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Doses of radiation to the pericardium, instead of heart, are significant for survival in patients with non-small cell lung cancer

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Abstract

Background and purpose: Higher cardiac dose was associated with worse overall survival in the RTOG0617 study. Pericardial effusion (PCE) is a common cardiac complication of thoracic radiation therapy (RT). We investigated whether doses of radiation to the heart and pericardium are associated with PCE and overall survival in patients treated with thoracic radiation for non-small cell lung cancer (NSCLC).

Materials and Methods: A total of 94 patients with medically inoperable/unresectable NSCLC treated with definitive RT in prospective studies were reviewed for this secondary analysis. Heart and pericardium were contoured consistently according to the RTOG1106 Atlas, with the great vessels and thymus of the upper mediastinal structures included in the upper part of pericardium,

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only heart chambers included in the heart structure. Clinical factors and dose-volume parameters associated with PCE or survival were identified via Cox proportional hazards modeling. The risk of PCE and death were mapped using DVH atlases.

Results: Median follow-up for surviving patients was 58 months. The overall rate of PCE was 40.4%. On multivariable analysis, dosimetric factors of heart and pericardium were significantly associated with the risk of PCE. Pericardial V30 and V55 were significantly correlated with overall survival, but presence of PCE and heart dosimetric factors were not.

Conclusion: PCE was associated with both heart and pericardial doses. The significance of pericardial dosimetric parameters, but not heart chamber parameters, on survival suggests the potential significance of radiation damage to the cranial region of pericardium.

Keywords

NSCLC; Pericardial dose; Heart dose; Pericardial effusion

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide (1). Approximately two-thirds of lung cancer patients receive radiation therapy (RT) at least once during the course of treatment with either definitive or palliative intent (2). Biological and clinical evidence suggest that a higher radiation dose might provide better local tumor control and may prolong survival in patients with non-small cell lung cancer (NSCLC) (3). However, delivery of higher dose RT also increases the risk of radiation-related damage to organs at risk (OARs), including the heart and pericardium (4, 5). Pericardial effusion (PCE) is one of the common cardiac toxicity after RT and the rate of PCE has been reported to range from 20 to 45% (6–8). Unfortunately, studies on PCE and its impact on survival are limited in NSCLC. It is unclear whether high-dose radiation to the heart or pericardium contributes to poor survival in patients treated with concurrent chemoradiotherapy. RTOG 0617 reported that the higher radiation dose (74 Gy) arm had a significantly inferior survival and notably higher number of treatment-related deaths, compared to the standard-dose arm (60 Gy) (9, 10). Un-reported toxicity such as PCE from higher dose irradiation of the heart and pericardium may partially contribute to these results (9–11). Several studies have confirmed the association of heart dose with inferior survival (12, 13), but other studies did not find a significant association (14, 15). We hypothesized that high-dose radiation to the heart/pericardium has a negative impact on the survival of NSCLC patients treated with radiation. Specifically, this study aimed to investigate whether: 1) the dosimetry of the heart and/or pericardium is associated with PCE; 2) the presence of PCE or dosimetric factors for the heart and/or pericardium correlate with overall survival in patients treated with thoracic RT.

Materials and Methods

Study population

This study included consecutive patients with medically inoperable or unresectable NSCLC enrolled on prospective clinical trials from two medical centers (details of the 4 prospective trials including the chemotherapy regimen are summarized in Appendix A1) that were

approved by their respective institutional review boards. Written informed consent was obtained from all patients before enrollment into the trials. All patients had histologically proven stage I-III NSCLC and a Karnofsky performance status (KPS) ≥70.

Treatment

All patients received definitive, fractionated radiotherapy with or without concurrent chemotherapy. Computed tomography (CT)-based treatment planning was performed on simulation scans of the entire thorax. Intravenous contrast-enhanced CT was implemented whenever possible. Radiotherapy was mostly delivered using a 3D conformal technique. A total dose of 60-85.5 Gy was delivered with 2-3.8 Gy daily fractions given over 6-7 weeks using 6-16 MV photons. Tumor delineation was contoured and edited according to the best judgment of the treating radiation oncologist. The total dose delivered to the planning target volume (PTV) was limited when necessary by tolerance limits of critical organs at risk (OARs) per standard practice, or to a mean lung dose of less than 20 Gy or lung normal tissue complication probability (NTCP) of less than 15-17.2% for patients treated in dose escalation studies. The maximum spinal cord dose was limited to ≤ 50 Gy, maximum brachial plexus dose ≤ 66 Gy, heart 1/3 volume ≤ 60 Gy, 2/3 ≤ 45 Gy, and 3/3 ≤ 40 Gy.

Dosimetric analyses of heart and pericardium

The heart and pericardium were outlined on each axial planning CT scans according to the RTOG 1106 trial atlas recommendations (http://www.rtog.org/CoreLab/ContouringAtlases/LungAtlas.aspx). Superiorly, the pericardium started one slice (3 mm) above the superior end of the aortic arch, the normal heart started one slice (3 mm) below the pulmonary artery trunk passing the midline. Inferiorly, the pericardium and heart are exactly the same, ending at the pericardial apex at the diaphragm, with inclusion of all the heart chambers, great vessels and coronary vessels, pericardium, and fatty tissue around these structures.

The superior part of pericardium contains fatty tissue, residual thymus and parts of the great vessels (e.g. subclavian artery, left carotid artery, innominate artery, ascending aorta, descending aorta, pulmonary artery, superior vena cava). Cumulative dose-volume histograms (DVHs) of the heart and pericardium were computed from treatment plans using UM Plan. Heart and pericardial radiation dose was analyzed as a continuous variable with a focus on mean dose, as well as the volumes receiving 5 Gy (V5) , 30 Gy (V30) and 55 Gy (V55), as V5 and V30 were significant factors for overall survival in the RTOG 0617 study (10) and V55 was selected as a representative point of volume for high dose, which was also recently reported as a significant factor for pericardial effusion (7). All computed dosimetric factors are physical doses, without consideration of fractionation effect.

Dose-Volume Atlases

As recommended by the QUANTEC group (16, 17), dose-volume atlases were mapped for the risk of PCE and death. The format and usage of these files are described in the word file in the electronic Appendix A2.

Follow-up and PCE evaluation

Patients were followed up in the clinic and with chest CT scans at 3, 6, 9, 12, 18, and 24 months after RT, and yearly thereafter. Additional CT or PET-CT scans were performed as clinically indicated. Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. The development of a PCE was evaluated by follow-up chest CT scans. PCE was measured independently by radiation oncologists with confirmation by a report from a radiologist. The time to PCE was calculated from the beginning of RT to the date of reported PCE. Patients without PCE were censored at death or last follow-up. Overall survival (OS) was calculated from the beginning of RT to the date of death or censored to the last follow-up.

Statistical analysis

The primary endpoints of this study were PCE and overall survival. The following factors were included in the risk analysis: gender, age, prescribed tumor dose, chemotherapy, smoking, chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), hypertension, histology, karnsofsky performance status (KPS), stage, gross tumor volume (GTV) volume, tumor location, as well as mean dose, V5, V30 and V55 of heart and pericardium. The correlations between above assessed variables and PCE or OS were computed with the Cox proportional hazards model in univariable and multivariable analyses. A univariable *P* value of 0.05 was defined as the threshold at which to select parameters for multivariable analysis. The X-tile software (Version 3.6.1, Yale University, New Haven, CT, USA) was used to determine the optimal cut-off values of identified covariates for overall survival. Log-rank tests were then performed using the cut-off splits for each variable. Analyses were carried out using SPSS 17.0 software and $p<0.05$ was considered significant.

Results

A total of 94 patients were eligible and their characteristics are shown in Table 1. Median age was 66 years (range, 43-85 years). Seventy-eight patients (83.0%) were male, 71 (75.5%) had centrally located primary tumors, and 76 (80.9%) had stage III disease. Chemotherapy was administered to 79 (84.0%) patients. The median prescribed radiation dose was 70 Gy (range, 45-85.5 Gy) and the median gross tumor volume (GTV) was 129.6 cc (range, 2.1–802.9 cc). The median mean dose and maximum dose to the heart were 13.9 Gy (range, 0.2-46.9 Gy) and 72.9 Gy (range, 0.8-99.7 Gy), respectively.

The median follow-up for surviving patients was 58 months (range 44-124). The rate of PCE was 40.4% (38 of 94 patients), and the median observed time to onset of PCE was 5.4 months from the beginning of RT (range, 1.0-24.7 months), as shown in Fig. 1a.

Table 2 lists the clinical and dosimetric factors associated with PCE. Univariable analysis demonstrated that prescribed dose, chemotherapy, hypertension and GTV were significantly ($p<0.05$) associated with PCE, while gender, age, smoking status, COPD, CVD, histology, KPS, stage and tumor location were not.

The relationship between DVH parameters of both heart and pericardium (V5-V80) and PCE are shown in Fig. 1b. As shown in Table 2, univariable analysis demonstrated that the risk of PCE was correlated significantly with all input dosimetric parameters, including heart and pericardial mean dose, V5, V30 and V55. The dosimetric parameters were entered into the multivariable analysis separately, one by one, not together, as they were strongly linearly correlated with each other. Prescription dose, hypertension, heart doses (mean, V5 and V55) and pericardial doses (mean, V5, V30 and V55) remained statistically significant in multivariable analysis (Table 2).

The median overall survival for all patients was 22.2 months (Fig. 2a). Under univariable Cox analysis, the development of PCE was not significantly associated with survival (HR 0.732, 95% CI 0.458-1.170, p=0.192, Table 3). The log-rank test demonstrated no significant difference in survival between patients with and without PCE (median survival 22.2 vs 21.4 months, p=0.190, Fig. 2b).

Table 3 lists the clinical and dosimetric factors associated with overall survival. Univariable analysis demonstrated that gender, prescription dose, KPS, pericardial V30 and V55 were significantly correlated with survival, while age, chemotherapy, smoking, COPD, CVD, hypertension, histology, stage and tumor location were not significantly associated (Table 3). Under multivariable analysis, prescribed dose, KPS, pericardial V30 and V55 remained statistically significant (Table 3). Interestingly, the heart doses (mean, V5, V30 and V55) were not significantly associated with survival. Since pericardial dosimetric parameters were significant factors for survival, X-tile computation demonstrated that the cutoff points for pericardial V30 and V55 were 29% and 21%, respectively. Fig. 2c, d shows the difference in survival using these pericardial V30 and V55 cutoff values. When the pericardial V30 was ≤ 29%, overall survival was significantly better. Median survival was 13.3 months and 35.8 months for patients with pericardial V30 >29% and ≤ 29% (log-rank p=0.003), respectively. The difference in survival for patients with pericardial V55 > 21% and ≤ 21% was also significant (13.3 months and 30.0 months, respectively; log-rank p=0.013).

Figure 3 show the DVH mapping atlases for PCE and survival. Since multiple dosimetric factors were significant, we developed maps of DVH atlases which gave the observed complications in DVHs passing above the mapped position. The probability that the true rate of PCE >50% and death >75% were picked, and that could produce differences in the likelihood across the DVH space. Figures 3a and 3b show maps of probability that the rate of PCE is >50%. The increase in this risk with radiation dose to heart/pericardium, particularly >35 Gy (red area), is clearly seen. There is also a high risk of PCE for large volumes of heart/pericardium exposed to low doses of radiation. Areas of low toxicity probability are identified in the lower left of the maps (blue area). Figures 3c and 3d show maps of probability that the true rate of death is >75%. High-dose radiation to the pericardium, particularly around 55 Gy (orange area), increases the probability of death.

Discussion

PCE is a known radiation-related cardiac toxicity. In our study, the incidence of PCE was 40.4%, suggesting that PCE may be a common toxicity post-thoracic radiotherapy in

NSCLC (18, 19). The high rate of PCE in our series is likely due to our definition based on radiographic criteria and to the fact that the majority of patients received concurrent chemotherapy. Other factors, including chemotherapy may be associated with the occurrence of PCE. Concurrent or induction chemotherapy was found to increase the risk of cardiac toxicity, including PCE. In the study of Ning et al., adjuvant chemotherapy, rather than the concurrent or induction, was the most strongly associated factor with PCE on multivariate analysis(7). Cardiac toxicity has been associated with several chemotherapeutic agents used to treat NSCLC, including platinum-based agents (20), taxanes (21), vinorelbine (22) and gemcitabine (23). PCE are also reported after the use of targeted therapy (24) and immune checkpoint inhibitors (25). In the present study, chemotherapy was a significant risk factor for the development of PCE in univariable analysis, but was only of borderline significance in multivariable analysis. One possible reason is the relatively small size of this study. It is difficult to distinguish the exact role of chemotherapy and dosimetric parameters. We do not have enough radiation alone to perform meaningful analysis. But we further analyzed the association of dosimetric parameters with PCE in patients treated with concurrent chemoradiation by excluding the 15 patients treated with radiation therapy alone. The results were similar to the whole group that the all dosimetric parameters were significantly associated with inferior survival (electronic Appendix A3). These findings may indicate that the chemotherapy may be overshadowed by dosimetric parameters in lung cancer patients since large volumes of heart and pericardium often received high-dose irradiation. Future study with larger number of cases is needed.

Cardiac dosimetric parameters are widely used to predict the risk of radiation-related cardiac toxicities including PCE, though the reported results vary considerably. There is no definitive consensus about the most reliable and safe cut-off level because of the strong correlations among these dosimetric parameters (26). Some studies have noted that cardiac dosimetric parameters, such as mean heart/pericardium dose, max heart/pericardium dose, pericardial V30 and total radiation dose to mediastinum, are significantly associated with cardiac toxicities with inclusion of PCE (18, 27–30). The present study found that the risk of PCE was associated with several cardiac parameters (e,g. mean heart/pericardial dose, heart/pericardial V5, heart/pericardial V55 and pericardial V30). This is consistent with a recent study in which a wide range of cardiac parameters (e.g. V20-V65) predicted the occurrence of PCE (7). The DVH atlas analysis also confirmed these associations and more clearly illustrated the presentation of high-risk DVHs.

High-dose RT may cause cardiac toxicity, which may offset the benefit of RT and contribute to death (11, 31, 32). However, in our study, the presence of PCE was not significantly associated with survival. To our knowledge, this is the first study to investigate the association between PCE and survival in NSCLC. In our study, pericardial V30 and V55 were significantly associated with inferior survival on the multivariable analysis, but pericardial V55, rather than pericardial V30, was visibly remarkable on the DVH atlas. The reason for these conflicting results is unclear, but may be due to the bias of different models, and may suggest that the high dose volume of pericardium (V55) is more important than lower dose volume (V30) for survival correlates. Nevertheless, our results support the theory that minimizing cardiac doses is important in the treatment of NSCLC (9, 11, 33), and

suggest that constraining dosimetric factors to minimize radiation to the pericardium, specifically limiting pericardial V55 to ≤ 21%, may improve outcomes.

The survival impact of heart dosimetric factors has been controversial. In RTOG 0617, heart V5 and V30 significantly correlated with unfavorable survival (9). Stam et al. reported the significant associations of heart V5, V30 with overall survival, but not heart V50 (12). The other report by Speirs confirmed the association of heart V50 with survival (13). In contrast, several recent secondary analyses of randomized trials did not report the association between heart doses and overall survival in NSCLC patients receiving RT, even though these factors were associated with cardiac toxicity (8, 34–36). Wang et al. reported that the mean dose, V5 and V30 of heart/left ventricle were not associated with survival (8), and Guberina et al. reported that heart V5 could not be validated as a prognostic factor for survival (34). Similarly, a prior study from Michigan reported that heart mean dose, V5, V30 and V50 were not significantly associated with OS (35). Tucker et al. did not found that the heart dose had an independent effect on survival in 468 patients (14). The reason for these conflicting results is unclear, but may be partially explained by variations in heart delineations, particularly regarding inclusion of full pericardium or not. Indeed, there is no consistent and strict definition of heart contour, and most studies did not specify the heart definition. Our experience with patients enrolled on RTOG1106 revealed remarkable variations in heart definition from institution to institution, despite the trial mandate to use the RTOG atlas (posted on website since 2010, with heart contouring ends at one slide before the pulmonary trunk passing the midline). Some centers included the full pericardium with inclusion of large vessels in the upper mediastinum, while others only included the heart chambers. Since the heart is inseparable from the inferior pericardium, the dosimetric parameters of the pericardium and heart are significantly correlated with each other, making it difficult to determine the individual role of each structure (18). Our study of using RTOG atlas to contour heart and pericardium separately, revealed that pericardial doses were associated with unfavorable survival, while heart doses were not. This is consistent with a recent study by McWilliam et al reporting that radiation dose to heart base (i.e. superior part of mediastinum), rather than the conventional heart mean dose, V5 and V30, was associated with survival (15). It is also possible that the insignificant correlation of above mentioned recent studies (8, 14, 35) contribute to the use of RTOG atlas without inclusion of superior mediastinum. This finding suggests that doses to the upper mediastinum may be more important than those to the heart chambers. However, studies with larger sample sizes are needed to validate this. The biologic reasons underlying these results are unclear, but it is possible that radiation to the immune cells in the superior part of pericardial field (e.g. residual thymic tissue and lymph nodes) may play a more important role than than the cardiac parenchyma in determining radiation-related mortality in NSCLC. This is consistent with the recent findings that the effective RT dose to immune structures, rather than the heart dose, was the most significant independent negative prognostic factor in RTOG 0617 after concurrent chemoradiation, and in early stage NSCLC patients after SBRT treatment (37, 38).

This study is limited by the relatively small number of patients and the retrospective nature of the analysis, although all patients were enrolled into prospective clinical trials. This study is also limited by the fact that the dose of RT was computed by an inhouse planning system

which no longer a state-of-the-art system. Nevertheless, the results are interesting and hypothesis generating, and have immediate clinical relevance.

In summary, PCE is common in patients with stage I-III NSCLC who were treated with radiation-based therapy. Several dosimetric factors of both the heart and pericardium are significantly associated with the risk of PCE. However, PCE and heart doses are not significantly associated with survival, while pericardial doses, particularly V30 and V55, do correlate significantly with unfavorable survival. Our data suggest that radiation to the pericardium, likely the superior part of the pericardium, may cause lethal toxicity independent of the development of PCE. The risk of death may be decreased by minimizing the dose of radiation to the pericardium, upper mediastinum. Larger studies are needed to validate these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights:

- Pericardial effusion is significantly associated with heart/pericardial dosimetric factors.
- Pericardial effusion does not have a significant effect on survival.
- The irradiated volume of pericardium, rather than the heart dose, is associated with inferior survival.
- The risk of death may be decreased by minimizing the dose to pericardium.

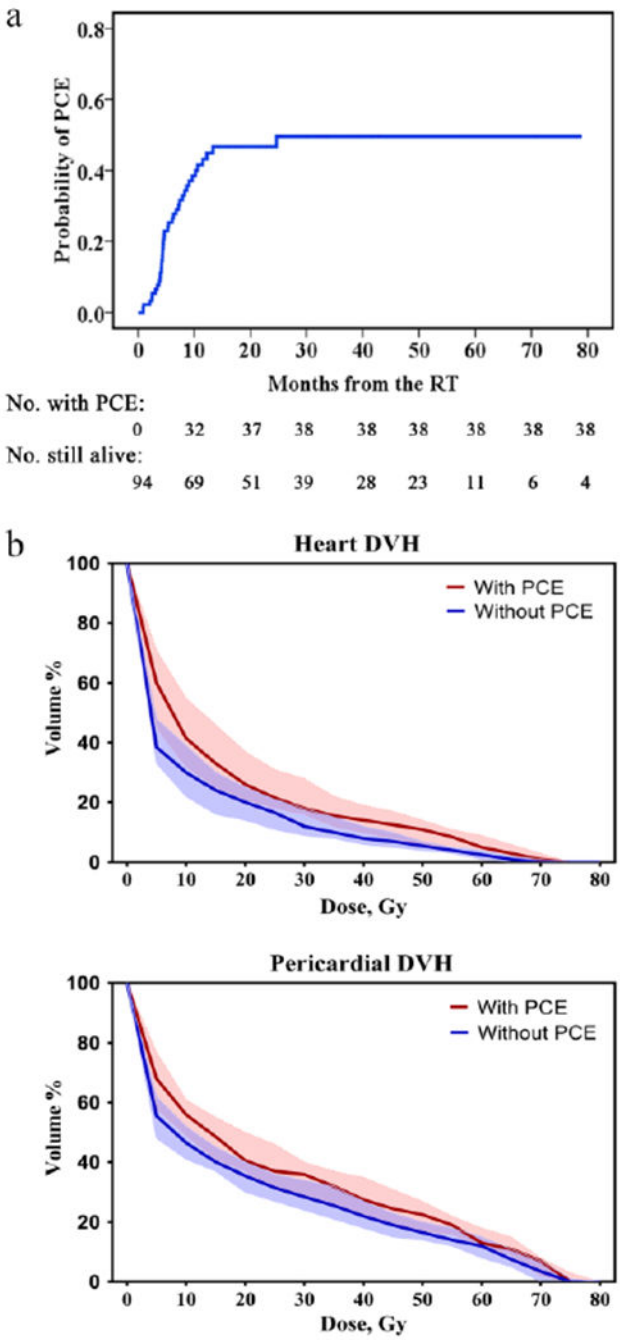

Fig.1.

Pericardial effusion and heart/pericardial dosimetry. (a) Cumulative risk of pericardial effusion in 94 patients, (b) Median heart and pericardial dose-volume histograms (DVH) of 94 patients with or without pericardial effusion (PCE), the color bands represent the 95% CI.

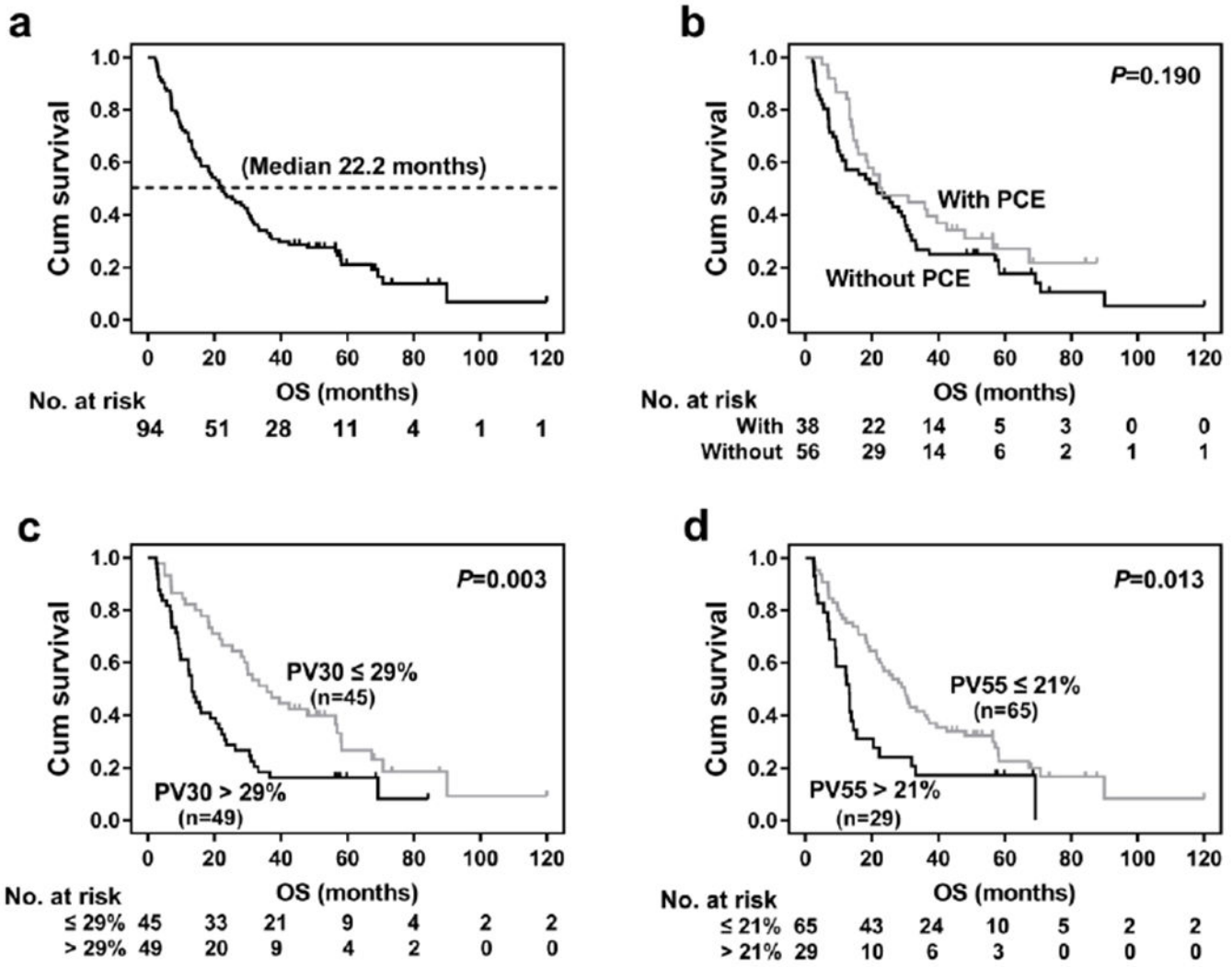

Fig.2.

Pericardial effusion and overall survival. (a) Survival curve of all patients. (b) Survival difference in patients with or without PCE. (c) Survival difference in patients with pericardial V30 > 29% vs. V30 ≤ 29%. (d) Survival difference in patients with pericardial V55 > 21% vs. V55 ≤ 21%.

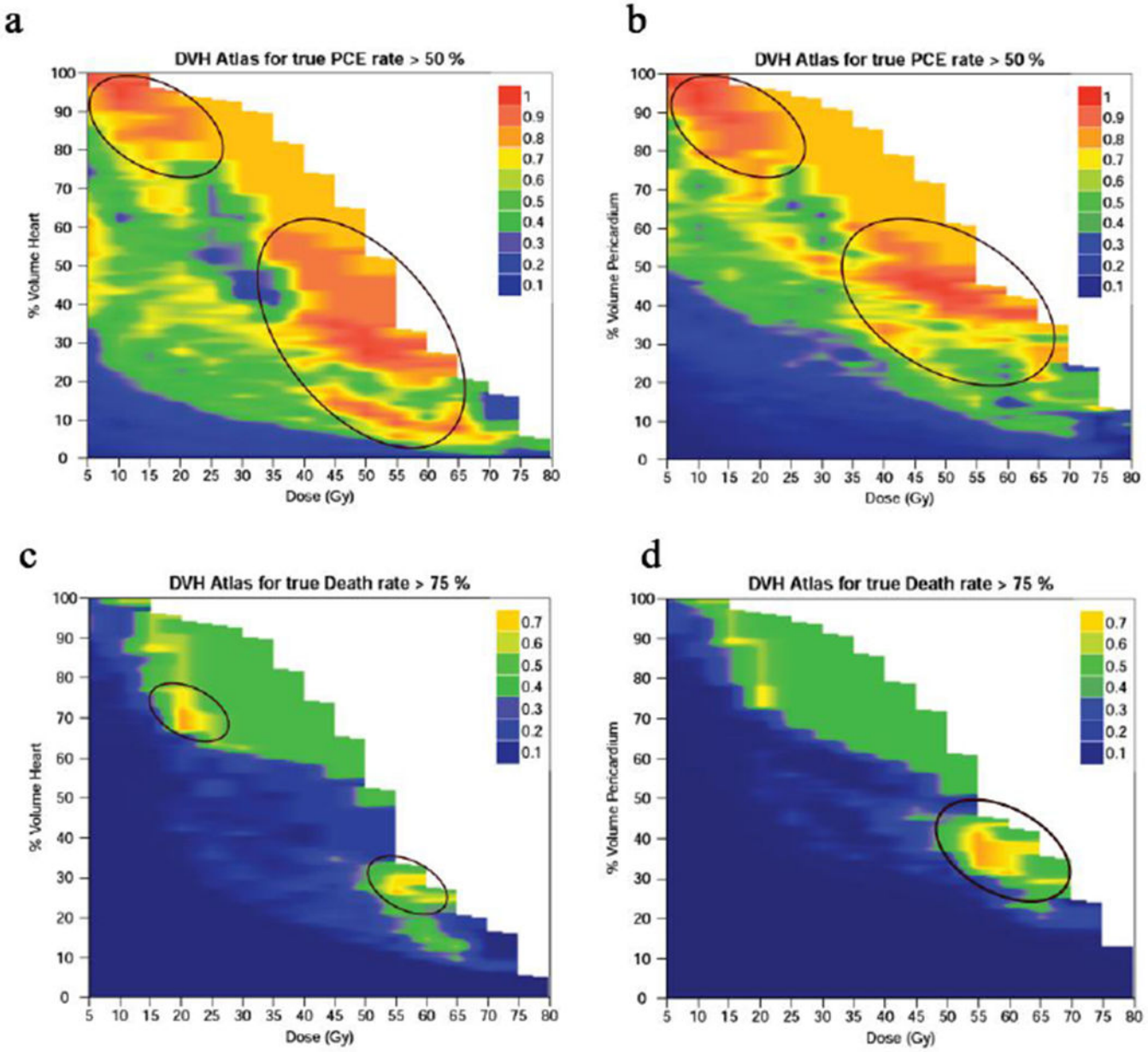

Fig.3.

DVH atlases of heart and pericardium. Maps of the probability that the true rate of PCE is >50% for DVHs passing over the mapped point in the dose-volume plane, for (a) the heart and (b) the pericardium. Maps of probability that the true rate of death is >75% for DVHs passing over the mapped point in the dose-volume plane, for (c) the heart and (d) the pericardium.

Table 1

Clinical and dosimetric characteristics of patients

Factors	No. of patients (%)	Factors	No. of patients (%)
Ages		CVD	
<=65	43 (45.7%)	no	56 (59.6%)
>65	51 (54.3%)	yes	38 (40.4%)
Gender		Hypertension	
male	78 (83.0%)	no	41 (43.6%)
female	16 (17.0%)	yes	53 (56.4%)
Stage		COPD	
I	11 (11.7%)	no	51 (54.3%)
II	7 (7.4%)	yes	43 (45.7%)
III	76 (80.9%)	Primary tumor location	
Histology		central	71 (75.5%)
adenocarcinoma	15 (16.0%)	lateral	23 (24.5%)
squamous cell	31 (33.0%)	Prescribed dose (Gy)	
large cell	1 (1.1%)	<70 (median)	35 (37.2%)
NSCLC NOS	47 (50.0%)	>= 70 (median)	59 (62.8%)
KPS		GTV (cc)	
<80	14 (14.9%)	< 129.6 (median)	47 (50.0%)
>=80	80 (85.1%)	>= 129.6 (median)	47 (50.0%)
Smoking		Mean heart dose (Gy)	
no	10 (10.6%)	< 13.9 (median)	47 (50.0%)
yes	84 (89.4%)	>= 13.9 (median)	47 (50.0%)
Chemotherapy		Heart max dose (Gy)	
no	15 (16.0%)	< 72.9 (median)	47 (50.0%)
yes	79 (84.0%)	>= 72.9 (median)	47 (50.0%)

Abbreviations: COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; NSCLC NOS: non-small cell lung cancer, not otherwise specified; KPS: Karnofsky performance status; PCE: pericardial effusion; GTV: gross tumor volume.

Table 2

Univariable and multivariable cox regression analysis for PCE

Factors	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender	1.494 (0.707-3.157)	0.293	NA	NA
Ages	0.976 (0.948-1.005)	0.109	NA	NA
Prescribed $Dose_{Gy}$	0.951 (0.915-0.988)	**0.011**	**0.943 (0.905-0.982)**	**0.005** *
Chemotherapy	4.434 (1.066-18.440)	**0.041**	4.024 (0.951-17.032)	0.059 *
Smoking	3.514 (0.842-14.674)	0.085	NA	NA
COPD	0.618 (0.322-1.187)	0.148	NA	NA
CVD	0.662 (0.328-1.335)	0.249	NA	NA
Hypertension	0.441 (0.230-0.846)	**0.014**	**0.464 (0.237-0.906)**	**0.025** *
Histology	1.251 (0.952-1.645)	0.109	NA	NA
KPS	1.023 (0.989-1.059)	0.191	NA	NA
Stage	1.915 (0.995-3.686)	0.052	NA	NA
GTV $volume_{CC}$	1.002 (1.000-1.003)	**0.044**	1.001 (0.999-1.002)	0.319 *
Location	0.440 (0.182-1.065)	0.069	NA	NA
Mean heart $dose_{Gy}$	1.053 (1.021-1.085)	**0.001**	**1.041 (1.004-1.079)**	**0.028**
Heart $V5_{Gy}$	1.018 (1.007-1.029)	**0.001**	**1.016 (1.003-1.029)**	**0.019**
Heart $V30_{Gy}$	1.025 (1.008-1.042)	**0.004**	1.018 (0.999-1.036)	0.061
Heart $V55_{Gy}$	1.072 (1.035-1.111)	**<0.001**	**1.053 (1.010-1.098)**	**0.016**
Mean Pericardial $dose_{Gy}$	1.066 (1.028-1.105)	**0.001**	**1.050 (1.009-1.093)**	**0.016**
Pericardial $V5_{Gy}$	1.026 (1.011-1.041)	**0.001**	**1.022 (1.004-1.039)**	**0.014**
Pericardial $V30_{Gy}$	1.033 (1.013-1.052)	**0.001**	**1.022 (1.002-1.043)**	**0.030**
Pericardial $V55_{Gy}$	1.056 (1.024-1.088)	**<0.001**	**1.039 (1.005-1.074)**	**0.022**

Abbreviations: COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; NSCLC NOS: non-small cell lung cancer, not otherwise specified; KPS: Karnofsky performance status; PCE: pericardial effusion; GTV: gross tumor volume. NA= not applicable, as it was not tested due to their limited significance under univariable analysis. The dosimetric parameter was entered into multivariable analysis separately one by one, not together.

Asterisk (*) represent average HR (95% CI) and P values.

Table 3

Univariable and multivariable cox regression analysis for survival

Factors	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender	0.481 (0.239-0.968)	**0.040**	0.512 (0.252-1.039)	0.064 *
Ages	1.019 (0.999-1.039)	0.062	NA	NA
Prescribed $Dose_{Gy}$	0.958 (0.933-0.984)	**0.002**	**0.963 (0.936-0.990)**	**0.009** *
Chemotherapy	0.887 (0.485-1.622)	0.698	NA	NA
Smoking	1.302 (0.646-2.622)	0.460	NA	NA
COPD	0.753 (0.474-1.196)	0.229	NA	NA
CVD	0.967 (0.607-1.539)	0.886	NA	NA
Hypertension	1.351(0.851-2.145)	0.202	NA	NA
Histology	1.122 (0.934-1.349)	0.220	NA	NA
KPS	0.973 (0.951-0.996)	**0.020**	**0.973 (0.949-0.997)**	**0.029** *
Stage	1.293 (0.914-1.829)	0.147	NA	NA
GTV $volume_{CC}$	1.001 (1.000-1.002)	0.192	NA	NA
Location	0.655 (0.381-1.129)	0.128	NA	NA
Mean heart $dose_{Gy}$	1.014 (0.992-1.036)	0.217	NA	NA
Heart $V5_{Gy}$	1.004 (0.997-1.012)	0.262	NA	NA
Heart $V30_{Gy}$	1.009 (0.996-1.022)	0.170	NA	NA
Heart $V55_{Gy}$	1.022 (0.991-1.053)	0.162	NA	NA
Mean Pericardial $dose_{Gy}$	1.021 (0.997-1.040)	0.082	NA	NA
Pericardial $V5_{Gy}$	1.006 (0.996-1.015)	0.232	NA	NA
Pericardial $V30_{Gy}$	1.014 (1.001-1.027)	**0.035**	**1.019 (1.004-1.033)**	**0.010**
Pericardial $V55_{Gy}$	1.024 (1.002-1.047)	**0.032**	**1.030 (1.006-1.054)**	**0.014**
PCE events (yes or no)	0.732 (0.458-1.170)	0.192	NA	NA

Abbreviations: COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; NSCLC NOS: non-small cell lung cancer, not otherwise specified; KPS: Karnofsky performance status; PCE: pericardial effusion; GTV: gross tumor volume. NA= not applicable, as it was not tested due to their limited significance under univariable analysis. The dosimetric parameter was entered into multivariable analysis separately one by one, not together.

Asterisk (*) represent average HR (95% CI) and P values.