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REVIEW

Advances in dosimetry and biological predictors of radiation-induced esophagitis

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Objective: To summarize the research progress about the dosimetry and biological predictors of radiation-induced esophagitis.

Methods: We performed a systematic literature review addressing radiation esophagitis in the treatment of lung cancer published between January 2009 and May 2015 in the PubMed full-text database index systems.

Results: Twenty-eight eligible documents were included in the final analysis. Many clinical factors were related to the risk of radiation esophagitis, such as elder patients, concurrent chemoradiotherapy, and the intense radiotherapy regimen (hyperfractionated radiotherapy or stereotactic body radiotherapy). The parameters including D_{max}, D_{mean}, V_{20}, V_{30}, V_{50}, and V_{55} may be valuable in predicting the occurrence of radiation esophagitis in patients receiving concurrent chemoradiotherapy. Genetic variants in inflammation-related genes are also associated with radiation-induced toxicity.

Conclusion: Dosimetry and biological factors of radiation-induced esophagitis provide clinical information to decrease its occurrence and grade during radiotherapy. More prospective studies are warranted to confirm their prediction efficacy.

Keywords: lung cancer, esophagitis, radiation injuries, predictors

Introduction

Increasing use of radiotherapy or concurrent chemoradiotherapy (CCRT) for thoracic cancer (lung, esophageal, or breast cancer) inevitably leads to radiation esophagitis (RE), which emerged as responses to esophageal mucosa irradiation.[1] During radiotherapy, the esophageal mucosa within the radiation field can incur congestion, edema, or erosion, which are associated with the clinical symptoms including dysphagia, odynophagia, and substernal pain, and even late esophageal stricture, stenosis, and tracheoesophageal fistula.[2] These adverse side effects are dose-limiting factors that impair the treatment outcome and patient's quality of life.

Several scoring systems for clinical RE have been developed and reported in the medical literature. The studies cited in the present report mostly used the Radiation Therapy Oncology Group (RTOG) scoring system. Some studies used the Common Terminology Criteria for Adverse Events or the National Cancer Institute Common Toxicity Criteria scale. In general, grade 1 toxicity does not affect patients' daily life too much without the need of medical intervention. Grade 2 or higher grade toxicities were recognized as clinically significant, which means medicine is indispensable.[3] More importantly, a number of dosimetric parameters and biological factors have shown to be correlated with RE, mainly for lung cancer patients.

Prevention and treatment of RE is the key to improve the efficacy of radiotherapy for the thoracic cancer. The purpose of our study was to summarize published dosimetric

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parameters and biological predictors for RE toxicity in recent 5 years for potential clinical use and provide recommendations for future research in the field.

Methods

RE-related clinical studies were incorporated, which analyzed the relationship between RE and parameters regardless of single parameter or not. In addition, dosimetric parameters predicting RE were constrained to the research for lung cancer radiotherapy without limitation of histology type or clinical stage. No standard chemotherapy regimen was required.

Using radiation-induced esophagitis, radiation-induced esophageal injury as terms, the related lung cancer literature published between January 2009 and May 2015 in the PubMed full-text database index systems was searched. Inclusion criteria were: 1) the characteristics of clinical and radiation dose on radiation-induced esophagitis; 2) the research progress on influencing factors of radiation-induced esophagitis; 3) the research status on biological factors of radiation-induced esophagitis. The reports about the treatment of RE or studies in abstract form were excluded.

Results

Using the mentioned search strategy, 28 studies were identified. Of these studies, 21 assessed dosimetric parameters of RE (Table 1), three reported biological predictors, while four studies assessed other factors. The relationship between dose–volume histogram parameters cutoff points and RE risk is summarized in Table 2. Most studies focused on acute RE, while only two studies assessed both acute and chronic RE. Two studies assessed any grade of RE, five studies assessed grade 2 or greater RE, and four studies assessed grade 3 or greater RE as the clinically important toxicity, respectively. Nineteen studies graded RE using RTOG criteria, while one study used the common toxicity criteria[4] and another used the common terminology criteria.[5] We summarized the results from five aspects as below.

Effect of radiotherapy fraction

The incidence and extent of esophagitis are correlated with radiotherapy fraction. Higher acute esophagitis (AE) rates are seen with increased RT aggressiveness as hyperfractionation, accelerated, and stereotactic body radiotherapy.

The strong relationship between hyperfractionated CCRT and severe AE was demonstrated in RTOG database analysis for 528 locally advanced non-small-cell lung cancer (LA-NSCLC).[6] Watkins et al[7] analyzed 48 limited-stage small-cell lung cancer (SCLC) patients, who received hyperfractionated-accelerated radiotherapy (median dose 45 Gy, range 42–51 Gy), 1.5 Gy bid with concurrent chemotherapy. RTOG grade 3 AE occurred in eleven patients. Mean esophageal dose (D_{mean}; P=0.002) and relative volume dosimetric area under curve (P=0.004) demonstrated the significant association between grade 3 acute esophagitis. The most strongly associated dosimetric volume was V_{15} (grade 3 esophagitis rates of 15% as $V_{15}<60\%$ vs 64% as $V_{15}>60\%$). Grant et al[8] also reported 130 limited-stage SCLC patients treated with the hyperfractionated-accelerated radiotherapy protocol, 25 patients developed severe acute esophagitis. Eight patients (6%, 128 eligible) experienced esophageal stricture, with six cases in 23 patients who experienced prior grade 3 acute esophagitis (26%) and another two cases in 105 patients with acute esophagitis ≤grade 2 (2%). D_{mean} and $V_{5–40}$ were the significant predictors of acute esophagitis. Patients with $V_5\geq74\%$ had higher risk of acute grade 3 esophagitis (44.4% as $V_5\geq74\%$ vs 12.6% as $V_5<74\%$). V_{45} was the only significant dosimetric predictor for esophageal stricture (esophageal stricture rates 1.3% as $V_{45}<37.5\%$ vs 13.7% as $V_{45}\geq37.5\%$, P=0.0497). Zehentmayr et al[9] investigated dosimetric predictors for ≥grade 2 RE in 66 patients with LA-NSCLC treated with accelerated radiotherapy (1.8 Gy bid). Twenty-three patients (35%) experienced ≥grade 2 RE. On multivariate analysis, $V_{38}>34\%$ (P=0.007) was the most significant predictor for ≥grade 2 RE. Mauguen et al[10] found hyperfractionated or accelerated radiotherapy increased acute esophagitis rates compared with conventional fractionation radiotherapy for NSCLC (19% vs 9%) and SCLC (25% vs 12%). However, some studies considered that hyperfractionated or accelerated radiotherapy did not increase the incidence of RE. Manapov et al[11] reported that absolute esophageal volume included in the 95% isodose (>42.8 Gy) was the only significant variable (P=0.03) predicting severe acute esophagitis (>grade 2). Bar-Ad et al[12] reported that dose per fraction of 1.8 Gy had a lower risk of ≥grade 2 acute esophagitis as compared with dose per fraction of 2 Gy (P=0.011).

Due to the difference between conventional fraction irradiation and hypofractionated therapy including stereotactic body radiotherapy (SBRT), dosimetric constraints in conventional fraction irradiation could not be applied in hypofractionated setting. SBRT plays more and more important role in treating cancer from central lung zone. Therefore, it is imperative to investigate esophageal complications from SBRT. A retrospective analysis assessed

Table 1 Summary of dosimetric predictors of radiation-induced esophagitis in patients

Author	N	Cancer type	Treatments	Endpoints	Results (dosimetric parameters significantly associated with RE)
Watkins et al[7]	48	Limited-stage SCLC	3D-CRT (42–51 Gy, 1.5 Gy bid) + concurrent chemotherapy (platinum-based)	≥grade 3 AE, RTOG criteria	MED RV-AUC V_{15}
Jonathan et al[8]	130	Limited-stage SCLC	3D-CRT (42–51 Gy, 1.5 Gy bid) + concurrent chemotherapy (platinum-based)	≥grade 3 AE, RTOG criteria + esophageal stricture	MED $V_{5–40}$ V_{45}
Franz et al[9]	166	Stage II–IIIb NSCLC	3D-CRT (73.8–90 Gy, 1.8 Gy bid) + sequential chemotherapy (platinum-based + gemcitabine or pemetrexed)	≥grade 2 AE, RTOG criteria	V_{38}
Manapov et al[11]	82	Stage IIIa/b NSCLC	3D-CRT (45 Gy, 1.5 Gy bid) + sequential chemotherapy (carboplatin/paclitaxel)	≥grade 2 AE, RTOG criteria	Absolute esophageal volume included in the 95% isodose (>42.8 Gy)
Bar-Ad et al[12]	49	Stage IIIa/b NSCLC	3D-CRT (55.8–74 Gy, 1.5 or 1.8 Gy) + concurrent chemotherapy (platinum-based)	≥grade 2 AE, RTOG criteria	The total volume of the esophagus and larger dose per fraction (2 vs 1.8 Gy)
Wu et al[13]	125	Stage I–IV central lung	SBRT (30–60 Gy, ≥6 Gy in five fractions or fewer)	≥grade 2 AE, RTOG criteria	D_{max}≤52.9 BED_{10}, D_5cc≤26.3 BED_{10}
Topkan et al[16]	41	Stage IIIa/b NSCLC	3D-CRT or IMRT (51.3–66.1 Gy) + concurrent chemotherapy (platinum-based)	≥grade 2 AE, RTOG criteria	V_{55}
Zhu et al[17]	157	Stage I–IV NSCLC	3D-CRT (40–76.5 Gy, 1.8–2.0 Gy) ± concurrent chemotherapy (various regimens)	≥grade 2 AE, RTOG criteria	V_{50}
Rodriguez et al[18]	59	Stage II–IIIb NSCLC	3D-CRT (57.41–66.69 Gy, 1.8–2.0 Gy) + concurrent chemotherapy (various regimens)	AE, RTOG criteria	V_{50}
Zhang et al[19]	76	Stage II–IV NSCLC	3D-CRT or IMRT (56–66 Gy, 1.8 or 2.0 Gy) + concurrent chemotherapy (cisplatin, docetaxel/vinorelbine)	AE, RTOG criteria	V_{40} V_{50} chemotherapy agents
Kwint et al[4]	139	Stage I–IIIb NSCLC	IMRT (66 Gy in 24 fractions, 2 Gy per fraction, 5 days per week) + concurrent chemotherapy (low-dose cisplatin)	≥grade 2 AE, common toxicity criteria 3.0	V_{50}
Kuroda et al[5]	32	Stage III NSCLC	3D-CRT (66 Gy/33 Fr, 72 Gy/36 Fr, 78 Gy/39 Fr) + concurrent chemotherapy (cisplatin/vinorelbine)	AE, common terminology criteria	V_{35}
Caglar et al[20]	109	Stage IIIa/b NSCLC	3D-CRT (50–54 Gy, 60–68 Gy) + concurrent chemotherapy (carboplatin/paclitaxel, cisplatin/etoposide)	≥grade 3 AE, RTOG criteria + esophageal stricture	MED V_{45}–V_{60} V_{55}
Ozgen et al[21]	72	Lung cancer	3D-CRT (55–62.3 Gy) + concurrent chemotherapy (cisplatin daily)	≥grade 2 AE, RTOG criteria	MED
Huang et al[22]	374	Stage I–IIIb NSCLC	3D-CRT (≥60 Gy) ± concurrent or sequential chemotherapy (various regimens)	≥grade 2 AE, RTOG criteria	MED
Palma et al[23]	1,082	Stage I–IIIb NSCLC	3D-CRT or IMRT (14–81.6 Gy) + concurrent chemotherapy (platinum-based)	≥grade 2 AE, RTOG criteria	V_{60}

Abbreviations: 3D-CRT, 3D conformal radiotherapy; AE, acute esophagitis; BED_{10}, biological equivalent doses with $\alpha/\beta = 10$ Gy; D_{max}, maximum esophageal dose; D_5cc, dose to the hottest 5cc; IMRT, intensity-modulated radiation therapy; MED, mean esophageal dose; NSCLC, non-small-cell lung cancer; RE, radiation esophagitis; RTOG, Radiation Therapy Oncology Group; RV-AUC, relative volume dosimetric area under curve; SBRT, stereotactic body radiotherapy; SCLC, small-cell lung cancer.

Table 2 Relationship between DVH cutoff points and clinically significant acute esophagitis risk in the literature

Author	Outcome	DVH–acute esophagitis relationships
Watkins et al[7]	≥grade 3	If $V_{15\ Gy}$<60% then ≥grade 3 AE risk =15% If $V_{15\ Gy}$≥60% then ≥grade 3 AE risk =64%
Jonathan et al[8]	≥grade 3 esophageal stricture	If $V_{5\ Gy}$<74% then ≥grade 3 AE risk =12.6% If $V_{5\ Gy}$≥74% then ≥grade 3 AE risk =44.4% If $V_{45\ Gy}$<37.5% then esophageal stricture rate =1.3% If $V_{45\ Gy}$≥37.5% then esophageal stricture rate =13.7%
Franz et al[9]	≥grade 2	If $V_{38\ Gy}$<34% then ≥grade 2 AE risk ≤30%
Topkan et al[16]	≥grade 2	If $V_{55\ Gy}$<35% then ≥grade 2 or 3 AE risk =31% If $V_{55\ Gy}$≥35% then ≥grade 2 or 3 AE risk =76%
Rodriguez et al[18]	≥grade 2	If $V_{50\ Gy}$<30% then ≥grade 1 AE risk =47.3% If $V_{50\ Gy}$≥30% then ≥grade 1 AE risk =73.3%
Zhang et al[19]	≥grade 2	If $V_{40\ Gy}$<23% and concurrent chemotherapy then ≥grade 2 AE risk =33.3% If $V_{40\ Gy}$≥23% and concurrent chemotherapy then ≥grade 2 AE risk =89.1%
	≥grade 3	If $V_{50\ Gy}$<26.5% and concurrent chemotherapy then ≥grade 3 AE risk =6.7% If $V_{50\ Gy}$≥26.5% and concurrent chemotherapy then ≥grade 3 AE risk =38.7%
Kuroda et al[5]	≥grade 2	If $V_{35\ Gy}$<20% then ≥grade 2 AE risk =35.7% If $V_{35\ Gy}$≥20% then ≥grade 2 AE risk =88.9%
Ozgen et al[21]	≥grade 2	If MED <28 Gy then ≥grade 2 AE risk =0% If MED ≥28 Gy then ≥grade 2 AE risk =60.7%

Abbreviations: AE, acute esophagitis; DVH, dose–volume histogram; MED, mean esophageal dose in Gy.

esophageal toxicity in 125 SBRT patients, using biological equivalent doses with α/β =10 Gy (BED_{10}).[13] Dose to the hottest 5cc (D_5cc) and maximum dose of the esophagus (D_{max}) were the best predictors of ≥grade 2 acute RE. To keep the acute RE rate <20%, it was suggested to keep D_{max} ≤52.9 Gy and D_5cc ≤26.3 Gy. In addition, D_5cc should be kept <16.8, 18.1, and 19.0 Gy, D_{max} should be kept <27.6, 30.2, and 32.2 Gy, for 3, 4, and 5 fractions of SBRT, respectively.

Dose–volumetric parameters

CCRT was widely administrated in treating inoperable LA-NSCLC and improved local control and overall survival compared with radiotherapy alone.[14] However, the acute toxicity also increased[15] (RTOG 9410 trial investigating three different regimens reported a 45% of grade 3 acute esophagitis in the CCRT arm). Physical factors are important basis for predicting acute esophagitis and formulating radiotherapy planning in 3D conformal radiotherapy or intensity-modulated radiation therapy. The parameters include the absolute volume, mean dose (D_{mean}), or percentage of a reference volume (V_{dose}), or maximum dose (D_{max}) of the esophagus. Topkan et al[16] found V_{55} was the only dosimetric predictor for RTOG grade 2 or greater acute esophagitis on multivariate analysis: V_{55}<35% had a 31% risk of RE grade 2 or 3, and the risk increased to 76% as V_{55}≥35% (P=0.01). Zhu et al[17] reported that grade 2 or 3 RE occurred in 24% in the radiotherapy-alone group and 52% in the CCRT group. They found that V_{50} was the only significant factor in multivariate analysis. Rodriguez et al[18] revealed that V_{50} was the most statistically significant factor (grade ≥1 RE risk: 47.3% as V_{50}<30%, 73.3% as V_{50}≥30%). V_{50} was also the significant predictor for RE ≥grade 3 in the study by Kwint et al.[4] Zhang et al[19] demonstrated that, in CCRT, V_{40} was the significant factor associated with grade ≥2 RE (33.3% as V_{40}<23% vs 89.1% as V_{40}≥23%) and V_{50} was significantly correlated with grade 3 RE (6.7% as V_{50}<26.5% vs 38.7% as V_{50}≥26.5%). Kuroda et al[5] revealed that V_{35} was the only dosimetric predictor for grade ≥2 RE on multivariate analysis. Caglar et al[20] found that D_{mean} and V_{45}–V_{60} were significantly associated with the risk of grade ≥3 RE. V_{55} and V_{60} for the entire esophagus (Esoph) and esophagus in-field ($Esoph_{in}$) significantly correlated with development of esophageal stricture. V_{55} $Esoph_{in}$ to 50% was the best cutoff point for acute esophagitis. Both Ozgen et al[21] and Huang et al[22] reported that D_{mean} was significantly correlated with grade ≥2 RE. Palma et al[23] reported that V_{60} was the best predictor of RE, while V_{60}>17% conferred the higher risk of grade ≥3 RE.

Multiple parameters analysis

Given the heterogeneity among studies, and the limitation of single predicting factor, some research focused on multiple parameter analysis about the predicting factors for RE. Gu et al[24] found that radiation sensitization, length of irradiated esophagus, average dose of irradiated esophagus,

and V_{50} were independent factors for the occurrence of RE. Zhang et al revealed that lymph nodes stage, pretreatment weight loss ≥5%, concurrent chemotherapy, and the use of late-course hyperfractionated radiotherapy were significantly associated with grade 2 and 3 RE.[25] Dose–volume parameters correlating RE included D_{mean}, D_{max}, and relative volume ($rV_{15–60}$).

Multiple volumetric metrics were reported as the absolute volume or area, relative volume or area, and circumferential measures, which made it difficult for dosimetric recommendations. However, by comparison of reports with similar radiotherapy protocol, some consistent conclusion could be drawn. Among the ten studies using CCRT, nine studies assessed one or all of following parameters: maximum esophageal dose, mean esophageal dose, median esophageal dose, or total esophageal dose. All ten studies assessed V_{dose}. Three studies assessed irradiated esophagus length and volume, three studies assessed the normal tissue complication probability, and one study assessed relative and absolute volume of the esophagus in the radiation field. All these parameters significantly correlated with RE in the original studies. Of these parameters, six (D_{max}, D_{mean}, V_{20}, V_{30}, V_{50}, and V_{55}) were evaluated in five or more studies and significantly associated with RE (Table 3). By further analysis, it was found that D_{max}, D_{mean}, V_{20}, V_{30}, V_{50}, and V_{55} were correlated with acute RE, and D_{mean} and V_{55} were correlated with both acute RE and late esophageal stricture.

Table 3 Number and percentage of studies demonstrating a significant relationship between dosimetric parameters and RE

Dosimetric parameter	Number of studies	Significant results with acute RE (%)
D_{total} esophagus	2	1/2 (50)
D_{mean}	9	8/9 (89)
D_{max}	7	6/7 (86)
Irradiated esophagus length	3	3/3 (100)
Irradiated esophagus volume	3	3/3 (100)
V_5	3	2/3 (67)
V_{10}	4	2/4 (50)
V_{15}	5	3/5 (60)
V_{20}	9	7/9 (78)
V_{25}	5	3/5 (60)
V_{30}	9	7/9 (78)
V_{35}	7	4/7 (57)
V_{40}	9	6/9 (67)
V_{45}	8	5/8 (63)
V_{50}	10	7/10 (70)
V_{55}	8	6/8 (75)
V_{60}	9	6/9 (67)
V_{65}	2	0/2 (0)

Abbreviations: D_{mean}, mean esophageal dose in Gy; D_{max}, maximum esophageal dose; RE, radiation esophagitis.

Biological predictors of radiation-induced esophagitis

Biological factors, such as genetic variation play an important role in radiation-induced normal tissue damage. Discriminating patients with high risks of treatment-related toxicities based on biological factors could optimize treatment decision and lead to personalized radiotherapy.

Transforming growth factor-beta 1 (TGF-β1) elevated dramatically in response to radiation exposure.[26] Common variants located in TGF-β1 have been found to have connection with late normal tissue complications after irradiation. Recently, an increasing number of studies related variants in TGF-β1 to RE. Hildebrandt et al[27] found that nine TGF-β1 single nucleotide polymorphisms (SNPs) were associated with a 1.5- to 4-fold increase of esophagitis risk, including three PTGS2 (COX2) variants: rs20417, rs5275, and rs689470. The cumulative effect of these SNPs on risk was dose-dependent, as evidenced by a significantly increased risk of either toxicity with an increasing number of genotypes. Another study showed that the CG/GG genotype of HSPB1 rs2868371 was associated with significantly lower risk of grade ≥3 RE than the CC genotype.[28] Yuan et al[29] also found TGF-β1 genotype was associated with RE in NSCLC patients. Patients with TGF-β1 509CC had greater grade RE than T allele carriers. Therefore, TGF-β1 SNP could be used as a predictive biomarker for the studied endpoint and might be used for guiding therapy intensity or interventions for toxicity in NSCLC patients.

Other factors

Recent studies have investigated the correlation between RE with imaging and hematology parameters. Court et al[30] found that CT imaging could be used to quantify radiation-induced injury to the esophagus. Esophagus expansion on CT images has potential as an objective of toxicity. Yuan et al[31] and Nijkamp et al[32] found that 2-[fluorine-18]fluoro-2-deoxy-D-glucose uptake in esophagus increased during radiotherapy and this increase reflected the degree of RE. Tang et al[33] used the physiologic acute phase response (APR) score as risk factors to predict RE: platelet counts ≥377×10^3/μL, hemoglobin <12.9×10^3 d/L. Based on these two risk factors, an APR score was defined as 0 (no risk factors), 1 (either risk factor), or 2 (both risk factors). More esophagitis occurred in patients with a grade 2 APR score ($P<0.05$).

Conclusion and prospect

Present review summarized the physical and biological predictors of RE in recent reports, mainly for NSCLC. Currently,

there was no clear threshold of volumetric parameters in predicting RE, because a wide range of V_{dose} parameters significantly correlated with severe acute esophagitis. Future studies should not only investigate the correlation, but also address the cutoff value.

These findings provide useful information for RE prevention, especially as dosimetry parameters for intensity-modulated radiation therapy plans. The research of biomarkers of normal tissue radiosensitivity provided new pathway for the prediction and treatment of RE. Future analyses of esophagitis should employ multivariate factors models. Further multicenter study with a larger number of patients is warranted to validate these physical and biological factors in predicting RE.

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Disclosure

The authors declare no conflicts of interest in this work.

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