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Heart Dosimetry is Correlated with Risk of Radiation Pneumonitis after Lung-Sparing Hemithoracic Pleural IMRT for Malignant Pleural Mesothelioma

Ellen D. Yorke, PhD^{‡,x}, Andrew Jackson, PhD^{‡,x}, Li Cheng Kuo, MS[‡], Anthonia Ojo, BS^{*}, Kelly Panchoo, BA^{*}, Prasad Adusumilli, MD[^], Marjorie G. Zauderer, MD[#], Valerie W. Rusch, MD[^], Annemarie Shepherd, MD^{*}, and Andreas Rimner, MD^{*}

[‡]Department of Medical Physics, Memorial Sloan Kettering Cancer Center, New York, New York

^{*}Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY

[^]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

[#]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Abstract

Purpose/Objective—To determine clinically helpful dose-volume and clinical metrics correlating with symptomatic radiation pneumonitis (RP) in malignant pleural mesothelioma

Corresponding author: Ellen Yorke, PhD, Department of Medical Physics, Memorial Sloan Kettering Cancer Center, 1275 York Ave, Box 22, New York, New York 10065; Tel (212) 639-8637; Fax (212) 717-3010; yorkee@mskcc.org.

^xThese authors have contributed equally

Ellen D. Yorke	No COI
Andrew Jackson	NIH Grants RO1 CA129182 and NIH Grant P30 CA008748
Li Cheng Kuo	No COI
Anthonia Ojo	No COI
Kelly Panchoo	No COI
Prasad Adusumilli	No COI
Marjorie G. Zauderer	No COI
Valerie W. Rusch	No COI
Annemarie Shepherd	No COI
Andreas Rimner	Grants from Varian Medical Systems and Boehringer Ingelheim; Financial Support from Bristol Myers Squibb

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(MPM) patients with two lungs treated with hemithoracic intensity modulated pleural radiation therapy (IMPRINT).

Methods and Materials—Treatment plans and resulting normal organ dose-volume histograms of 103 consecutive MPM patients treated with IMPRINT (2/2005–1/2015) to the highest dose

50.4 Gy satisfying departmental normal tissue constraints were uniformly recalculated. Patient records provided maximum RP grade (CTCAE v4.0), clinical and demographic information. Correlations analyzed with the Cox model were: Grade 2 RP (RP2+) and Grade 3 RP (RP3+) with clinical variables, with volumes of PTV and PTV-Lung overlap and with mean dose, percent volume receiving dose D, (V_D), highest dose encompassing % volume V, (D_V), and heart, total, ipsilateral, and contralateral lungs volumes.

Results—Twenty-seven patients had RP2+ (14 with RP3+). Median prescription dose was 46.8 Gy (39.6 to 50.4 Gy, 1.8Gy/fraction). Median age was 67.6 years (42 to 83 years). There were 79 males, 40 never-smokers, 44 with left-sided MPM. There were no significant ($p < 0.05$) correlations with clinical variables, prescription dose, total lung dose-volume metrics and PTV-Lung overlap volume. Dose-volume correlations for heart were RP2+ with V_D (35 D 47 Gy, V_{43} strongest at $p=0.003$), RP3+ with V_D (31 D 45 Gy), RP2+ with D_V (5 V 30%), RP3+ with D_V (15 V 35%) and mean dose. Significant for ipsilateral lung were RP2+ with V_D (38 D 44 Gy), RP3+ with V_{41} , RP2+ and RP3+ with minimum dose; for contralateral lung, RP2+ with maximum dose. Correlation of PTV with RP2+ was strong ($p<0.001$) and also significant with RP3+.

Conclusions—Heart dose correlates strongly with symptomatic RP in this large cohort of MPM patients with two lungs treated with IMPRINT. Planning constraints to reduce future heart doses are suggested.

Keywords

Radiation pneumonitis; mesothelioma; pleural IMRT; cardiac dose

Introduction

Malignant pleural mesothelioma (MPM) is an aggressive cancer that is frequently treated with a combination of chemotherapy and radical surgery when discovered at an early stage. Despite resources brought to bear, median survival reported in recent studies is less than 2 years¹. Pleurectomy/decortication (P/D), a lung-sparing surgery, is increasingly preferred over extrapleural pneumonectomy (EPP)² but leaves the patient with two intact lungs at risk of radiation pneumonitis (RP) should the patient receive adjuvant radiation therapy (RT). We developed a novel method of delivering hemithoracic intensity modulated pleural RT (IMPRINT) covering the entire hemithoracic pleura that has proved feasible and safe for MPM patients who have unresectable disease or have undergone lung-sparing surgical resection^{3–5}. While this technique shapes the dose distribution to conform to the target and maximally spare underlying lung, dose is inevitably delivered to the lungs, heart and other thoracic and upper abdominal organs at risk (OARs). RP is the major dose-limiting toxicity in these treatments. In this analysis, we sought to develop MPM-specific treatment planning constraints based on evidence from our IMPRINT experience to date. Here we present the

first and largest analysis of the dosimetric and clinical factors that might predict symptomatic RP in this group of patients.

Methods

We identified all patients with two intact lungs treated in our department for MPM with definitive or adjuvant IMPRINT from 2/2005 to 1/2015. Patients were immobilized supine in a custom mold with arms above head. At simulation, they underwent a computerized tomography (CT) scan for treatment planning under gentle free-breathing. A pre-treatment ^{18}F -fluorodeoxyglucose positron-emission tomography (^{18}F -FDG PET) scan was acquired at or shortly before simulation which, together with the CT scan, was used for gross tumor volume (GTV) delineation⁵. For planning and evaluation, the GTV was removed from the ipsilateral and total lung volumes. The clinical target volume (CTV) was the parietal and visceral pleura (not including the fissures), extending superior-inferior from the thoracic inlet to the insertion of the diaphragm, typically at the bottom of L2, laterally along the ribs and medially along the mediastinal pleura, pericardium and hilum. Since 2008, information from a respiratory correlated CT scan was incorporated to form an internal target volume (ITV). The PTV was generated from the ITV by adding a 6 mm margin on its interior side and a 10 mm outer margin, with the latter extended to cover the entire thickness of the ipsilateral hemithorax chest wall. Treatments were delivered with sliding window IMRT using 6 to 9 6-MV photon beams, approximately equispaced over a 200° to 240° range encompassing the ipsilateral lung or, since 9/2014, with Volumetric Modulated Arc Therapy. Entrance through the contralateral lung was avoided.

The planning goal was to deliver 50.4 Gy (1.8 Gy/fraction) to the PTV, subject to the guidelines and limit constraints of Table E1 (www.redjournal.org). For total lung and heart these were adopted from department criteria for conventionally fractionated non-small-cell lung cancer (NSCLC); contralateral lung guidelines were specifically added for MPM patients in 2011. Other OAR criteria were adopted from department constraints for conventionally fractionated abdominal treatments. ‘Guidelines’ could be violated at the physician’s discretion, but if no plan satisfying ‘limits’ could be generated, prescription dose was decreased in 1.8 Gy increments until they were satisfied. There were no specific ipsilateral lung guidelines but planners used optimization constraints to achieve some sparing. Figure 1 shows a typical dose distribution; further planning details have been previously published^{3–5}.

Seven cases were planned with the Eclipse™ system (Varian Medical Systems) with calculations done with the Analytical Anisotropic Algorithm (AAA). The others had been planned with a previously described in-house system that used a pencil-beam algorithm^{6, 7}. Images, beams and intensities for these plans were imported into Eclipse and the volumetric dose distributions were recalculated with AAA. Heart and lung contours were reviewed by a board-certified radiation oncologist; if necessary heart contours were modified to comply with RTOG’s heart atlas before dosimetric analysis.

The dose-volume histograms (DVHs) for the ipsilateral, contralateral, combined lungs and heart were exported for further analysis. Clinical data were obtained from the patient

records, including age, gender, smoking history, histology, chemotherapy, treatment laterality, treatment start/end dates, date of death or last followup, maximum RP grade and its onset time.

Patients were clinically assessed for toxicity at least weekly during RT, and after completion at approximately 4 weeks, 3 months and every 3 months thereafter. Radiographic assessment was obtained every 3 months with a chest CT. Effusions were tapped when indicated and feasible for diagnostic/therapeutic purposes and sent for cytology. Pulmonary toxicity was graded according to the NCI Common Terminology Criteria for Toxicity and Adverse Event reporting (CTCAE) Version 4.0⁸. Systemic steroids were typically initiated for grade 2 RP, and any hospitalization or oxygen need for the management of RP was considered at least grade 3 RP.

The Cox Proportional Hazards (CPH) model was used to analyze correlation of Grade 2 and above (RP2+) and Grade 3 and above (RP3+) RP with clinical variables and with the following dose-volume factors for heart, total lung, ipsilateral, and contralateral lungs: mean dose; percent OAR volume receiving dose D, (V_D), with dose incremented from 1 to 49 Gy in 2 Gy intervals; the highest dose D encompassing percent OAR volume V, (D_V), with V in 5% intervals from 0 to 100%. Influence of the absolute volume of these normal tissues and of the PTV and PTV-ipsilateral lung overlap were also analyzed. Since our aim was to provide treatment planning guidance, dosimetric correlations were termed significant if they were positive (increased RP for increased metric) and the p-value was below 0.05; we considered $0.05 < p < 0.1$ a trend.

Results

General Characteristics

Patient characteristics are shown in Table 1. There were a total of 103 patients. Median age was 67.6 years (42–83 years). There were 79 males; 40 patients were never-smokers. Forty-four patients had left-sided disease. Most patients (n=85) had epithelioid histology; 4 had sarcomatoid and 14 mixed histology. For surgical status, 12 had no surgery, 20 were found unresectable upon surgical exploration, 25 had partial P/D, 36 had P/D and 10 had extended P/D. Of the 71 patients with surgery, 38 had microscopic residual disease and 33 had gross residual disease. All but 8 patients received chemotherapy as part of their treatment, typically 4 cycles of a platinum/pemetrexed doublet.

Twenty-seven patients developed RP2+: 13 Grade 2, 11 Grade 3, 2 Grade 4, 1 Grade 5. The median (range) prescription dose was 46.8 Gy (39.6–50.4 Gy). At the end of the study interval (7/2015), 67 patients had died (median survival 12.3 months from radiation start). Median followup from start for the remaining patients was 18.5 months. Fifty-nine deaths were attributed to mesothelioma, one to toxicity.

Correlations with Radiation Pneumonitis: Univariate CPH analysis

Clinical variables—There was no significant correlation of RP2+ or RP3+ incidence with any of the analyzed clinical variables. These included age, chemotherapy (yes, no), gender, laterality, pre-treatment KPS, smoking status, type of surgery, and histology. Correlation

with prescription dose was not significant (NS). Disease was left sided in 29/76 patients without RP, 15/27 with RP2+ and 9/14 with RP3+, but laterality correlation was NS (p-values for RP2+ and RP3+ are 0.21, 0.11 respectively).

Normal Tissues—Table 2 summarizes the significant univariate correlations with symptomatic RP. Table E2 (www.redjournal.org) summarizes magnitudes and ranges of these variables with regard to RP.

Heart: As shown in Figures 2a and b, there was significant correlation between V_D and RP2+ for 35Gy < D < 47 Gy (minimum $p = 0.0029$ for V_{43Gy}) and with RP3+ for 31 Gy < D < 45 Gy (minimum $p = 0.011$ for V_{41Gy}). There was also significant correlation (Figure E2, www.redjournal.org) of D_V with RP2+ for 5% < V < 30% (minimum $p = 0.011$ for $D_{10\%}$) and with RP3+ for 15% < V < 35% (minimum $p = 0.017$ for $D_{25\%}$). Mean heart dose (MHD) was significantly correlated with RP3+ ($p = 0.033$), with a trend for RP2+ ($p = 0.07$). The median value of V_{43Gy} was 16%; Kaplan-Meier (K-M) curves of freedom from RP2+ split at the median (Figure 3a) were significantly separated (p -value = 0.01, log-rank test). Absolute heart volume was NS. Heart dosimetric variables were strongly dependent on disease laterality; for right-sided mesothelioma, median MHD was 21.9 Gy (14.06–29.1 Gy) and median V_{40Gy} was 16.8% (14.5–32.3%); for left-sided mesothelioma, MHD was 28.1 Gy (26.9–29.2 Gy) and median V_{40Gy} was 25.5% (9.7–37.6%).

Total Lung: No significant positive correlations were found for total lung dose-volume metrics. Since the mean lung dose (MLD) planning constraint was strictly enforced and prescription dose was capped at 50.4 Gy, MLD was close to 20 Gy for most patients (Figure E1, www.redjournal.org). Median MLD was 19.9 Gy (14.3–21.1 Gy).

Ipsilateral Lung: Because the C-shaped PTV surrounds the entire ipsilateral lung outer surface, the mean ipsilateral lung dose (MILD) was high, with median 39.4 Gy (30–49.9 Gy). There was significant correlation between RP2+ and V_D for 39 Gy < D < 43 Gy (minimum $p = 0.034$ for V_{43Gy}) and between RP3+ and V_{41Gy} ($p = 0.046$). There was significant correlation between RP2+ and RP3+ and minimum ipsilateral lung dose, $D_{100\%}$, ($p = 0.015$ and 0.013, respectively). Figures 2 and E2 summarize ipsilateral V_D and D_V correlations with RP2+ and RP3+. There was a correlation trend between RP2+ and MILD ($p = 0.062$) but none for RP3+. Overall, heart variables were more strongly correlated with RP than those for ipsilateral lung. The ipsilateral lung was likely affected by surgery or disease: its median volume was 1211 cc (372–2306 cc), smaller than the contralateral lung. There was no correlation between RP and ipsilateral lung volume.

Contralateral Lung: Planners chose beam directions to avoid entrance through contralateral lung and were strongly encouraged to use optimization constraints to limit contralateral lung dose (Table E1). The median contralateral lung mean dose was 6 Gy (3.7–10.3 Gy). Ten patients exceeded our 8 Gy contralateral mean dose guideline but none exceeded the V_{20Gy} 7% guideline (maximum was 4.6%). It was difficult to achieve the V_{5Gy} 25% guideline, which was exceeded in 90% of patients. There was significant correlation between RP2+ and $D_{0\%}$, the maximum contralateral lung dose ($p = 0.04$), but other dosimetric correlations were NS. Median contralateral lung volume was 1624 cc (747–

2937 cc). There was negative correlation between RP2+ and absolute contralateral lung volume- that is, larger volume implied higher RP2+ risk ($p=0.011$).

PTV—The PTVs were large, with median volume 2937 cc (1080–6500 cc). Much of the PTV was outside lung; median lung-PTV overlap volume was 554 cc (12–1080 cc). PTV had strong correlation with RP2+ ($p=0.00083$) and significant though weaker with RP3+ ($p=0.036$). However, the PTV-lung overlap volume correlation with RP was NS.

Bivariate CPH Models—Bivariate CPH models combining PTV size with significant dosimetric factors were investigated. For RP2+, significant models were: PTV ($p = 0.0051$) and Heart V_{43Gy} ($p = 0.014$); and PTV ($p = 0.046$) and Heart D_{10} ($p = 0.041$). Multivariate metrics based on these variables were $x = 0.000224 * PTV + 0.0596 * \text{Heart } V_{43}$ and $y = 0.000637 * PTV + 0.103 * \text{Heart } D_{10}$, where units of PTV, Heart V_{43Gy} and the Heart D_{10} are cc, %, and Gy respectively. Figure 3b shows K-M curves of freedom from RP2+ which are significantly split at the median x (the stronger model). There were no other significant multivariate models for RP2+ or RP3+.

Discussion and Conclusions

IMPRINT is a promising method for treating patients with unresectable MPM or after lung-sparing P/D. We previously reported treatment toxicity for the first 36 IMPRINT patients³ and failure patterns for a larger subset⁹. These patients, who are included in this study, received a median dose of 48.6 Gy in 27 fractions. In that initial experience, 7 patients (20%) developed RP3+.

Recently we published a prospective bi-institutional phase II study on IMPRINT safety using a different cohort⁵. Eight of the 27 evaluable patients had RP2+, with 2 experiencing RP3+ but no higher RP⁵. Twenty-four patients analyzed here were also in that study.

Minatel et al¹⁰ reported on 20 patients treated with tomotherapy to 50 Gy in 25 fractions with concomitant boost to 60 Gy for known residual disease. Maximum lung toxicity was Grade 3; 5 patients experienced RP2+. Contralateral lung V_{5Gy} was higher in patients with RP2+ than those without¹¹.

In this analysis of 103 patients, 27 had RP2+, including 14 with RP3+. We found strong correlation between symptomatic RP and heart doses. Correlation between heart doses and RP from thoracic RT has thus far been controversial. Animal experiments have suggested a connection between heart irradiation and pulmonary toxicity^{12–14}. A retrospective study of 209 NSCLC patients treated with conformal RT (3DCRT) to doses between 50 and 84 Gy found strong correlation of RP with higher heart doses, including D_V (V being 5, 10 and 15%); V_D (10, 50, 55 and 60 Gy) and generalized equivalent uniform dose with $a=10$ (stresses higher doses)¹⁵. Univariate dosimetric heart correlations were stronger than those for lung; their strongest multivariate model included heart $D_{10\%}$, lung $D_{35\%}$ and maximum dose. A recent publication on the RTOG 0617¹⁹ trial identified low heart doses (V_{5Gy} and V_{30Gy}) as significant predictors of overall survival (as opposed to RP). However, an early retrospective study of 78 NSCLC patients, perhaps limited by small sample size¹⁶, found no

significant correlation with heart $D_{5\%}$, $D_{\max}$ or mean dose, no heart dose correlation was reported in a recent meta-analysis¹⁷ and none was mentioned by the QUANTEC review¹⁸.

We used the findings of this study to provide new guidelines that correlate with complications yet give enough flexibility to develop plans in a clinically reasonable time frame. These are complex plans, often taking 1–2 planning days after receiving physician's contours. We have long used multi-level planning constraints for other disease sites to combine evidence-based OAR protection and planning feasibility. For such cases, the planner knows the preferred prescription dose and works to reach it while meeting Level 1 as well as the other OAR guidelines and limits. If reasonable efforts, including consulting other planners, cannot meet Level 1 with an otherwise acceptable plan, the planner attempts Level 2, often after discussion with the physician. If Level 2 is not already satisfied by the achieved plan, the planner may change beams or optimization parameters. If the planner still cannot reach Level 2 or 3 or planning time runs out, the physician's choices are to reduce prescription dose or to accept minor violations or to seek peer review consensus, or to request 'dose painting' lower dose to lower risk regions. Examples are provided in Appendix A1 (www.redjournal.org).

Table 3 shows the revised constraints, including multi-level heart constraints which acknowledge that (not surprisingly) attained heart dosimetric indices were larger for patients with left sided disease. Heart Level 1, which corresponds to the study's third quartile V_{40Gy} (24% for right-sided, 31% for left-sided) is preferred. Level 2 is acceptable if planner cannot reach Level 1. Right-sided Level 2 is similar to constraints for the analyzed cases (Table E1), with V_{40Gy} used to avoid confusing planners with two different V_{doses} . Left-sided Level 2 is also the heart limit and is identical to Level 3 for right-sided disease. Beyond this limit the above-described physician choices are made. Since our planners readily achieved at least the mean heart dose guidelines of Table E1, we are confident that the multi-level constraints will not impede workflow. One other guideline, for ipsilateral lung, was added- the 3rd quartile of ipsilateral V_{40Gy} . The MLD limit was not changed because while MLD was not significantly correlated with RP in this study, most dose-volume analyses of radiation-induced pulmonary toxicity show at least mild correlation with MLD¹⁸. We caution that our null result may be due to the small MLD range in our data (Figure E1) resulting from strict planning constraints, and recommend keeping these in effect.

But going forward, additional surveillance and aggressive toxicity management at the earliest sign of radiation pneumonitis may be key to minimizing severe toxicities, in left-MPM or large PTV patients who might be identified as at high risk for developing RP.

There was strongly significant correlation of RP with the PTV size, though not with the volume of PTV intersecting lung. We sought but did not find a linkage between PTV and significant features of the dose distribution that correlate with RP, such as ipsilateral $D_{100\%}$ or heart mean dose. It is possible that larger PTV is associated with a more significant systemic inflammatory response. If a PTV is particularly large, the physician may counsel and monitor the patient differently but treatment planning cannot mitigate this factor. The univariate correlation of larger contralateral lung volume with increased RP2+ risk did not remain significant on multivariate analysis. The NS correlation of MLD with symptomatic

RP or with the other dosimetric variables may be due to its lack of variation in this cohort. Similarly, perhaps because most patients had chemotherapy, chemotherapy has NS correlation with RP.

For MPM patients with EPP, low dose to the remaining lung is important in determining lung toxicity²⁰. For patients with two functioning lungs, our planners have been strongly encouraged to keep contralateral lung doses as low as possible. However, because we found only contralateral $D_{0\%}$ was significantly correlated with RP, we are not tightening the Table E1 contralateral V_D guidelines and will not demand excessive effort to meet the difficult V_{5Gy} guideline. However, the new ipsilateral lung guideline encourages reducing V_{40Gy} below its third quartile value, 66.5%.

As we accrue patients, we will learn whether the new constraints reduce RP incidence. We plan to correlate symptomatic RP with baseline pre-RT pulmonary function tests, functional VQ scans, radiographic normal tissue features, and potential pathophysiologic biomarkers to better identify high-risk patients for early intervention. Reference 5 reported a trend ($p=0.09$) between low diffusing capacity of carbon monoxide (DLCO) and RP2+. We hope to strengthen the dosimetric correlations observed here and better understand the role of large PTV as a risk factor and how heart dose may interact with other dosimetric or clinical factors.

We also recognize the need to improve long-term strategies to prevent late fibrosis following symptomatic RP, such as a combination of prednisone to suppress subacute inflammation with nintedanib to suppress conversion from subacute inflammation to pulmonary fibrosis (NCT02496585; www.clinicaltrials.gov).

The major weaknesses of this study are that it involves a single institution and a single RT technique and thus requires independent validation. Superior contralateral lung and heart doses from proton therapy may reduce toxicity for future patients^{21,22} and suggest dosimetric improvements for photon treatments. Its major strength is that it represents the single most exhaustive analysis of dosimetric predictors of RP in patients treated with IMPRINT. It is also the first study to identify cardiac dose as a significant predictor of RP in patients with MPM treated with adjuvant IMRT. Future work will need to independently validate our results and focus on identifying better predictors of RP2+ and RP3+ in this unique patient population that can be used by treatment planners and physicians for generating plans that minimize chances of serious toxicity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Summary

Hemithoracic intensity modulated pleural radiation therapy is a promising component of trimodality therapy for malignant pleural mesothelioma patients with two lungs. We used Cox Proportional Hazards to analyze clinical and dosimetric correlates of symptomatic radiation pneumonitis for 103 sequential patients with this treatment. Neither clinical variables nor total lung metrics had significant correlation. Cardiac doses (especially V_D for $35 < D < 47$ Gy) and PTV volume were most strongly correlated with this endpoint.

Figure 1.
A typical IMPRINT dose distribution. Doses shown are between 30 and 64 Gy

Figure 2.
p-values for correlation of RP2+ (2a) and RP3+ (2b) with dose, D, in V_D for heart and ipsilateral lung.

Figure 3.

Kaplan-Meier curves for freedom from RP2+ for the best univariate (heart V_{43} , Figure 3a) and bivariate (PTV in cubic centimeters and heart V_{43Gy} , Figure 3b) models. In both 3a and 3b, times for the following numbers at risk (NAR) are 50, 100, 200, 500, and 1000 days. In 3a, data is split at the V_{43Gy} median (16%). NAR at these times are, for $V_{43Gy} < 16\%$: 49, 47, 31, 17, and 5 respectively and for $V_{43Gy} > 16\%$: 46, 36, 26, 10, and 2 respectively. In 3b, data is split at the median of the multivariate Cox model metric, $x = 9.4$. For $x < 9.4$, NAR are: 47, 45, 32, 16 and 5 respectively and for $x > 9.4$: 48, 38, 25, 11, and 2 respectively.

Table 1

Characteristics of patient cohort.

Characteristic	No symptomatic RP (76 cases, 73.8% of total)	RP2+ (27 cases, 26.2% of total)	Percent of total
Average Age (y) at RT start [range]	66.5 [43–84.1]	70.1 [57–83.7]	
Gender			
Male	56	23	76.7%
Female	20	4	23.3%
Laterality			
Left	29	15	42.7%
Right	47	12	57.3%
Smoking history			
Never	34	6	38.8%
Former or Current	42	21	61.2%
Chemotherapy			
Yes	69	26	92.2%
No	7	1	7.8%
Histologic Type			
Epithelioid	62	23	82.5%
Sarcomatoid	4	0	3.9%
Biphasic	10	4	13.6%
Surgery			
None	10	2	11.7%
Extended Pleurectomy/Decortication	8	2	9.7%
Pleurectomy/Decortication	27	9	35%
Partial Pleurectomy	16	9	24.3%
Unresectable or exploratory	15	5	19.4%

Table 2

The p value and hazard ratio (HR) with 95% confidence interval in square brackets, for significant and trending variables from univariate CPH analysis. Variables with $p > 0.1$ are marked “NS”. For D_V and V_D the most significant dose or % volume is also stated. Note that the size of the hazard ratio is dependent on the variable units. For the PTV and contra-lateral lung volumes in cc, this results in hazard ratios close to one.

RP Grade	Variable	Heart	Ipsi Lung_not_GTV	Contra Lung	PTV
RP2+	Mean Dose (Gy)	P=0.07 HR=1.09 [0.993, 1.2]	P=0.062 HR=1.09 [0.996, 1.19]	NS	—
	D (Gy); Most Significant V_D	43 Gy; p=0.0029 HR=1.07 [1.02, 1.12]	43 Gy; p=0.034 HR=1.02 [1, 1.04]	NS	—
	V (%); Most Significant D_V	10%; p=0.011 HR=1.13 [1.03, 1.25]	100% (min dose) p=0.015 HR=1.07 [1.01, 1.14]	D_0 (max dose) P=0.04 HR=1.04 [1, 1.07]	—
	Volume (cc)	NS	NS	** P=0.011 HR=1.0011 [1.0002, 1.002]	P=0.00083 HR=1.0007 [1.0003, 1.0011]
RP3+	Mean Dose (Gy)	P=0.033 HR = 1.18 [1.01, 1.37]	NS	NS	—
	D (Gy); Most Significant V_D	41 Gy; p=0.011 HR=1.1 [1.02, 1.18]	41 Gy; p=0.046 HR=1.03 [1, 1.06]	NS	—
	V (%); Most Significant D_V	25%; p=0.017 HR=1.13 [1.02, 1.24]	100% (min dose) p=0.013 HR=1.09 [1.02, 1.17]	NS	—
	Volume (cc)	NS	NS	NS	P=0.036 HR=1.0006 [1.0, 1.0011]

** The risk of RP increases as contralateral lung volume increases.

Table 3

IMPRINT planning constraints based on this paper's analysis. New constraints are shaded. Heart Level 1 is preferred; Level 2 is 'acceptable' if planner cannot reach Level 1; Level 3 is a limit, beyond which prescription dose is reduced. For ipsilateral lung, $V_{40\text{Gy}}$, rather than $V_{43\text{Gy}}$, was chosen as significant and more easily read from the planning system DVH.

Structure	Criteria	Comments
PTV	D95 94%, V95 94%, D05 115%	
Non-specific tissue	Hot spots inside PTV	
Contralateral lung	$V_{5\text{Gy}}$ 25%, $V_{20\text{Gy}}$ 7%	Guideline
	Mean Dose 8 Gy	Guideline
Ipsilateral lung	$V_{40\text{Gy}}$ 66.5%	Guideline
Total lung_not_GTV (Lungs~)	Mean Dose 20 Gy preferred	Mean Dose 21 Gy is limit (<20 Gy preferred)
	$V_{20\text{Gy}}$ 37%–40%	Guideline
	Lyman-Kutcher-Burman NTCP 25%	Limit
Spinal Cord	Dmax 50 Gy	Limit
Heart	Level 1 Right Side: $V_{40\text{Gy}}$ 25%	Attempt Level 1 first; If Level 1 compromises coverage, attempt Level 2. For right side, if Level 2 is exceeded, attempt Level 3, which is the limit. If the limit is exceeded, consult the physician
	Level 1 Left Side: $V_{40\text{Gy}}$ 35%	
	Level 2 Right Side: $V_{40\text{Gy}}$ 35%	
	Level 2 Left Side: Mean Dose 30 Gy and Level 3 Limit for Right Side	Limit
Esophagus	Mean Dose 34 Gy, V60 17%	Guidelines
Bowel	Dmax PTV Dmax (~ 55 Gy) D05% 45 Gy	D05=50 Gy is limit
Stomach_not_PTV	Mean Dose 30 Gy	Guideline
Kidneys	$V_{18\text{Gy}}$ 33%	Guideline: each kidney evaluated separately. V50 50% for ipsilateral kidney is limit
Liver	Mean dose 30 Gy	Guideline: 31 Gy is limit
	$V_{30\text{Gy}}$ 50%	Guideline