
Surgery performed	
No	20
Yes	25
V20	
<35%	42
>35%	3

CCT, concurrent chemotherapy; IMRT, intensity-modulated radiotherapy; RT, radiotherapy; RTCT-Sx, radiotherapy with concurrent chemotherapy followed by surgery; RTP, non-IMRT computer-based radiotherapy planning.

($p = 0.02$) and DLCO ($p = 0.001$) done at 3 months after radiation. Change in DLCO values from baseline also had statistical correlation with WDC at 3 months ($p = 0.006$). Similarly, a change of $\geq$20 l in FEV1 had a correlation with WDC at 3 months which was statistically significant ($p = 0.02$). However, these had no significant correlation with incidence of acute RP ($p = 0.126$).

The V5, V10, V20, V30 and V50 calculated from the DVH were divided into various subgroups with cut-off values in the steps of 5%. From this, it was found that when V30 values were $\geq$20%, it significantly correlated with the incidence of acute pneumonitis ($p = 0.007$) as shown in Figure 1. The value of WDC at 3 months also had a positive correlation with V5 ($p = 0.02$), V30 ($p = 0.04$) and V50 ($p = 0.02$) but not with V10 ($p = 0.128$) or V20 ($p = 0.259$).

Similar correlations were computed for the incidence of chronic pneumonitis at 9 months after RT treatment. The change in DLCO values from baseline to 9 months after RT also had significant correlation with WDC, as was seen at 3 months.

The WDC were then further divided into various cut-off value subgroups. It was seen that a WDC of $\geq$50 ft correlated significantly with VC and DLCO changes at 9 months. But this correlation was not seen with the incidence of RP at 9 months.

Among the various protocol used for treatment of carcinoma of oesophagus, it was observed that the maximum decrease in walk distance was in patients who received neoadjuvant chemotherapy followed by radical chemoradiotherapy (mean = 60 ft) and this was more so at 9 months (mean = 100 ft) after RT.

On running a regression analysis using scatter plot between 6MVT and PFT ratios (Figure 2),

https://doi.org/10.1017/S146039691000035X Published online by Cambridge University Press

Table 3. WDC characteristics at 3rd and 9th month after radiation

Frequency parameter	WDC at 3 months	WDC at 9 months
Valid (*n*)	45	44
Missing (*n*)	0	1[a]
Mean (ft)	65.33	102.36
Standard deviation	42.59	51.69
Minimum (ft)	5.00	−22.00
Maximum (ft)	276.00	313.00

[a]One subject was not evaluable at 9 months, as the patient expired at 5th month after RT due to medical reasons not related to the disease or its complications.

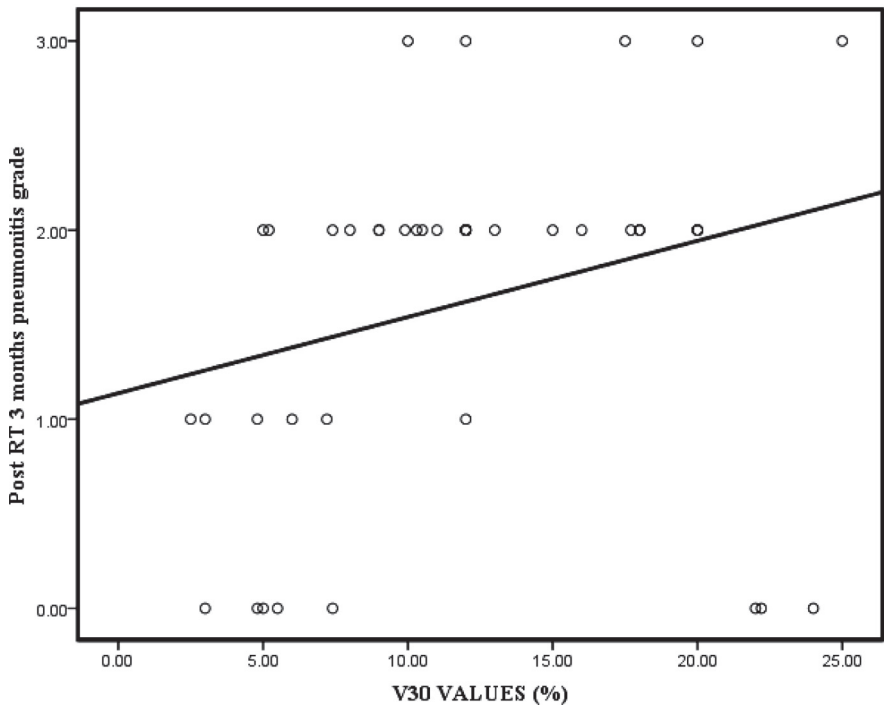

Figure 1. Relation between V30 and incidence of acute pneumonitis at 3 months. V30 ≥20% results in more incidence of pneumonitis. V30, volume of the lung receiving 30 Gy or more (%).

it was observed that 6MVT/VC values of ≤4 ft/l had a statistically significant correlation with the incidence of clinically symptomatic RP at 9 months. Patients with values more than 4 ft/l either had no or an asymptomatic grade 1 pneumonitis.

However, there was no correlation of the incidence of RP or WDC with patient and disease characteristics.

DISCUSSION

Accurate prediction of RP has always been a challenge and various surrogates used for it have been assessed in different studies. Most relevant indications for 6MWT are for evaluating the response to medical interventions in patients having cardiopulmonary diseases. It has also been used as a predictor of morbidity in patients having lung injury due to medical treatment.

https://doi.org/10.1017/S146039691000035X Published online by Cambridge University Press

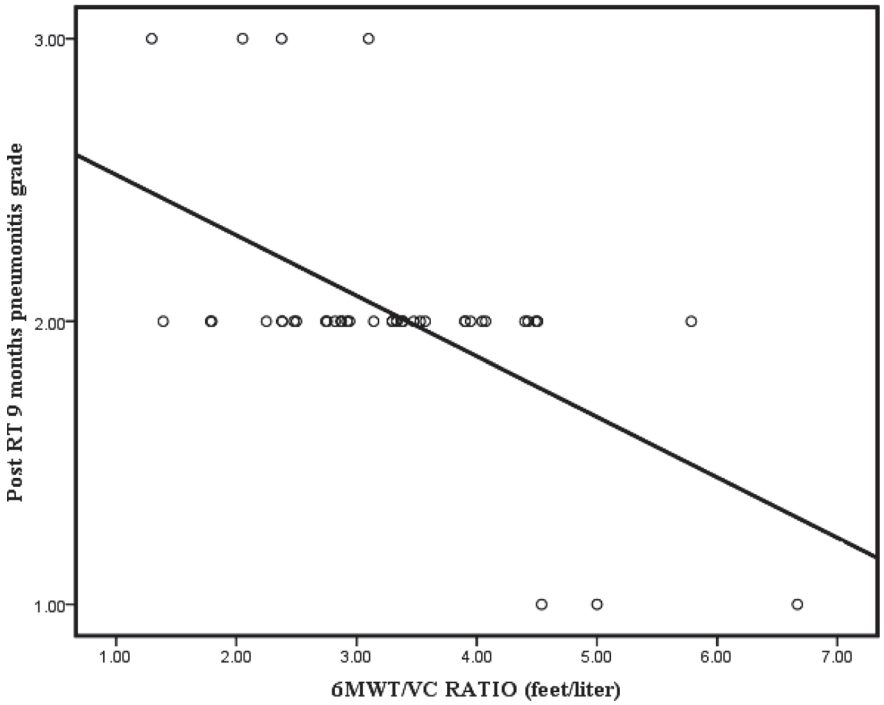

Figure 2. Relationship between 6MWT/VC ratio and incidence of pneumonitis at 9 months. Values of 6MWT/VC ≤4 ft/l, results in greater incidence of clinically symptomatic grade 2 or more pneumonitis. 6MWT, six-minute walk test value; VC, vital capacity value.

It has been observed that the average six-minute walk distance (MWD) reported in literature is between 500 and 580 m.[27] In our cohort of patients, it was seen that the value of MWD was in the range of 74–163 m.

Holland et al.[17] reported a reduction of 29–34 m in MWD in subjects with diffuse parenchymal lung disease who had no improvement after an 8-week exercise program. However, even this minimal change was statistically significant. In our study the mean change at 3 months after RT treatment was ~20 m and at 9 months, the value was 31 m. However, it did not correlate with incidence of RP.

Mao et al.[35] found a weak correlation between PFT and 6MWT and suggested that they both might be measuring different physiological functions. In our study, the WDC correlated significantly with the changes in VC and DLCO values. We also found a statistically significant correlation between ≥20 l change in FEV1 and reduction in WDC at 3 months. This indicates that when FEV1 values reduce by ≥20 l, then there is also a significant reduction in MWD, thus reflecting an overall poor cardiopulmonary status of the patient. This might suggest that they are probably measuring almost the same overall cardiopulmonary functions as far as RP in patients undergoing thoracic irradiation for carcinoma of oesophagus is concerned.

Hernando et al.[11] reported a V30 cut-off value of 18% that divided the population into a low and intermediate risk group (i.e., 6% versus 24% observed RP cases). In our study, among all the volumes of lung evaluated we also observed a similar cut off of 20% which resulted in 45% incidence of RP ($p = 0.007$) at 3 months after RT.

Miller et al.[29] calculated the predictive capacities of 6MVT and PFT for the development of RP but they found no direct correlation among different variables used. In our study, WDC of ≥50 m correlated significantly with VC and

https://doi.org/10.1017/S146039691000035X Published online by Cambridge University Press

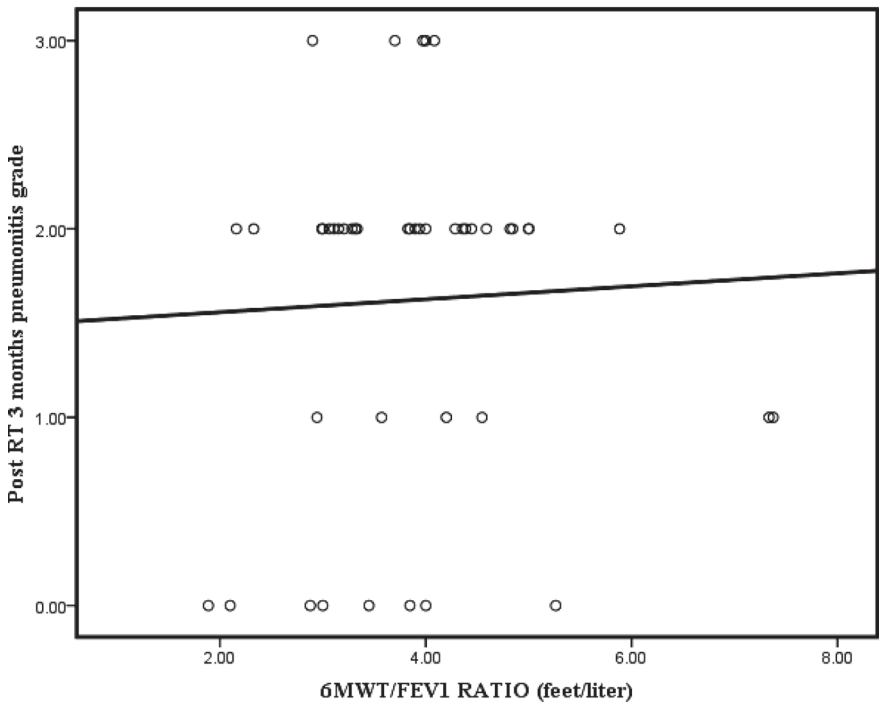

Figure 3. Relation between 6MWT/FEV1 in predicting the risk of pneumonitis. 6MWT, six-minute walk test value; FEV1, forced expiratory volume in 1 second.

DLCO components of PFT. However, these did not correlate with the incidence of RP. These researchers further stated that if the 6MWT/FEV1 ratio was $\leq$22 ft/l, then there was no increased incidence of RP. However, we could not find a strong correlation among these two variables in assessing the risk of pneumonitis as seen in scatter plot regression analysis (Figure 3).

It was observed that only 6MWT/VC values of $\leq$4 ft/l had a statistically significant correlation with the incidence of pneumonitis at 9 months than in patients with values $\geq$4 ft/l who suffered a maximum of asymptomatic grade 1 RP. This again might be suggesting that this ratio could probably be used as a predictor of chronic RP.

Our study could not establish any significant correlation of RP with either patient or any of the disease characteristics, suggesting that these parameters might be addressing to different physiologic processes as has been documented in literature in patients undergoing thoracic irradiation for lung carcinoma.[29]

CONCLUSION

Prediction of RP is a challenging task and various surrogates used for it have been assessed in different studies. WDC and changes in PFT correlated strongly at both 3 and 9 months. WDC values of $\geq$50 ft and had statistical significant correlation in change in VC and DLCO values. FEV1 values of $\geq$20 l resulted in significant reduction in MWD. This signifies that these parameters are supplementary to each other for assessing the lung function status, but their individual role in predicting both acute and chronic RP is weak.

A 6MWT/VC value of $\leq$4 ft/l can be used to predict the incidence of chronic pneumonitis, thus emphasizing the fact that, both 6MWT and PFT are complementary to each other in assessing the risk of radiation-induced lung dysfunction in the management of carcinoma of oesophagus.

These tools for RP prediction need further studies with more correlations in different

https://doi.org/10.1017/S146039691000035X Published online by Cambridge University Press

ways so that they can effectively be used in clinical practice.

References

1. Tucker SL, Liu HH, Wang S, Wei X, Liao Z, Komaki R, Cox JD, Mohan R. Dose-volume modeling of the risk of postoperative pulmonary complications among esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery. Int J Radiat Oncol Biol Phys 2006; 66:754–761.
2. Bosset JF, Gignoux M, Triboulet JP, Tiret E, Mantion G, Elias D, Lozach P, Ollier JC, Pavy JJ, Mercier M, Sahmoud T. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. N Engl J Med 1997; 337:161–167.
3. Lee HK, Vaporciyan AA, Cox JD, Tucker SL, Putnam JB Jr, Ajani JA, Liao Z, Swisher SG, Roth JA, Smythe WR, Walsh GL, Mohan R, Liu HH, Mooring D, Komaki R. Postoperative pulmonary complications after preoperative chemoradiation for esophageal carcinoma: correlation with pulmonary dose-volume histogram parameters. Int J Radiat Oncol Biol Phys 2003; 57:1317–1322.
4. Wang SL, Liao Z, Vaporciyan AA, Tucker SL, Liu H, Wei X, Swisher S, Ajani JA, Cox JD, Komaki R. Investigation of clinical and dosimetric factors associated with postoperative pulmonary complications in esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery. Int J Radiat Oncol Biol Phys 2006; 64:692–699.
5. Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, Okawara G, Rosenthal SA, Kelsen DP. INT 0123 (Radiation Therapy Oncology Group 94–05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 2002; 20:1167–1174.
6. Marks LB, Munley MT, Bentel GC, Zhou SM, Hollis D, Scarfone C, Sibley GS, Kong FM, Jirtle R, Jaszczak R, Coleman RE, Tapson V, Anscher M. Physical and biological predictors of changes in whole-lung function following thoracic irradiation. Int J Radiat Oncol Biol Phys 1997; 39:563–570.
7. Anscher MS, Kong FM, Marks LB, Bentel GC, Jirtle RL. Changes in plasma transforming growth factor beta during radiotherapy and the risk of symptomatic radiation-induced pneumonitis. Int J Radiat Oncol Biol Phys 1997; 37:253–258.
8. Anscher MS, Kong FM, Jirtle RL. The relevance of transforming growth factor beta 1 in pulmonary injury after radiation therapy. Lung Cancer 1998; 19:109–120.
9. Anscher MS, Kong FM, Andrews K, Clough R, Marks LB, Bentel G, Jirtle RL. Plasma transforming growth factor beta1 as a predictor of radiation pneumonitis. Int J Radiat Oncol Biol Phys 1998; 41:1029–1035.
10. Graham MV, Purdy JA, Emami B, Harms W, Bosch W, Lockett MA, Perez CA. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 1999; 45:323–329.
11. Hernando ML, Marks LB, Bentel GC, Zhou SM, Hollis D, Das SK, Fan M, Munley MT, Shafman TD, Anscher MS, Lind PA. Radiation-induced pulmonary toxicity: a dose-volume histogram analysis in 201 patients with lung cancer. Int J Radiat Oncol Biol Phys 2001; 51:650–659.
12. Fay M, Tan A, Fisher R, Mac Manus M, Wirth A, Ball D. Dose-volume histogram analysis as predictor of radiation pneumonitis in primary lung cancer patients treated with radiotherapy. Int J Radiat Oncol Biol Phys 2005; 61:1355–1363.
13. Kocak Z, Yu X, Zhou SM, D'Amico TA, Hollis D, Kahn D, Tisch A, Shafman TD, Marks LB. The impact of preradiotherapy surgery on radiation-induced lung injury. Clin Oncol (R Coll Radiol) 2005; 17:210–216.
14. Kwa SL, Lebesque JV, Theuws JC, Marks LB, Munley MT, Bentel G, Oetzel D, Spahn U, Graham MV, Drzymala RE, Purdy JA, Lichter AS, Martel MK, Ten Haken RK. Radiation pneumonitis as a function of mean lung dose: an analysis of pooled data of 540 patients. Int J Radiat Oncol Biol Phys 1998; 42:1–9.
15. Schraube P, Schell R, Wannenmacher M, Drings P, Flentje M. [Pneumonitis after radiotherapy of bronchial carcinoma: incidence and influencing factors]. Strahlenther Onkol 1997; 173:369–378.
16. Miller KL, Shafman TD, Marks LB. A practical approach to pulmonary risk assessment in the radiotherapy of lung cancer. Semin Radiat Oncol 2004; 14:298–307.
17. Holland AE, Hill CJ, Conron M, Munro P, McDonald CF. Small changes in six-minute walk distance are important in diffuse parenchymal lung disease. Respir Med 2009; 103:1430–1435.
18. Flaherty KR, Andrei AC, Murray S, Fraley C, Colby TV, Travis WD, Lama V, Kazerooni EA, Gross BH, Toews GB, Martinez FJ. Idiopathic pulmonary fibrosis: prognostic value of changes in physiology and six-minute-walk test. Am J Respir Crit Care Med 2006; 174:803–809.
19. Chetta A, Aiello M, Foresi A, Marangio E, D'Ippolito R, Castagnaro A, Olivieri D. Relationship between outcome measures of six-minute walk test and baseline lung function in patients with interstitial lung disease. Sarcoidosis Vasc Diffuse Lung Dis 2001; 18:170–175.
20. Baughman RP, Sparkman BK, Lower EE. Six-minute walk test and health status assessment in sarcoidosis. Chest 2007; 132:207–213.
21. Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting small differences in functional status: the Six Minute Walk test in chronic lung disease patients. Am J Respir Crit Care Med 1997; 155:1278–1282.
22. Puhan MA, Mador MJ, Held U, Goldstein R, Guyatt GH, Schünemann HJ. Interpretation of treatment changes

in 6-minute walk distance in patients with COPD. Eur Respir J 2008; 32:637–643.

23. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med 2000; 161: 646–664.
24. Tucker SL, Liu HH, Wang S, Wei X, Liao Z, Komaki R, Cox JD, Mohan R. Dose-volume modeling of the risk of postoperative pulmonary complications among esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery. Int J Radiat Oncol Biol Phys 2006; 66:754–761.
25. Kutcher GJ, Burman C. Calculation of complication probability factors for non-uniform normal tissue irradiation: the effective volume method. Int J Radiat Oncol Biol Phys 1989; 16:1623–1630.
26. Lyman JT. Complication probability as assessed from dose-volume histograms. Radiat Res Suppl 1985; 8: S13–S19.
27. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166:111–117.
28. Common Terminology Criteria For Adverse Events Version 3 (CTCAE v6). Published in August 2006.
29. Miller KL, Kocak Z, Kahn D, Zhou SM, Baydush A, Hollis D, Folz RJ, Tisch A, Clough R, Yu X, Light K, Marks LB. Preliminary report of the 6-minute walk test as a predictor of radiation-induced pulmonary toxicity. Int J Radiat Oncol Biol Phys 2005; 62:1009–1013.
30. Tsujino K, Hirota S, Endo M, Obayashi K, Kotani Y, Satouchi M, Kado T, Takada Y. Predictive value of dose-volume histogram parameters for predicting radiation pneumonitis after concurrent chemoradiation for lung cancer. Int J Radiat Oncol Biol Phys 2003; 55:110–115.
31. Nutting CM, Bedford JL, Cosgrove VP, Tait DM, Dearnaley DP, Webb S. A comparison of conformal and intensity-modulated techniques for oesophageal radiotherapy. Radiother Oncol 2001; 61:157–163.
32. Söderström S, Brahme A. Which is the most suitable number of photon beam portals in coplanar radiation therapy?. Int J Radiat Oncol Biol Phys 1995; 33:151–159.
33. Stein J, Mohan R, Wang XH, Bortfeld T, Wu Q, Preiser K, Ling CC, Schlegel W. Number and orientations of beams in intensity-modulated radiation treatments. Med Phys 1997; 24:149–160.
34. Hulscher JB, van Sandick JW, de Boer AG, Wijnhoven BP, Tijssen JG, Fockens P, Stalmeier PF, ten Kate FJ, van Dekken H, Obertop H, Tilanus HW, van Lanschot JJ. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med 2002; 347:1662–1669.
35. Mao J, Zhang J, Zhou S, Das S, Hollis DR, Folz RJ, Wong TZ, Marks LB. Updated assessment of the six-minute walk test as predictor of acute radiation-induced pneumonitis. Int J Radiat Oncol Biol Phys 2007; 67:759–767.

https://doi.org/10.1017/S146039691000035X Published online by Cambridge University Press