

Correlation of Clinically Significant Radiation Esophagitis With Dose-volume Histogram Parameters in Lung Cancer

Jim Rose¹, George Rodrigues², Michael Lock², David D'Souza²

The University of Western Ontario¹ and the Department of Radiation Oncology², London Regional Cancer Program, London, ON

ABSTRACT

Objective: With dose escalation and increasing use of concurrent chemotherapy, radiation esophagitis (RE) remains a common treatment-limiting acute side effect. The advent of 3DCT planning has enabled investigators to study esophageal dose-volume histogram (DVH) parameters as predictors of RE. The aim of this investigation is to systematically assess the value of dosimetric parameters reported in the literature in predicting severity of RE and to provide recommendations for future research in the field.

Materials and Methods: Both prospective and retrospective clinical studies assessing the relationship between various dosimetric parameters and RE in the treatment of inoperable lung cancers and thymomas were included in this systematic analysis. Our search strategy included a variety of electronic medical databases, textbooks and bibliographies. Information relating to the relationship between dosimetric parameters, patient demographics, tumor characteristics and radiation/chemotherapy treatment with RE were extracted and analyzed.

Results: A total of 18 published studies were found to be suitable for analysis. Eleven of these studies assessed dosimetric parameters contributing to acute RE while the remainder assessed acute and chronic RE together. The overall published prevalence of RE (all grades) ranged from 6.9 % to 79.1%. Considerable heterogeneity of esophageal contouring practices, reported information, and RE outcome definitions exists in the literature. Few well-developed models including DVH metrics with or without other relevant prognostic factors to predict the risk of significant RE exist in the literature.

Conclusions: Further clarification of the predictive relationship between standardized dosimetric parameters and RE outcomes is essential to develop efficient radiation treatment planning in locally-advanced NSCLC. We propose that future studies assessing this relationship should focus on a smaller subset of the available parameters (V10, V20, V30, V40, V50 and mean esophageal dose) that have shown consistent correlation between the DVH parameter and RE.

METHODS AND MATERIALS

Research question

To what extent to dosimetric parameters currently used in the literature predict for RE in the context of radical external-beam radiation therapy for thoracic malignancies?

Systematic Review Procedures

Prospective and retrospective clinical studies assessing the relationship between dosimetric parameters and RE were included. Included studies could assess single or multiple dosimetric parameters alone or in conjunction with other clinical or biological parameters. Studies described only in abstract format were excluded from analysis. Patients diagnosed with non-small cell lung cancer (NSCLC), small-cell lung cancer (SCLC), thymoma or well-differentiated thymic carcinoma of any stage, including recurrences, were eligible. Patients were also eligible regardless of the chemotherapy regimen used, if any. Studies that include a minority of lung cancer patients with lung cancer were allowed in the review if radical doses were utilized. The study search was conducted in order to generate a comprehensive list of relevant studies. Electronic databases were searched from 1966 to December 2006 (MEDLINE, CANCERLIT, CINAHL, Cochrane Library). Reference sections of all identified studies were searched for relevant studies for inclusion. Major clinical oncology and radiation textbook reference lists were searched for relevant studies for inclusion. Several expert thoracic radiation oncologists and physicists were consulted for additional resources of published and unpublished data.

A list of all relevant articles was created and independently assessed by two reviewers. Study parameters that were assessed included patient and disease demographics, radiation dose and technique, clinical endpoints used in each study, dosimetric parameters studied and dosimetric parameters that were associated with RE. For each dosimetric parameter that was studied, the number of studies including that dosimetric parameter and the percentage of those studies showing a significant relationship with RE were determined. Dosimetric parameters that were included in less than 5 studies were not included in further analysis.

CONCLUSIONS

Future research into the association between dosimetric parameters and RE should include the following:

- Detailed, uniform reporting of patient, tumor, and treatment demographics.
- Detailed specification of CT contouring practices and dosimetric parameter calculation methods.
- Standardization of the RE scoring system (NCI CTC) and timeline (acute vs chronic).
- Future studies analyzing the relationship between dosimetric parameters and RE should include V₅₀, Dose_{MEAN}, V₄₀, V₄₅, V₂₀, and V₃₀ as well as a focused collection of clinically relevant parameters.
- Reporting of dosimetric parameter operating characteristics such as specificity, sensitivity, accuracy, and odds ratio with 95% CI which would allow conclusions to be drawn about the predictability of dosimetric parameters for RE.

This systematic review demonstrated that the best-studied dosimetric predictors were V₅₀, Dose_{MEAN}, V₄₀, V₄₅, V₂₀, and V₃₀. The current state of research, however, does not allow us to use dosimetric parameters to predict the occurrence of RE. Future research including the above recommendations is needed to clarify this relationship.

RESULTS

Table 1. Number and percentage of studies demonstrating a significant relationship between various dosimetric parameters and RE.

Dosimetric Parameter	Number of Studies Including Dosimetric Parameter	Percentage of Studies With Significant Results
V 50	12	75*
Dose _{MEAN}	9	89*
V 40	8	75*
V 45	7	71*
V 20	5	80*
V 30	5	80*
V 55	8	63
V 60	9	44
V 65	6	33
Length	5	40
Dose _{MAX}	5	63

Table 2. Summary of investigations defining selected dosimetric predictors of esophageal toxicity.

Author	N	Disease Demographics	Technique	Contouring	Degree of RE Evaluated	Dosimetric Parameters Studied	Dosimetric Parameters Significantly Associated with RE
Kahn et al.	236	Lung cancer	3D-CRT	External surface; lung apices to GE junction	AE + CD, RTOG criteria	Dose _{MEAN} , V _{DOSE}	Dose _{MEAN} , V _{50 Gy, 60 Gy}
Wei et al.	215	Stage I-IV NSCLC, SCLC	3D-CRT± concurrent ± induction chemotherapy	External surface; lower cricoid to GE junction	≥ grade 3 AE + CE	Dose _{MEAN} , aV _{DOSE} , rV _{DOSE}	Dose _{MEAN} , aV _{15 Gy-45 Gy} , rV _{10 Gy-45 Gy}
Qiao et al.	208	NSCLC, SCLC	3D-CRT ± sequential and concurrent chemotherapy	Thoracic inlet to diaphragm	≥ grade 3 AE + CE, RTOG criteria	Dose _{MEAN} , Dose _{MAX} , V _{DOSE}	Dose _{MEAN} , Dose _{MAX}
Singh et al.	207	NSCLC, SCLC, undifferentiated large cell	3D-CRT + concurrent or sequential chemotherapy	Thoracic inlet to diaphragm	≥ grade 3 AE, RTOG criteria	Dose _{MEAN} , Dose _{MAX} , V _{DOSE}	Dose _{MEAN} , Dose _{MAX}
Ahn et al.	196	Stage I-III NSCLC	3D-CRT ± sequential and concurrent chemotherapy	Lung apices to GE junction	AE + CE, RTOG criteria	Dose _{MEAN} , Dose _{MAX} , V _{DOSE} , CIRC _{DOSE} , LETT _{DOSE}	Dose _{MEAN} , Dose _{MAX} , V _{50 Gy} , CIRC _{2-50 Gy, > 70 Gy} , LETT _{2-50 Gy}
Bradley et al.	166	Stage I-III NSCLC	3D-CRT ± sequential and concurrent chemotherapy	Internal and external surfaces; thoracic inlet to diaphragm	≥ grade 2 AE, RTOG criteria	SA _{DOSE} , V _{DOSE}	SA _{5-70 Gy} , V _{< 70 Gy}
Belderbos et al.	156	Stage I-III NSCLC	3D-CRT ± concurrent and/or sequential chemotherapy	2 cm above jugulum to GD junction	≥ grade 2 AD, RTOG criteria	V100% _{DOSE} , LETT _{DOSE}	V100% _{20-60 Gy} , LETT _{> 40 Gy, > 65 Gy}
Kim et al.	124	Stage I-III NSCLC, SCLC	3D-CRT ± sequential and concurrent chemo	External surface; lower cricoid cartilage to GE junction	≥ grade 3 AD, RTOG criteria	V _{DOSE} , Dose _{MAX} , % Length	V _{58 Gy-65 Gy} , Dose _{MAX}
Chapet et al.	122	NSCLC	3D-CRT ± sequential chemotherapy	External surface contoured from first rib to GE junction	≥ grade 2 AE, RTOG criteria	V _{DOSE} , Dose _{MAX}	V _{40-70 Gy} , Dose _{MAX}
Choy et al.	114	Stage IIIa/b NSCLC	RT + concurrent chemotherapy	N/R	AE, RTOG criteria	Length	None
Werner-Wasik et al.	105	NSCLC, SCLC	RT ± chemotherapy	N/R	AE, RTOG criteria	Length	None
Maguire et al.	91	NSCLC	3D-CRT± chemotherapy	External surface contoured on each slice from lung apex to GE junction	AE + CE, RTOG criteria	V _{DOSE} , SA _{DOSE} , LETT _{DOSE} , CIRC _{DOSE}	V _{50 Gy} , SA _{50 Gy} , LETT _{2-50 Gy} , CIRC _{2-50 Gy}
Rosenman et al.	62	Stage IIIa/b NSCLC	3D-CRT+ induction, concurrent chemotherapy	N/R	AE + CE, RTOG criteria	Length	Length
Takeda et al.	61	Stage I-IV and recurrent NSCLC, SCLC, thymoma, thymic cancer	RT ± concurrent chemotherapy	External surface; lower cricoid to GE junction	AE, RTOG criteria	Dose _{MEAN} , Dose _{MAX} , V _{DOSE}	Dose _{MEAN} , V _{≥ 10 Gy, > 25 Gy}
Patel et al.	36	Stage IIIa/b NSCLC	3D-CRT with induction chemotherapy	External surface; cricoid cartilage to GE junction	≥ grade 2 AE, RTOG criteria	V _{DOSE} , Length	V _{50 Gy}
Takeda et al.	35	Stage I-IV and recurrent NSCLC and SCLC	3D-CRT ± sequential and concurrent chemotherapy	External surface; lower cricoid junction to GE junction	AE, RTOG criteria	Dose _{MAX} , V _{DOSE}	Dose _{MEAN} , V _{≥ 10 Gy, > 25 Gy}
Hirota et al.	26	Stage III and recurrent NSCLC	3D-CRT + concurrent chemotherapy	External surface; lower cricoid to GE junction	Modified NCI-CTC score	V _{DOSE} , LETT _{DOSE} , Dose _{MEAN} , Dose _{MAX}	V _{≥ 40 Gy, > 55 Gy} , Dose _{MEAN}
Langer et al.	13	Stage II/IIIb NSCLC	RT+ neoadjuvant chemotherapy	N/R	AE, criteria N/R	Length	Length