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<sub>max</sub>, D<sub>mean</sub>, V<sub>20</sub>, V<sub>30</sub>, V<sub>40</sub>, and V<sub>50</sub> 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...
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 and another used the common terminology criteria. 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 seen with increased RT aggressiveness as hyperfractionation, radiotherapy fraction. Higher acute esophagitis (AE) rates are correlated with effect of radiotherapy fraction.

The incidence and extent of esophagitis are correlated with common terminology criteria.

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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). Watkins et al 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 $V_{45}$ (grade 3 esophagitis rates of 15% as $V_{45}<60\%$ vs 64% as $V_{45}>60\%$). Grant et al 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 $\leq$ grade 2 (2%). $D_{mean}$ and $V_{5-40}$ were the significant predictors of acute esophagitis. Patients with $V_{45} \geq 74\%$ had higher risk of acute grade 3 esophagitis (44.4% as $V_{45} \geq 74\%$ vs 12.6% as $V_{45}<74\%$). $V_{45}$ was the only significant dosimetric predictor for esophageal stricture (esophageal stricture rates 1.3% as $V_{45}<37.5\%$ vs 13.7% as $V_{45} \geq 37.5\%$, $P=0.0497$). Zehentmayr et al investigated dosimetric predictors for $\geq$ grade 2 RE in 66 patients with LA-NSCLC treated with accelerated radiotherapy (1.8 Gy bid). Twenty-three patients (35%) experienced $\geq$ grade 2 RE. On multivariate analysis, $V_{38} \geq 34\%$ ($P=0.007$) was the most significant predictor for $\geq$ grade 2 RE. Mauguen et al 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 hyperfractionation or accelerated radiotherapy did not increase the incidence of RE. Manapov et al 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 ($>\text{grade 2}$). Bar-Ad et al reported that dose per fraction of $1.8$ Gy had a lower risk of $\geq$ 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

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Cancer type</th>
<th>Treatments</th>
<th>Endpoints</th>
<th>Results (dosimetric parameters significantly associated with RE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watkins et al7</td>
<td>48</td>
<td>Limited-stage SCLC</td>
<td>3D-CRT (42–51 Gy, 1.5 Gy bid) + concurrent chemotherapy (platinum-based)</td>
<td>≥grade 3 AE, RTOG criteria</td>
<td>MED RV-AUC V15</td>
</tr>
<tr>
<td>Jonathan et al8</td>
<td>130</td>
<td>Limited-stage SCLC</td>
<td>3D-CRT (42–51 Gy, 1.5 Gy bid) + concurrent chemotherapy (platinum-based)</td>
<td>≥grade 3 AE, RTOG criteria</td>
<td>MED V15 V45 V15</td>
</tr>
<tr>
<td>Franz et al9</td>
<td>166</td>
<td>Stage II–III NSCLC</td>
<td>3D-CRT (73.8–90 Gy, 1.8 Gy bid) + sequential chemotherapy (platinum-based)</td>
<td>≥grade 2 AE, RTOG criteria</td>
<td>V38</td>
</tr>
<tr>
<td>Manapov et al11</td>
<td>82</td>
<td>Stage IIIa/b NSCLC</td>
<td>3D-CRT (45 Gy, 1.5 Gy bid) + sequential chemotherapy (platinum-based)</td>
<td>≥grade 2 AE, RTOG criteria</td>
<td>Absolute esophageal volume included in the 95% isodose (&gt;42.8 Gy)</td>
</tr>
<tr>
<td>Bar-Ad et al12</td>
<td>49</td>
<td>Stage IIIa/b NSCLC</td>
<td>3D-CRT (55.8–74 Gy, 1.5 or 1.8 Gy) + concurrent chemotherapy (platinum-based)</td>
<td>≥grade 2 AE, RTOG criteria</td>
<td>The total volume of the esophagus and larger dose per fraction (2 vs 1.8 Gy)</td>
</tr>
<tr>
<td>Wu et al13</td>
<td>125</td>
<td>Stage I–IV central lung</td>
<td>SBRT (30–60 Gy, ≥6 Gy in five fractions or fewer)</td>
<td>≥grade 2 AE, RTOG criteria</td>
<td>Dmax = 52.9 BED10, D5cc = 26.3 BED10 V50</td>
</tr>
<tr>
<td>Topkan et al14</td>
<td>41</td>
<td>Stage IIIa/b NSCLC</td>
<td>SBRT (30–60 Gy, ≥6 Gy in five fractions or fewer)</td>
<td>≥grade 2 AE, RTOG criteria</td>
<td>V50</td>
</tr>
<tr>
<td>Zhu et al15</td>
<td>157</td>
<td>Stage I–V NSCLC</td>
<td>3D-CRT (40–76.5 Gy, 1.8–2.0 Gy) ± concurrent chemotherapy (various regimens)</td>
<td>≥grade 2 AE, RTOG criteria</td>
<td>V50</td>
</tr>
<tr>
<td>Rodriguez et al18</td>
<td>59</td>
<td>Stage II–III NSCLC</td>
<td>3D-CRT (57.41–66.69 Gy, 1.8–2.0 Gy) + concurrent chemotherapy (various regimens)</td>
<td>≥grade 2 AE, RTOG criteria</td>
<td>V50</td>
</tr>
<tr>
<td>Zhang et al19</td>
<td>76</td>
<td>Stage II–IV NSCLC</td>
<td>3D-CRT or IMRT (56–66 Gy, 1.8 or 2.0 Gy) + concurrent chemotherapy (cisplatin/docetaxel/vinorelbine)</td>
<td>≥grade 2 AE, common toxicity criteria 3.0</td>
<td>V50 chemotherapy agents</td>
</tr>
<tr>
<td>Kwint et al19</td>
<td>139</td>
<td>Stage I–IIb NSCLC</td>
<td>IMRT (66 Gy in 24 fractions, 2 Gy per fraction, 5 days per week) + concurrent chemotherapy (low-dose cisplatin)</td>
<td>≥grade 2 AE, common toxicity criteria 3.0</td>
<td>V50</td>
</tr>
<tr>
<td>Kuroda et al20</td>
<td>32</td>
<td>Stage III NSCLC</td>
<td>IMRT (66 Gy/33 Fr, 72 Gy/36 Fr, 78 Gy/39 Fr) + concurrent chemotherapy (cisplatin/docetaxel/vinorelbine)</td>
<td>AE, common terminology criteria</td>
<td>V50</td>
</tr>
<tr>
<td>Caglar et al20</td>
<td>109</td>
<td>Stage IIIa/b NSCLC</td>
<td>IMRT (50–54 Gy, 60–68 Gy) + concurrent chemotherapy (cisplatin/docetaxel/vinorelbine)</td>
<td>≥grade 3 AE, RTOG criteria</td>
<td>MED V50 V15 V50</td>
</tr>
<tr>
<td>Ozgen et al21</td>
<td>72</td>
<td>Lung cancer</td>
<td>IMRT (55–62.3 Gy) + concurrent chemotherapy (cisplatin/docetaxel/vinorelbine)</td>
<td>≥grade 2 AE, RTOG criteria</td>
<td>MED</td>
</tr>
<tr>
<td>Huang et al22</td>
<td>374</td>
<td>Stage I–IIb NSCLC</td>
<td>3D-CRT (≥60 Gy) ± concurrent or sequential chemotherapy (various regimens) (platinum-based)</td>
<td>≥grade 2 AE, RTOG criteria</td>
<td>V50</td>
</tr>
<tr>
<td>Palma et al23</td>
<td>1,082</td>
<td>Stage I–IIb NSCLC</td>
<td>3D-CRT or IMRT (14–81.6 Gy) + concurrent chemotherapy (platinum-based)</td>
<td>≥grade 2 AE, RTOG criteria</td>
<td>V50</td>
</tr>
</tbody>
</table>

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.
esophageal toxicity in 125 SBRT patients, using biological equivalent doses with $\alpha/\beta = 10$ Gy (BED10).13 Dose to the hottest 5cc ($D_{cc}$) and maximum dose of the esophagus ($D_{max}$) were the best predictors of $\geq$ grade 2 acute RE. To keep the acute RE rate $< 20\%$, it was suggested to keep $D_{cc} \leq 52.9$ Gy and $D_{cc} \leq 26.3$ Gy. In addition, $D_{cc}$ should be kept $< 16.8, 18.1, \text{and} 19.0$ Gy, $D_{max}$ should be kept $< 27.6, 30.2, \text{and} 32.2$ 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 increased15 (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 al16 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 $V_{55} \geq 35\%$ ($P = 0.01$). Zhu et al17 reported that grade 2 or 3 RE occurred in $24\%$ in the radiotherapy-alone group and $52\%$ in the CCRT group. They found that $V_{55}$ was the only significant factor in multivariate analysis. Rodriguez et al18 revealed that $V_{50}$ was the most statistically significant factor (grade $\geq 1$ RE risk: $47.3\%$ as $V_{50} < 30\%$, $73.3\%$ as $V_{50} \geq 30\%$). $V_{50}$ was also the significant predictor for RE $\geq$ grade 3 in the study by Kwint et al.4 Zhang et al19 demonstrated that, in CCRT, $V_{50}$ was the significant factor associated with grade $\geq 2$ RE (33.3% as $V_{40} < 23\%$ vs 89.1% as $V_{40} \geq 23\%$) and $V_{50}$ was significantly correlated with grade 3 RE (6.7% as $V_{50} < 26.5\%$ vs 38.7% as $V_{50} \geq 26.5\%$). Kuroda et al15 revealed that $V_{35}$ was the only dosimetric predictor for grade $\geq 2$ RE on multivariate analysis. Caglar et al20 found that $D_{mean}$ and $V_{45} - V_{60}$ were significantly associated with the risk of grade $\geq 3$ 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 al21 and Huang et al22 reported that $D_{mean}$ was significantly correlated with grade $\geq 2$ RE. Palma et al23 reported that $V_{60}$ was the best predictor of RE, while $V_{60} > 17\%$ conferred the higher risk of grade $\geq 3$ 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 al24 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 $\geq 5\%$, 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 $D_{\text{mean}}\max$, $D_{\text{max}}\max$, 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 $V_{\text{dose}}$. 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 ($D_{\text{max}}\max$, $D_{\text{mean}}\max$, $V_{20}$, $V_{30}$, $V_{50}$, and $V_{55}$) were evaluated in five or more studies and significantly associated with RE (Table 3). By further analysis, it was found that $D_{\text{max}}\max$, $D_{\text{mean}}\max$, $V_{20}$, $V_{30}$, $V_{50}$, and $V_{55}$ were correlated with acute RE, and $D_{\text{mean}}\max$ and $V_{15}$ were correlated with both acute RE and late esophageal stricture.

### 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-$\beta 1$) elevated dramatically in response to radiation exposure. $^{26}$ Common variants located in TGF-$\beta 1$ have been found to have connection with late normal tissue complications after irradiation. Recently, an increasing number of studies related variants in TGF-$\beta 1$ to RE. Hildebrandt et al $^{27}$ found that nine TGF-$\beta 1$ 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 $\geq 3$ RE than the CC genotype. $^{29}$ Yuan et al $^{29}$ also found TGF-$\beta 1$ genotype was associated with RE in NSCLC patients. Patients with TGF-$\beta 1$ 509CC had greater grade RE than T allele carriers. Therefore, TGF-$\beta 1$ 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 hematologic 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 $\geq 377\times 10^{9}$/$\mu$L, hemoglobin $<12.9\times 10^{3}$ 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 \( V_{\text{dose}} \) 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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