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Is there a selection bias in radiotherapy dose escalation protocols?

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Abstract

Background: In dose escalation trials, normal tissue constraints generally remain constant while the tumor dose is increased. Since tumor dose and normal tissue constraints are competing demands, a point will be reached at which the tumor dose cannot be increased without exceeding normal tissue constraints. We therefore investigated the existence of a selection bias using a virtual radiotherapy dose escalation trial.

Materials and Methods: In nine patients with non-small-cell lung cancer, the tumor dose was escalated from 66 Gy to 78 Gy in 4-Gy dose levels using intensity modulated radiotherapy planning, while limiting normal tissue dose constraints remained constant. Dosimetric, radiobiological and other planning parameters were compared at the 66-Gy dose level for patients eligible for all dose levels and those eligible only for lower dose levels.

Results: Seven of nine patients were eligible for all dose levels (group E ‘eligible’). Two of nine patients (group I ‘ineligible’) qualified only for lower total doses (95% CI 0.075, 0.6, sign.). In group E, mean planning target volumes were smaller (132 versus 404 cm³, n.s.), monitor units per fraction were significantly lower (448 versus 802, p=0.0008), and the average composite score for plan quality was better than in group I (0.012 versus 0.068, n.s.). Average tumor control probabilities were higher (0.33 versus 0.23, n.s.), and normal tissue complication probabilities lower for group E than I.

Conclusion: Patients eligible for higher dose levels had significantly superior estimated outcome parameters. A method to eliminate this source of error in the interpretation of dose escalation trials is suggested.

Keywords

Dose escalation; Lung cancer; Normal tissue toxicity; Intensity modulated radiotherapy; Selection bias

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Conflicts of Interest None of the authors has any actual or potential conflict of interest.

Introduction:

Increasing tumor dose in radiotherapy is associated in general with better tumor control. Normal tissue toxicity is considered the major factor limiting higher doses to the tumor. To increase conventionally accepted doses under controlled circumstances, dose escalation trials are performed. More and more data on dose- and volume-dependence of normal tissue toxicity are becoming available, particularly in the thorax,¹⁻⁶ and are incorporated as limiting factors in dose escalation trials. Recent dose escalation trials in non-small-cell lung cancer (NSCLC) patients using conformal three-dimensional treatment technology have shown that giving higher radiation doses can be accomplished safely.^{2, 7-12} While phase I dose escalation trials do not provide any insight on the impact of higher doses on treatment outcome, their results are relevant as a basis for phase II and phase III trials.

It has been shown that the pneumonitis risk—as the major toxicity for thoracic radiotherapy—depends on the lung volume exceeding a threshold dose of 20 Gy.³ Current studies therefore stratify patients according to the irradiated lung volume and the estimated pneumonitis risk, allowing higher dose levels only in patients with a small risk, *i.e.*, usually in tumors with a smaller volume.^{2, 7, 8, 12} Stratification reduces the issue of tumor size, tumor location and tumor stage as confounding factors in the interpretation of dose escalation trials. However, wide dose ranges in each stratification group might still introduce a selection bias by virtue of the fact that less favourable tumors will not be eligible for the higher dose levels. Although normal tissue dose limitations have repeatedly been identified as a factor limiting dose escalation in individual patients, to the best of our knowledge no systematical analysis involving clinical data has been performed until now.

In order to test the hypothesis of the existence of a selection bias, a virtual dose escalation trial was performed in patients with NSCLC. Dose planning was performed with the same increasing dose levels and constant normal tissue constraints for all patients. The aim was to determine whether all patients were eligible for all dose levels and, if not, to identify significant differences in clinical, dosimetric and radiobiological parameters between those patients that met or did not meet the required normal tissue dose limitations at any of the given dose levels.

Material and Methods:

Based on the CT data sets of nine sequentially chosen patients with inoperable NSCLC, a virtual dose escalation study was performed. Tumor location and tumor extent varied between the patients. Similar to other dose escalation studies (see table 1), a large variety of tumor stages was included in this study: Locoregional tumor stages ranged from T1N0 to T3N3, with both peripheral (two patients) and central tumor locations (seven patients). The tumors were situated in the upper or middle lobes in seven of nine patients. Enlarged mediastinal lymph nodes were diagnosed in six patients.

All patients had planning computed tomography (CT) scans of the thorax with continuous 2.5-mm slices using a multislice CT scanner (GE Healthcare Technologies, Waukesha, WI). The CT scans were part of respiration-correlated 4D CT data sets provided by the MD Anderson Cancer Center, Houston, TX.

Contouring of target volumes and normal tissue was performed manually using a commercially available planning system (Pinnacle, Version 6.2 and 7.7, Philips Medical Systems, Milpitas, CA). The gross tumor volume (GTV) was defined as all macroscopically identifiable tumor, including lymph nodes with a diameter of at least 1 cm in the short axis on CT. To obtain the clinical tumor volume (CTV), the GTV was expanded by an 8-mm margin toward lung tissue¹³ and a 5-mm margin around affected lymph nodes. The CTV contour was adjusted to not cross lobe boundaries and to not include the chest wall or organs situated in the

mediastinum, unless infiltrated by the tumor. Unaffected lymph node areas were not included in the CTV. For the planning target volume (PTV), an 8-mm margin was added isotropically to the CTV to account for internal motion and set-up errors. These margins are similar to other dose escalation studies with or without respiration management (table 1).

Intensity modulated radiotherapy (IMRT) planning was performed using the Pinnacle treatment-planning system (version 6.2) with the collapsed-cone convolution implementation of the superposition algorithm.¹⁴ All planning was performed for gated delivery during unforced end-expiration, since expiration is the most stable respiratory position with the longest duration in the breathing cycle,¹⁵⁻¹⁷ and gated IMRT for lung cancer is in common use at our institution.¹⁸ The prescribed dose was increased in 4-Gy dose levels from 66 Gy as a standard dose for NSCLC treatment to 70 Gy, 74 Gy and 78 Gy with a fractionation of 5×2 Gy/week. The objective of inverse planning was to deliver the prescribed dose to at least 95% of the PTV. In general, six coplanar non-opposed 6-MV beams with gantry angles 0, 20, 40 or 60 degrees from the anterior or posterior direction were chosen. Beam angles were selected depending on the tumor location. The initially chosen beam arrangement for the lowest dose level remained the same for all other dose levels to avoid subjectivity in plan generation and comparison.

While plan optimization was performed using objectives that are adjusted to the changes in total dose, *e.g.*, allowing a dose range of -10% and $+20\%$ of the prescribed dose,^{19, 20} normal tissue constraints were absolute values and remained identical for all dose levels. The total lung volume receiving 20 Gy (V_{20}) or higher was limited to 30% of the lung volume.³ The total lung volume was defined as the combined volume of the right and left lungs after subtraction of the GTV. Esophagus and spinal cord were expanded isotropically by 5 mm to obtain the respective planning organ-at-risk volumes (PRVs). The maximum allowed dose to the esophagus PRV was 55 Gy (V_{55}) to 30% of the organ volume and 45 Gy to the spinal cord PRV.^{1, 6} The heart dose was limited to 40 Gy (V_{40}) for 50% of the total heart volume.²¹

The 'optimal' plan was converted to a deliverable plan using segmental multileaf collimator (MLC) step-and-shoot leaf sequences generated for a 21EX linear accelerator (Varian Medical System, Palo Alto, CA). Minimum field size and minimum monitor units per segment were kept the same for all plans. Reoptimization of the segment weights was performed to reduce the difference between the 'optimal' and deliverable plans. Modifications of the planning technique might have resulted in unacceptable plans to become eligible for higher dose levels. Usually, however, lowering the dose to one organ compromises the dose to other structures. Moreover, it was not the aim of this study to investigate methods of plan optimisation, but rather to demonstrate a systematic problem in dose escalation studies that potentially results in clinically relevant selection biases for higher dose levels.

Based on the IMRT plans for the different dose levels, dose-volume histograms (DVHs) were calculated for the PTV and for all above-mentioned normal tissue structures. According to the results of the DVH evaluations, patients were then divided into two groups: those in whom normal tissue dose constraints were met at all dose levels (group E 'eligible') and those who were not eligible for higher doses (group I 'ineligible'), even though the planning objectives had been met at lower dose levels. For the two groups, different parameters were compared at the 66-Gy dose level:

Clinical and dosimetric parameters:

The clinical and dosimetric parameters evaluated were magnitude of PTVs, monitor units (MUs), overall plan quality, and DVHs for the tumor and the organs at risk. The overall plan quality is summarized in a score represented by a single number that accounts for the actually achieved dose distribution for the PTV and the organs at risk after the deliverable IMRT plan is generated, relative to the initially given constraints. This quality score is the weighted sum

of the plan subscores for individual anatomic structures. A plan subscore is a measure for the deviation from the specified dose, dose-volume, or dose-response objective for that structure. The better the plan quality, the lower the quality score.

Estimated radiobiological outcome parameters:

The tumor control probability (TCP) values were calculated based on the method of Webb and Nahum,²² using an α -value of 0.23 Gy^{-1} to describe the mean radiosensitivity of the cell population and a standard deviation σ_α of 0.05 Gy^{-1} . A clonogenic cell density of $10^5/\text{cm}^3$ was assumed. The TCP values were compared at the 66-Gy dose level. These parameters were determined by Webb²³ to provide the best fit for a clinical squamous cell carcinoma (SCC) data set compiled by Brenner.²⁴ Though the data compiled by Brenner was for SCC of the upper digestive and respiratory tracts, the TCP values derived here for NSCLC were reasonable across the range of volumes and doses investigated. Normal tissue complication probabilities (NTCPs) were calculated for the lung using the Lyman model²⁵ with a median toxic dose (TD_{50}) of 30.8 Gy, a steepness m of 0.37 and a volume component n of 0.99.²⁶ To calculate the NTCP values for the esophagus, a TD_{50} of 47 Gy, a steepness m of 0.36 and an n value of 0.69 were used.¹

A statistical analysis using a Fisher's exact test was performed to check the significance of a subgroup of two patients not reaching the higher dose levels. If patient eligibility were independent of the dose levels, one would expect the eligibility number to stay the same. The null hypothesis therefore is the proportion of the eligible patients at the lowest dose that becomes ineligible at the highest dose is zero.

Wilcoxon rank tests and t-tests were used to test the significance of differences in clinical, dosimetric and radiobiological parameters using a p-value <0.05 to reject the null hypothesis.

Results:

Altogether seven of nine patients were eligible for all dose levels (group E). Two patients did not meet the eligibility criteria at the 70- and 74-Gy dose levels, respectively, because the allowed lung dose limitations had been exceeded (group I). In the patient who failed to be eligible for the dose levels of 70 Gy and higher, the maximum allowed spinal cord dose also had been exceeded at the 78-Gy dose level. The second patient was ineligible for the 74- and 78-Gy dose levels only because of lung dose limits (Figure 1). One of the two patients in group I had a central left upper lobe tumor with mediastinal lymph nodes, the second had a peripheral right lower lobe tumor without enlarged lymph nodes. The fact that only seven of nine patients were eligible for all dose levels was statistically significant in the Fisher's exact test (95% CI 0.075, 0.6, significantly different from zero).

Clinical and dosimetric parameters:

The average PTV volume of group E was 132 cm^3 , compared with 405 cm^3 for group I ($p=0.24$). Consequently the average MUs per fraction for group E were lower than for group I (448 versus 802, $p=0.0008$). The overall plan quality score was better for group E, compared with group I (0.012 versus 0.068, $p=0.12$). The average dose to 95% of the PTV was higher in group E than in group I (65.25 Gy, range 64.64 – 65.52 Gy [SD 0.33 Gy] versus 63.32 Gy, range 63.05 – 63.58 Gy [SD 0.37 Gy], $p=0.047$), indicating that reaching the PTV objective was more difficult for group I. The results from the evaluation of the DVHs for normal tissue are shown in Table 2. The difference in lung V_{20} values was highly significant between group E and I ($p=0.0002$), with the group I patients on average having a 12% higher volume receiving doses above 20 Gy. Figure 2 gives an example of the lung DVHs of two patients; one of them was eligible for all dose levels, while the second was ineligible at the 74 and 78 Gy dose levels.

Estimated radiobiological outcome parameters:

The average TCP values were 33.1% (SD 7.5%) for group E and 22.7% (SD 9.2%) for group I ($p=0.10$). The average NTCP values for the lung were 2.1% (SD 0.8%) for group E and 9.7% (SD 1.4%) for group I ($p=0.028$). For the esophagus, NTCP values of 3.4% (SD 0.9%) for group E and 12.1% (SD 6.5%) for group I were calculated ($p=0.68$).

Discussion:

Eligibility criteria in radiotherapy dose escalation trials regularly include dose limitations to normal tissue. While normal tissue constraints generally remain constant in dose escalation trials, the tumor dose is increased for each dose level. Because tumor dose and normal tissue constraints are competing demands, a point will be reached at which tumor dose cannot be increased without exceeding normal tissue constraints. If this point is reached within the dose spectrum of a dose escalation trial, a selection bias might be introduced.

In this virtual dose escalation trial with NSCLC patients, we found that some patients were not eligible for higher dose levels even though they had met the eligibility criteria at the lower dose levels. As a result, the estimated outcome between the patients who had been eligible for higher doses and those who had met the selection criteria only for the lower doses was significantly different. This might have led to an inadequate determination of maximum tolerated doses (MTD). Though the sample size of this study was relatively small, the sample was large enough to demonstrate the presence of a selection bias with statistical significance, emphasizing the magnitude of the effect.

In a real trial, patients are enrolled in a study without knowing their definitive dose level. When it turns out later that patients are not eligible for higher dose levels because of normal tissue dose limitations, they are either excluded from the study or treated at lower dose levels. At the same time, patients with more favourable dosimetric parameters are recruited to higher dose levels. In general, planning objectives are met more easily for small tumors. Tumor size is considered a predictive factor for the treatment outcome in patients with NSCLC tumors^{9, 27-30} and might therefore confound results in dose escalation trials. Kong *et al.*⁸ reported that in their trial patients receiving lower doses generally had larger tumors. However, they found that radiation dose was a stronger predictor than tumor volume or tumor stage. Rosenzweig *et al.*¹⁰ suggested to subdivide tumors into small, intermediate and large tumors in order to better identify the MTD that is valid for a respective tumor size. In the RTOG 9311 protocol, patients were stratified according to lung V_{20} . Patients with a $V_{20} < 25\%$ had smaller tumors, compared with patients with a V_{20} between 25% and 36%, and were therefore eligible for higher dose levels.²

PTV size varies considerably depending on the use of respiration management and/or other image guidance strategies. In this study isotropic margins were used to imitate the concepts of current dose escalation studies, with the treatment scenario being respiratory-gated IMRT. If no respiration management, and/or other image guidance strategies had been assumed, a change of safety margins would have been appropriate depending on the methodology and patient-specific findings. Changing the safety margin might lead to a different portion of patients becoming eligible for higher dose levels. Motion-encompassing treatment without respiration management, including the target volumes from each phase of the 4D CT scan covering the whole range of tumor motion, will lead to an expansion of PTVs and a lesser percentage of patients eligible for the all dose levels. For example, creating the PTV comprising the CTVs of all respiratory phases, enlarged the PTVs of the two group I patients by a factor of 1.26. This resulted in an ineligibility of both patients even at the lowest dose level of this study. Reducing the CTV to PTV-safety margin from 8 to 5 mm by using improved image guidance still left one of the two patients ineligible for the 66 Gy dose level. Margin definition, respiration

management and image guidance are therefore important parameters to consider during the design and interpretation of dose escalation studies.

In two dose escalation trials, the authors mention that the patients who were not eligible for higher dose levels, were treated with lower doses.^{7, 10} In one of the reports, the lung dose limits were exceeded in nine of 104 patients.¹⁰ In the other study, which included 55 patients, only one patient did not meet the protocol threshold for spinal cord, and six patients received doses to the esophagus that were too high.⁷ In a third study, three patients were either ineligible for a certain dose level or eligibility could not be determined.² The exact background for ineligibility was not mentioned.

As we have shown in the present study, treating patients who are ineligible for higher dose levels, due to unfavourable tumor geometry, larger tumor size or mediastinal lymph node involvement, etc.,⁸ with lower doses introduces a statistically significant selection bias. With ranges between 9 and nearly 50 Gy for minimum and maximum dose levels in published dose escalation trials, this phenomenon is probably observed more frequently.

The use of constant normal organ dose limitations as part of the eligibility criteria already preselects more favourable patients for study enrollment. While this does not introduce a bias per se, it is important to remember that MTDs are only valid for specified patient and treatment criteria. As an example, the nine patients described in this study are a subgroup of a 13-patient cohort, in which four patients were not even eligible for the 66-Gy dose level. A comparison between the nine eligible and the four ineligible patients revealed higher NTCP values for lung and esophagus ($p=0.08$ and 0.06) and significantly lower TCP values ($p=0.02$) for the four ineligible patients.

To address the higher pneumonitis risk for higher lung doses, some studies have stratified patients according to calculated risks and allowed higher dose levels only for low-risk patients. Stratifications were performed according to the magnitude of the lung V_{20} , the NTCP values for the lung, or the relative mean lung dose levels.^{2, 7, 8, 10, 12} Although this differentiation is very helpful for delivering higher dose levels safely and for defining the MTD for subgroups of patients, doses might still vary up to >30 Gy⁷ within each risk group, resulting in a still significant potential for selection biases.

The interpretation and comparison of dose escalation studies is certainly a challenging task. Variations in clinical eligibility criteria—such as tumor stage, lung function parameters, and application and timing of chemotherapy—limit the direct comparability of studies. In addition, differences in technical parameters, such as treatment technique (IMRT versus 3D CRT), choice of safety margins and target volumes (*e.g.*, with or without elective lymph nodes), and use of different fractionation schemes, such as accelerated, normofractionated or hypofractionated treatments, obviate a direct comparison (see Table 1). As a result, the level of MTDs in eligible patients varies from 74 Gy to >100 Gy in studies in which the MTD has not even been reached. Moreover, different studies use different toxicity classification systems to define the MTD. Dosimetric eligibility criteria most commonly use lung dose as a limit, however, some studies also use cord dose, esophagus or heart dose to identify eligible patients. The selection bias observed in the present study adds to these factors, influencing the interpretation of dose escalation studies, and, as we have shown, is of clinical relevance.

How can this selection bias be reduced or eliminated? One straightforward method is to select only those patients for a dose escalation trial for whom normal tissue tolerances meet the eligibility criteria at the highest dose level of the study, irrespective of the dose level actually planned for each patient. This will guarantee that all patients within a trial or stratification group have similar planning parameters and comparable outcome estimates.

In conclusion, the present use of constant normal organ dose limitations is assumed to introduce a clinically relevant selection bias in dose escalation trials that might result in a generalization of treatment results that is applicable only to a subgroup of the patient population. This selection bias can be avoided by including only patients who qualify for all dose levels.

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Figure 1.

Dose comparison for a large central lung tumor. **(a)** 66-Gy and **(b)** 78-Gy dose levels for the same patient who was not eligible for doses ≥ 74 Gy. The macroscopic tumor is shaded red. The 20-Gy isodose is shown by the yellow line. The green line corresponds with the 66-Gy isodose in (a) and the 78-Gy isodose in (b). Note the larger 20-Gy isodose area with the higher total dose.

(a)

(b)

Figure 2.

Dose-volume histogram (DVH) comparison for (a) a patient eligible for all dose levels and (b) a patient eligible only for the 66- and 70-Gy dose levels. The solid lines are derived from the 66-Gy dose level, while the dashed lines are from the 78-Gy dose level. The black lines show the DVHs for the PTV, while the red lines stand for the lung DVHs. The black mark represents the critical dose limit of the lung ($V_{20} \leq 30\%$). Dose limits have not been met if the lung DVH line is above the black mark.

Table 1

Dose escalation trials in non-small-cell lung cancer (NSCLC).

Author	Patient #, tumor stage, tumor volume	Chemo	Doses	Safety margins	Normal tissue dose limits	MTD definition and results
Belderbos 2003 ⁷	55 pat., stage I-IIIB		Escalation from 54.0 to 101.3 Gy	PTV=GTV+1–1.5 cm, no elective LN	5 risk groups according to relative mean lung dose and NTCPs, Cord<50 Gy, whole heart <40 Gy, 1/3 heart <66 Gy, esophagus V _{eff} 30% for 80 Gy	Lung tox ≥G3 (SWOG), acute esophagitis ≥G3, late esophagitis ≥G2 (RTOG), any ≥G3 toxicities (RTOG) MTD not reached, 7 pat ineligible for planned dose step because of normal tissue dose limits (1 cord, 6 esophagus)
Bradley 2005 ²	179 pat, stage I-III, Median GTV: Group I 31.8 cm ³ , Group II 79.5 cm ³	I in 25 pat.	Group I 70.9, 77.4, 83.8, 90.3 Gy Group II 70.9, 77.4, 83.8 Gy Group III 64.5, 70.9, 77.4 Gy ED 2.15 Gy	PTV=GTV+1 cm or more, no elective LN	Group I: Lung V ₂₀ <25% Group II: Lung V ₂₀ 25–36% Group III: Lung V ₂₀ >36% Escalation according to 5 effective lung volume bins and NTCPs	RTOG >=G3 tox in >=15%, MTD Group I 83.9 Gy, Group II 77.4 Gy,
Kong 2005 ⁸	106 pat, stage I-III	I in 19% pat. (stage III)	3D CRT, 63.0–102.9 Gy (2.1 Gy)	CTV=GTV+0.5cm, PTV=CTV+1–1.5cm, no elective LN		Dose predictive for outcome
Rosenman 2002 ⁹	62 pat., stage IIIA+B median GTV _{prechemo} 94 cm ³ , GTV _{postchemo} 64 cm ³	I + C	PTV _{prechemo} 46 Gy appa, PTV _{postchemo} boost to 60,66,70,74 Gy	PTV = CTV + ≥1.5 cm, CTV _{prechemo} =GTV _{prechemo} +elective LN, CTV boost=GTV _{postchemo} +1cm	Cord <50 Gy, left ventricle ≤40 Gy Lung V ₂₀ ≤35% Brachial plexus <66 Gy	CLGB G3–4 nonhematological tox, RTOG for esophagitis, MTD not reached
Rosenzweig 2005 ¹⁰	104 pat, stage I-IIIB	I in 16% of pat. (only at 81 and 84 Gy dose level)	3D CRT, 70.2 Gy (1.8 Gy), 75.6 Gy (1.8 Gy), 81 Gy (1.8 Gy), 84 Gy (2 Gy); 90 Gy (2 Gy) only for T1/2 N0 tumors, but lower f _{dim}	start: with elective LN, later PTV=GTV +1–1.5cm, respiration management in 18 pat.	NTCP lung <25%, Cord <50 Gy	RTOG >= G3 tox in >20%, MTD 84 Gy, 9 pat. ineligible for planned dose step because of lung dose limits
RTOG 0117	Stage I-IIIB	C	3D CRT arm 175.25 Gy (2.15 Gy/fx) arm II 74 Gy (2 Gy/fx)	PTV=GTV+1 cm or more	Lung V ₂₀ ≤30%, Mean esophagus dose ≤35 Gy, esophagus V ₅₅ ≤30% spinal cord < 45 Gy, heart ≤40 Gy, liver ≤30 Gy, 1/2 liver ≤35 Gy Cord < 50 Gy Lung V ₂₀ ≤35% Brachial plexus <66 Gy	MTD 74 Gy (2 Gy/Fx)
Socinski 2004 ¹¹	29 pat., stage IIIA+B, Median GTV _{preinduction} 66 ml, GTV _{postinduction} 28 ml	I + C	PTV _{prechemo} 40–50 Gy appa, PTV _{postchemo} boost to 78/82/86/90 Gy oblique fields	PTV=GTV+1–2 cm, elective LN		CTC grade 3–4 nonhematological tox, G4 esophagus tox, MTD not reached,
Wu 2003 ¹²	50 pat., stage II-IIIB, Mean GTV 63cm ³ (range 32–308)	I + A	42 Gy (2Gy) appa, 3D CRT to 69, 72, 75, 78 Gy (3 Gy)	PTV=GTV + 1–2cm, elective LN	Group I: Lung V ₂₀ <25%, Group II: Lung V ₂₀ 25–37%, Group III: Lung V ₂₀ >37%, Cord <45 Gy	RTOG G3 pneumonitis in 20% or more, MTD not reached

3D: three-dimensional; A: adjuvant chemotherapy; C: concurrent chemotherapy; CLGB: Cancer and Leukemia Group B; CRT: conformal radiotherapy; CTC: Common Toxicity Criteria; CTV: clinical target volume; t_{dam} : parallel model fraction damaged parameter; G: grade; GTV: gross tumor volume; I: induction chemotherapy; LN: lymph nodes; MTD: maximum tolerated dose; NTCP: normal tissue complication probability; PTV: planning target volume; RTOG: Radiation Therapy Oncology Group; SWOG: South Western Oncology Group; V_{eff} : effective volume; V_x : Volume of a specified organ receiving dose of x Gy or more

Table 2
Dose—volume evaluation for group E`eligible' and I`ineligible' at the 66-Gy dose level.

	Group E		Group I		P-value
	Mean volume	Standard deviation	Mean volume	Standard deviation	
Lung V _{20 Gy} [%]	15.3	5.0	27.2	0.7	0.0002
Esophagus V _{55 Gy} [%]	7.7	5.4	16.9	12.7	0.23
Heart V _{40 Gy} [%]	2.7	2.6	18.1	11.7	0.16
Spinal cord D _{0.1 %} [Gy]	35.2	11.1	41.2	5.0	0.17

D_x: minimum dose received by volume x of a specified organ; V_x: Volume of a specified organ receiving dose of x Gy or more.