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Clinical characteristics and dose-volume histogram parameters associated with the development of pleural effusions in non-small cell lung cancer patients treated with chemoradiation therapy

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Abstract

Background—To investigate descriptive characteristics and dose metric (DM) parameters associated with development of pleural effusions (PIEf) in non-small cell lung cancer (NSCLC) treated with definitive chemoradiation therapy (CRT).

Materials and methods—We retrospectively assessed treatment records and follow-up imaging of 66 NSCLC patients to identify PIEf formation after CRT. PIEf association between mean heart dose (MHD), mean lung dose (MLD), heart V_5 – V_{60} (HV), and lung V_5 – V_{60} (LV) were evaluated using Cox Proportional Hazard Models.

Results—A total of 52% (34 of 66 patients) of our population developed PIEf and the actuarial rates at 6 months, 12 months, and 18 months were 7%, 30%, and 42%, respectively. Median time to diagnosis was five months (range 0.06–27 months). The majority of PIEfs were grade one (67%) and developed at a median of four (0.06–13) months, followed by grade two (15%) at a

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median 11 (5–12) months, and grade three (18%) at a median of 11 (3–27) months. On multivariate analysis, increasing HV₅–HV₅₀, LV₅–LV₅₀, MHD, and MLD were associated with greater risk of PIEf. Higher grade PIEf was also associated with higher doses of radiation to the heart, while lung DM parameters were not significantly associated with higher PIEf grades. At five-months post-CRT, MHD of 25 Gy was associated with a 100% chance of grade one PIEf, an 82% risk of grade two PIEf, and a 19% risk of grade three PIEf.

Conclusions—Post-CRT PIEf is common in NSCLC with the majority being grade one. Increasing heart and lung irradiation was associated with increased risk of PIEf. Increasing heart irradiation also correlated with development of increasing grades of PIEf. The impact of potential cardiopulmonary toxicity and resultant PIEfs after CRT requires additional study.

Introduction

Although combined chemoradiation therapy (CRT) affords a chance of cure for stage III non-small cell lung cancer (NSCLC), toxicities of this treatment can be significant [1]. Pleural effusion (PIEf) is a frequent, though poorly studied toxicity that may occur after CRT for NSCLC. Despite the observation that post-CRT PIEf commonly occurs, little has been published about this toxicity. To date, the exact mechanism of post-CRT PIEf remains unknown. Animal models and observational studies of Hodgkin's disease treated with RT suggest that the acute occurrence of PIEf is associated with pneumonitis, whereas the chronic occurrence is related to thoracic lymphatic fibrosis [2]. Currently, post-CRT PIEf has been best studied in esophageal cancer, where it is also a common toxicity of treatment and may be related to cardiac dysfunction from increasing radiation doses administered to cardiac tissues [3,4].

While there is a growing body of evidence to support cardiac toxicity as the etiology of PIEf, this may not explain all observed PIEfs. For example, malignant PIEf may be caused by direct pleural injury resulting in increased vascular permeability and lymphatic obstruction by the tumor [5]. Additionally, post-RT PIEf in breast cancer occurs simultaneously with radiation-induced parenchymal infiltrates of the lung [6]. Therefore, it is possible that pulmonary factors may also play a role in PIEf formation after CRT. Given that the majority of the clinical literature has previously focused on PIEfs occurring after RT for Hodgkin's disease and esophageal cancer [3,7], the lack of knowledge about PIEf following CRT in NSCLC remains a limitation in the attempt to avoid this possible toxicity [8]. Therefore, we sought to elucidate characteristics and dose metric (DM) criteria of post-CRT PIEf in NSCLC.

Material and methods

Patient population

We identified a cohort of 174 patients with histologically confirmed NSCLC who received definitive CRT between January 2003 and September 2012, and reviewed their records under an Institutional Review Board (IRB)-approved protocol. In total, 108 patients were excluded due to baseline PIEf before CRT (n = 40), RT alone (n = 12), or palliative RT (n = 7). Also, patients with intrathoracic recurrence (n = 30), radiation pneumonitis (n = 8) or pneumonia

(n = 1) within a 90-day window before or after PIEf were excluded. Finally, patients with malignant PIEf (n = 2) or who developed PIEf before CRT completion (n = 8) were removed. Patients with inoperable (due to medical comorbidities) stage I (n = 5) and II (n = 4) NSCLC who were treated with definitive CRT were included. Patients with stage IV oligometastatic NSCLC (n = 10), defined as a solitary extrathoracic metastasis, were included as these patients may achieve long-term survival rates comparable to stage III NSCLC [9]. Clinical staging was defined using the American Joint Committee on Cancer 6th edition criteria [10].

Treatment planning

RT was delivered through anteroposterior fields first to 40 Gy in 1.8 or 2 Gy per fraction per day followed by oblique fields to avoid the spinal cord for an additional 20–26 Gy for a typical total RT dose of 60–66 Gy. Varian Eclipse (Palo Alto, CA, USA) treatment planning version 11.4 of the analytic anisotropic algorithm was employed with tissue inhomogeneity corrections, with six- or 15-MV photons used to deliver the RT. A mixture of both three-dimensional conformal and intensity modulated radiation therapy was used. Radiation doses were prescribed to the planning target volume (PTV). The gross tumor volume (GTV) was defined as the primary tumor and any regionally involved nodes on computed tomography (CT) or pre-treatment positron emission tomography (PET) scan. PTVs were 0.5 cm beyond the clinical target volume (CTV) for patients treated with four-dimensional computed tomography (4DCT) and image guidance radiation therapy. For patients not treated with 4DCT or image guidance radiation therapy, PTV was one cm beyond the CTV. The radiation dose for the spinal cord was <50 Gy. The mean lung dose (MLD) was <20 Gy, Lung V₅ <60–70% and Lung V₂₀ <37%.

The typical chemotherapy regimen consisted of intravenous infusional drug delivery consisting of weekly paclitaxel (45 mg/m²) plus carboplatin (AUC = 2) or etoposide Day 1–5 and 29–33 (50 mg/m²) plus cisplatin Day 1, 8, 29, and 36 (50 mg/m²). RT was delivered after the administration of chemotherapy on days when both therapies were given.

Evaluation

After completion of CRT, patients were assessed at follow-up with chest CT scans, which were used to evaluate their tumor response, and for this study, to assess for the development of PIEfs. Chest CT scans were performed every three months for the first year, then every four months during years 2–3, and then every six months from years 3–5. PIEfs were retrospectively scored using the Common Terminology Criteria for Adverse Events version 4.0 (CTCAEv4.0). Grade one PIEf was defined as asymptomatic, identified by clinical or diagnostic observations only, and did not require intervention. Grade two PIEf was defined as symptomatic and required intervention (e.g. diuretics or limited therapeutic thoracentesis). Grade three PIEf was defined as symptomatic with respiratory distress and hypoxia and required surgical intervention including chest tube or pleurodesis. Patients with grade two and three PIEf who underwent diagnostic thoracentesis and cytology samples were examined for malignancy. Patients who received the same intervention multiple times (i.e. thoracentesis) were only counted once for the purposes of our analysis. However, patients who underwent multiple different interventions (i.e. thoracentesis and chest tube)

were each counted individually. PIEf was classified based on the patient's highest CTCAE score. The heart and lungs were contoured and delineated based on the RTOG guidelines put together by Kong et al. [11]. The heart was contoured to include the pericardium and the superior aspect was initiated at the bifurcation of the pulmonary trunk into the pulmonary arteries. Lungs were contoured to include all lung tissue minus the GTV. Most of the older (before 2006) plans had to be recalculated using fixed monitor units so that the dose-volume histograms could be viewed. Fraction sizes for the two phases were corrected separately using the biologically equivalent dose formula with an α/β ratio of three and subsequently summed prior to calculation of organ at risk DM parameters [12].

A DM parameter of V_x was the percentage of the total organ volume exceeding \times radiation dose. DM parameters were collected in increasing increments of 10 for heart V_{10} – V_{60} (HV), and lung V_{10} – V_{60} (LV), in addition to HV_5 , LV_5 , mean heart dose (MHD), and MLD. Baseline CT scans were retrospectively reviewed to identify tumors involving the pleura or chest wall [13].

Statistical analysis

Population and PIEf characteristics of patients were summarized using frequencies and proportions. The primary end point was time to development of PIEf. Time was measured from the end of CRT to development of PIEf or last known follow-up. Patients lost to follow-up or who did not develop PIEf were censored. Univariate analyses to identify predictors associated with PIEf were conducted using Cox Proportional Hazard Models. Multivariate models were then built based on one DM variable, and the most significant clinical variables on univariate analysis [tumor volume (TVol) and pleural involvement of the tumor (PI)]. Estimation of hazard ratio (HR) was reported along with 95% confidence intervals. Proportional hazard assumptions were checked by plotting Schoenfeld residuals. The secondary end point was time to development of different grades of PIEf. For that, we used a marginal approach proposed by Wei, Lin and Weissfeld (WLW) [14] to fit models to study an association of PIEf grade with each of the DM parameters to handle recurrent events in patients. To address correlations in times among different grades of PIEf, inferences were based on the robust sandwich variance estimate. The dose-response functions were drawn based on the fitted models using the WLW approach. We calculated the probability of developing different grade of PIEfs for varying values of DM at 5 and 10 months after CRT (these were median times to development of grade one, two and three PIEf). All analyses were conducted using SAS v9.4 (SAS Institute, Cary, NC) and $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics of all 66 patients are shown in Table 1. Median follow-up time was 13 months (range 0.2–73). Median age at diagnosis was 67 years. The majority of patients were male (56%), caucasian (80%), and had stage III disease (70%). Median TVol was 95 cm^3 . Median RT dose was 63 Gy and, when corrected for fraction size, 74 Gy.

In this population, 52% (34 of 66) of patients developed PIEf. The actuarial rates of PIEf at 6, 12 and 18 months were 7%, 30%, and 42%, respectively. Median time to diagnosis of

PIEf was five months (range 0.06–27 months). Grade one, two, and three PIEf occurred after CRT at a median of four months (0.06–13 months), 11 months (5–12 months), and 11 months (3–27 months), respectively. Descriptive characteristics of PIEfs are seen in Table 2. Most PIEfs were CTCAE grade one (67%, n = 23), ipsilateral to the primary tumor volume (79%, n = 27), and not loculated (88%, n = 30). Median TVol did not differ between grade one (138.6 cm³), grade two (91.3 cm³) and grade three (91.5 cm³) PIEf (p = 0.86). Only six patients who developed PIEf experienced new symptoms before diagnosis. Five patients experienced shortness of breath and one had cough. Symptoms were more common with larger PIEf. For example, three of the five patients who complained of shortness of breath had grade three PIEf while one had grade two PIEf. The patient with cough also had grade three PIEf.

Thoracentesis was performed in 26% (n = 9) of patients. Of those with available cytology, three PIEfs were exudative and two were transudative. For grade two PIEfs, interventions included PleurX catheter placement (6%, n = 2) at a median time of 16 months (14–18 months), chest tube placement (14%, n = 5) at a median time of 11 months (3–27 months), and chest tube pleurodesis (1.5%, n = 1) or VATS pleurodesis (1.5%, n = 1) at seven and three months, respectively. Four of the nine patients who underwent a thoracentesis did not have any further intervention. Two patients who underwent chest tube placement did not initially have a thoracentesis, and one patient who received a PleurX catheter did not initially have a thoracentesis.

On univariate analysis, factors significantly associated with increased risk of PIEf were HV₅–HV₆₀, LV₅–LV₅₀, MHD, and MLD (Supplemental Table, available online at <http://www.informahealthcare.com>). PI [HR 1.82; 95% CI (0.88–3.74); p = 0.10] trended towards significance.

On multivariate analysis (Table 3), HV₅–HV₅₀, LV₅–LV₅₀, MHD and MLD were all associated with increased risk of PIEf when adjusted for PI and TVol. For most models including a lung DM parameter, PI was also associated with increased risk of PIEf. For example, in the model containing LV₂₀, PI had a HR of 4.37 (95% CI 1.68–11.35; p = 0.002).

To identify DM parameters associated with different grades of PIEf, we used a marginal model to treat development of different grades of PIEf as different events. On univariate analysis, LV₅–LV₃₀ was associated with grade one PIEf, but not grade two or three PIEf. DM parameters greater than LV₃₀ did not correlate with any grade PIEf. However, HV₅–HV₆₀ and well as MHD were associated with development of grade one, two and three PIEf (Figure 1–3). We also calculated the risk of developing PIEf at a certain fixed time point. At 5-months post-CRT (median time to development of PIEf), MHD of 25 Gy was associated with a 100% chance of grade one PIEf, an 82% risk of grade two PIEf, and a 19% risk of grade three PIEf. At 10-months post-CRT (median time to development of grade two and three PIEf), MHD of 25 Gy was associated with 100% chance of grade one or two PIEf and an 18% chance of grade three PIEf. Risk of developing PIEf at other DM values can be seen in Table 4.

Discussion

Here we demonstrate that 52% of our patient population treated with CRT for NSCLC experienced PIEf at a median of 5 months after CRT. We also demonstrate that increasing doses of radiation to the heart and lungs during CRT were associated with development of PIEf after therapy. Higher grade PIEf was also associated with higher doses of radiation to the heart, unlike lung DM parameters. In total 67% of PIEfs were CTCAE grade one and 79% developed ipsilateral to the primary tumor volume. We were also able to calculate the probability of developing different grade PIEf based on radiation dose to the heart.

The etiology of PIEf is likely related to cardiopulmonary toxicity as demonstrated by the relationships between dose to the heart and lungs and the risk of PIEf. Given that cardiac dysfunction tends to cause transudative PIEfs and pulmonary injury tends to cause exudative PIEfs [15], the observation that our population experienced a mix of exudative and transudative PIEfs suggests that both pulmonary and cardiac factors could have played a role in PIEf development. From a pathological standpoint, irradiation of cardiac tissue can result in long-term injury including accelerated atherosclerosis, pericardial and myocardial fibrosis, conduction abnormalities, injury to cardiac valves, and possibly radiation pneumonitis [16–18]. Also, lung irradiation can cause pneumonitis, fibrosis, and vascular remodeling leading to pulmonary hypertension and cardiopulmonary dysfunction [19].

Hatakenaka et al. [20] demonstrated that CRT in esophageal cancer is associated with acute cardiac toxicity before treatment completion. Distal esophageal cancers demonstrated the greatest cardiac dysfunction through 40 Gy of treatment, possibly due to higher radiation dose to the left ventricle. Even though proximal tumors received lower doses of radiation to the left ventricle, they also demonstrated cardiac dysfunction before CRT completion. Furthermore, Gomez et al. studied esophageal cancer patients and found that brain natriuretic peptide, which is released in response to excessive stretching of heart muscle cells, increased from pre-treatment values at the end of CRT and first follow-up period [21]. Shirai et al. reported 35% of esophageal cancer patients who were treated with RT developed PIEf and correlated the occurrence of PIEf to HV₅–HV₆₀, LV₅₀, LV₆₀, and MHD. They also found that while only one third of patients had distal esophageal cancers, two thirds of PIEfs occurred in distal tumors, suggesting that cardiac rather than pulmonary parenchyma irradiation is the source of PIEf. Additionally, preexisting cardiac disease and co-irradiation of the heart may increase the risk of radiation-induced lung toxicity and PIEf formation [22]. Taken together, these findings provide support for a likely cardiopulmonary etiology of radiation-induced PIEf formation.

In our patient population, the proportion of patients with NSCLC receiving CRT who developed PIEf was 52%, most of which were grade one (67%). Our proportion appears elevated compared to other reports; however, all patients with malignant or infectious etiology of their PIEf were excluded, as were those who developed PIEf during CRT. Kwint et al. [23] reported PIEf to occur in 14% of lung cancer patients receiving RT. However, inclusion criteria for this study were total tumor dose \geq 44 Gy. Their study also contained a mixture of CRT and RT alone compared to our study, which included only CRT. Additionally, patient follow-up time was only six weeks after RT. However, our study

demonstrated PIEf formation up to 27 months after CRT, indicating the need for longer-term follow-up to determine the true incidence of PIEf.

In our study 21%, 41%, 14%, and 18% of patients had diabetes, hypertension, coronary artery disease, and hypercholesterolemia, respectively. In this population of NSCLC, 87% of patients were smokers, which could contribute to an underestimation of underlying cardiac disease. Such unidentified underlying cardiac disease could predispose patients to added cardiac toxicity with even lower doses of radiation. Finally, PI of the tumor was a borderline risk factor for PIEf development in our study and may support the previously proposed notion that pleural injury can be caused by increased vascular permeability and lymphatic blockage by tumor [5]. Along with underlying cardiac morbidities in our patients, these factors may help to explain the higher proportion of PIEf we observed in this study.

One weakness of this study is that the majority of patients did not undergo thoracentesis because most PIEfs were grade one. Therefore, the exact cytological composition of most of our patients' PIEfs is unknown. Additionally, the sensitivity of diagnosing malignant PIEf through a single thoracentesis ranges from 40% to 87% [24,25], so cytological evaluation of PIEf carries a risk for false negativity. Therefore, it is possible some malignant PIEf were included in our analysis.

Our results show that increasing radiation doses to the cardiac tissue and lung parenchyma are associated with higher risk of developing PIEf in NSCLC patients after definitive CRT. Based on our findings, continued efforts to reduce RT doses to the cardiac and pulmonary tissue are warranted in an attempt to reduce the incidence of PIEf. Additional studies evaluating functional outcomes of the heart and lungs after CRT in relation to their radiation doses are necessary.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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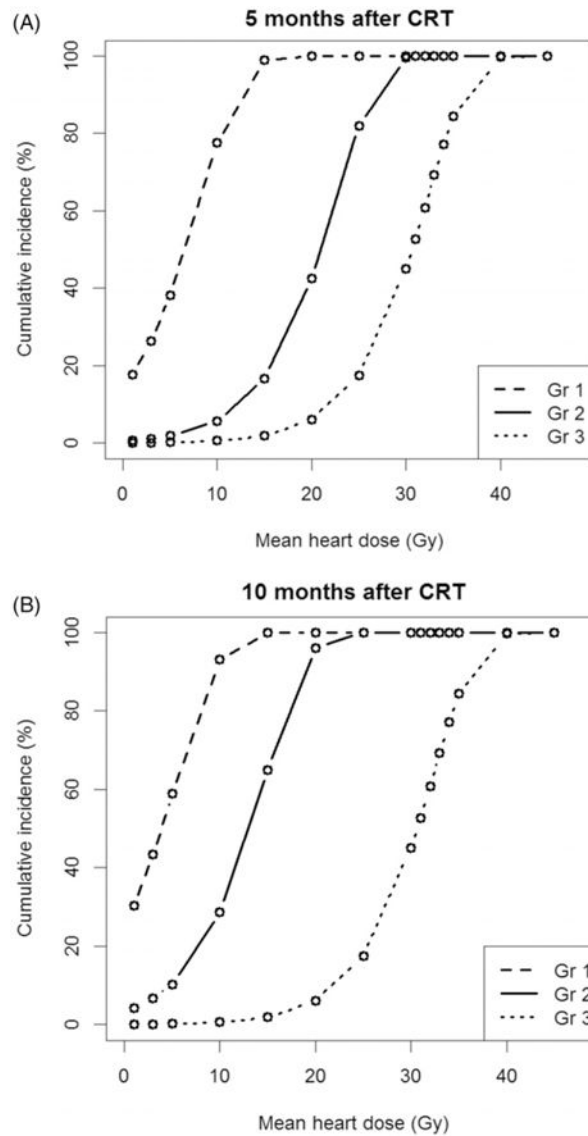


Figure 1. Risk of PIEf by grade based on Mean Heart Dose. (A) 5-months post-chemoradiation. (B) 10-months post-chemoradiation. Median mean heart dose: 16 Gy; Minimum mean heart dose: 0 Gy; Maximum mean heart dose: 48.7 Gy. CRT: chemoradiation therapy; Gr: grade; Gy: gray.

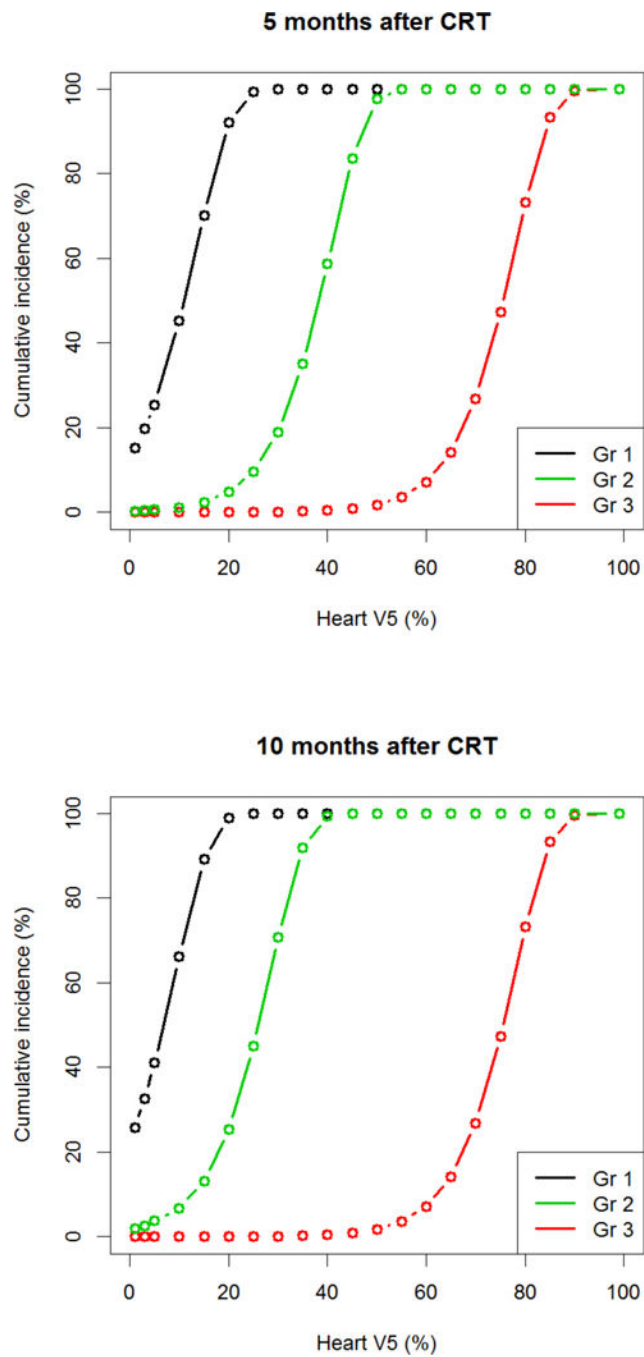


Figure 2. Risk of PIEf by grade based on Heart V₅. (A) 5-months post-chemoradiation. (B) 10-months post-chemoradiation. Median heart V₅: 44.5%; minimum heart V₅: 0%; maximum heart V₅: 100%. CRT: chemoradiation therapy; Gr: grade; Gy: gray.

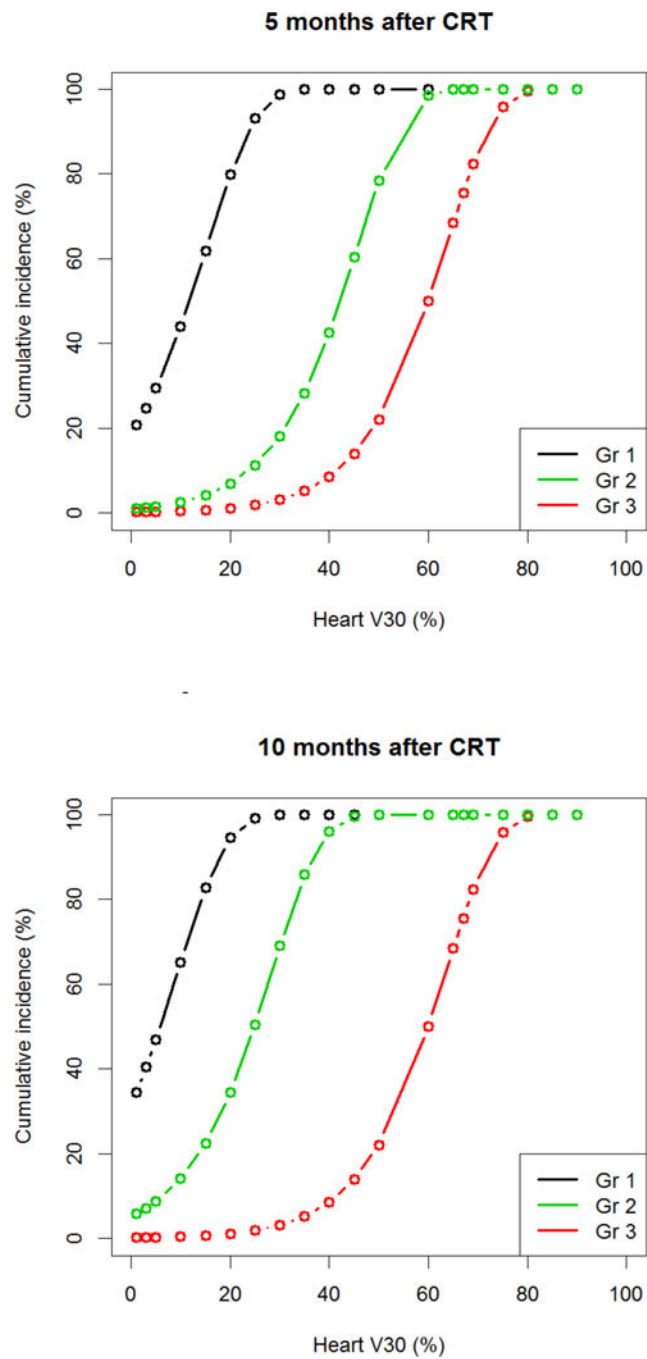


Figure 3. Risk of PLEf by grade based on Heart V₃₀. (A) 5-months post-chemoradiation. (B) 10-months post-chemoradiation. Median heart V₃₀: 20.6%; minimum heart V₃₀: 0%; maximum heart V₃₀: 92.6%. CRT: chemoradiation therapy; Gr: grade; Gy: gray.

Table 1

Baseline characteristics of patients.

Characteristics	Overall frequency	Percentage (%)
Gender		
Male	37	56
Female	29	44
Zubrod PS		
N/A	9	14
0	37	56
1	15	23
2	4	6
3	1	1
Race		
Caucasian	53	80
African	6	9
American	4	6
Hispanic	2	3
Asian	1	2
Hx of smoking		
Yes	57	86
No	9	14
Still smoking		
Yes	11	17
No	55	83
T stage		
N/A	3	5
T0	1	2
T1	9	14
T2	21	32
T3	16	24
T4	14	20
TX	2	3
N stage		
N/A	3	5
N0	7	11
N1	4	6
N2	22	33
N3	26	39
NX	4	6
Clinical stage		
IA	3	5
IB	2	3

Characteristics	Overall frequency	Percentage (%)
IIA	2	3
IIB	2	3
III	1	2
IIIA	15	22
IIIB	32	48
IV	9	14
Modality		
3DCRT	54	82
IMRT	5	8
Mix	7	10
Median TVol	95 cm ³	
Median dose	63 Gy	

IMRT: intensity modulated radiation therapy; Mix: a combination of 3DCRT and IMRT planning; PIEf: pleural effusion; PS: performance status; TVol: tumor volume; 3DCRT: three dimensional conformal radiation therapy; Hx: history; N/A: not available.

Table 2

Descriptive characteristics of 36 patients who developed pleural effusion.

Characteristic	Frequency (%)
CTCAE Grade	
Grade 1	23 (67)
Grade 2	5 (15)
Grade 3	6 (18)
Effusion site	
Ipsilateral	27 (79)
Contralateral	2 (6)
Bilateral	5 (15)
Thoracentesis	
Yes	9 (26)
No	25 (74)
Pleurodesis	
Chest tube	1 (3)
VATS	1 (3)
No	32 (94)
PleurX catheter	
Yes	2 (6)
No	32 (94)
Chest tube	
Yes	5 (14)
No	31 (86)
Loculation	
Yes	4 (12)
No	30 (88)
PIEf type	
Transudative	2 (40.0)
Exudative	3 (60.0)

PIEf: pleural effusion; CTCAE: Common Terminology Criteria for Adverse Events; VATS: Video-assisted thoroscopic surgery.

Table 3

Multivariate analysis of adjusted risk for PIEf development by dose metric parameter.

Variable	Hazard ratio (95% CI)
Lung V60	1.04 (0.97–1.11)
Lung V50	1.10 (1.02–1.17)
Lung V40	1.12 (1.05–1.18)
Lung V30	1.12 (1.05–1.19)
Lung V20	1.10 (1.04–1.15)
Lung V10	1.06 (1.02–1.10)
Lung V5	1.05 (1.02–1.08)
Mean lung dose	1.26 (1.12–1.41)
Heart V60	1.03 (0.99–1.06)
Heart V50	1.03 (1.004–1.05)
Heart V40	1.02 (1.002–1.04)
Heart V30	1.01 (1.0–1.03)
Heart V20	1.02 (1.003–1.03)
Heart V10	1.02 (1.004–1.03)
Heart V5	1.02 (1.01–1.03)
Mean heart dose	1.03 (1.01–1.06)

Models included one dosimetric parameter, pleural involvement of the tumor, and tumor volume. Each dose metric parameter was tested (one at a time) in a multivariate model adjusted for pleural involvement of the tumor and tumor volume.

PIEf: pleural effusion.

* p-Value based on Cox Proportional Hazard Model.

Table 4

Risk of developing PIEf at 5- and 10-months post-CRT.

	5-months post-CRT (%)	10-months post-CRT (%)
MHD of 25 Gy		
Grade 1 PIEf	100	100
Grade 2 PIEf	82	100
Grade 3 PIEf	19	18
HV ₅ of 65%		
Grade 1 PIEf	100	100
Grade 2 PIEf	100	100
Grade 3 PIEf	14	14
HV ₃₀ of 45%		
Grade 1 PIEf	100	100
Grade 2 PIEf	60	100
Grade 3 PIEf	14	14

CRT: chemoradiation therapy; HV: heart; MHD: mean heart dose; PIEf: pleural effusion.

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Table 5

Univariate analysis of adjusted risk for PIEf development by dose metric parameter

Variable	Hazard ratio [95% CI]	p-value
Tumor volume	1.001 [1.0 – 1.003]	0.13
Total dose	1.0 [0.99 – 1.001]	0.89
Pleural involvement	1.82 [0.88 – 3.74]	0.10
Gender (male)	0.86 [0.44 – 1.69]	0.66
Age	1.007 [0.97 – 1.04]	0.72
T stage		
T2	2.28 [0.75 – 6.93]	0.15
T3	1.05 [0.30 – 3.74]	0.93
T4	1.91 [0.55 – 6.61]	0.30
Chemotherapy		
Carboplatin	0.98 [0.34 – 2.87]	0.97
Cisplatin	0.89 [0.27 – 2.95]	0.89
Lung V60	1.03 [0.97 – 1.01]	0.27
Lung V50	1.07 [1.02 – 1.13]	0.009
Lung V40	1.08 [1.03 – 1.14]	0.0009
Lung V30	1.08 [1.03 – 1.14]	0.002
Lung V20	1.07 [1.03 – 1.12]	0.002
Lung V10	1.05 [1.02 – 1.08]	0.002
Lung V5	1.04 [1.01 – 1.06]	0.003
Mean Lung Dose	1.16 [1.07 – 1.27]	0.0006
Heart V60	1.04 [1.001 – 1.07]	0.04
Heart V50	1.03 [1.01 – 1.06]	0.0054
Heart V40	1.02 [1.006 – 1.04]	0.006
Heart V30	1.02 [1.004 – 1.03]	0.008
Heart V20	1.02 [1.007 – 1.03]	0.0018
Heart V10	1.02 [1.008 – 1.03]	0.001
Heart V5	1.02 [1.007 – 1.03]	0.0016
Mean Heart Dose	1.04 [1.02 – 1.07]	0.0018