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Oesophageal Dose–Volume Parameters and Acute Radiation Oesophagitis in Non-Small Cell Lung Cancer Treated With Definitive Intensity-Modulated Radiotherapy: A Prospective Observational Study

K C Jyothish*, C Ajithaashree, C Saranya, R Giridharan, S Jeva

Department of Radiation Oncology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai, Tamil Nadu, India

ABSTRACT

Background: Acute radiation oesophagitis can impair oral intake, treatment adherence and quality of life during definitive thoracic radiotherapy. Prospective data on oesophageal dose–volume predictors in patients treated with intensity-modulated radiotherapy (IMRT) in Indian practice are limited.

Methods: Thirty consecutive patients with stage I–III non-small cell lung cancer (NSCLC) receiving definitive IMRT to 60 Gy in 30 fractions were prospectively evaluated. Oesophageal Dmean, D2cc, V50 and V60 were extracted from planning dose–volume histograms. Acute oesophagitis was graded weekly using Radiation Therapy Oncology Group (RTOG) criteria, and dysphagia was assessed with the Dysphagia Symptom Questionnaire (DSQ). Spearman correlation and exploratory receiver operating characteristic (ROC) analyses were performed.

Results: Any-grade oesophagitis occurred in 27/30 patients (90.0%); grade 2 and grade 3 events occurred in 15 (50.0%) and 6 (20.0%), respectively, with no grade 4 events. Mean Dmean, D2cc, V50 and V60 were 25.1 ± 8.0 Gy, 57.6 ± 12.6 Gy, 9.6 ± 6.0 cm^3 and 4.0 ± 2.6 cm^3. All four metrics increased with peak RTOG grade ($p < 0.001$). D2cc showed the strongest correlation with peak grade ($r_s = 0.894$, $p < 0.001$). The apparent area under the curve for grade 3 oesophagitis was 0.958 for each metric, with exploratory thresholds of 31 Gy, 68 Gy, 13 cm^3 and 5.5 cm^3, respectively.

Conclusion: Higher mean and high-dose oesophageal exposure were strongly associated with acute oesophagitis during definitive IMRT. D2cc and V60 may complement Dmean in routine plan evaluation. Study-specific thresholds are exploratory and require external validation.

Keywords: Non-small cell lung cancer; Intensity-modulated radiotherapy; Radiation oesophagitis; Dose–volume histogram; D2cc; V60; Dysphagia

Address for correspondence:

K C Jyothish

Assistant Professor, Department of Radiation Oncology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai 600003, Tamil Nadu

Email: jyothishdr@gmail.com

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INTRODUCTION

Definitive concurrent chemoradiotherapy is an established curative-intent treatment for unresectable locally advanced NSCLC [1,2]. The gain in tumour control and survival comes with clinically relevant morbidity, among which acute radiation oesophagitis remains one of the most common and consequential toxicities for patients receiving Lung radiation. Symptoms generally develop after cumulative epithelial injury during the second or third treatment week and may progress to odynophagia, dysphagia, dietary restriction, dehydration, weight loss, hospital admission and interruption of radiotherapy or chemotherapy.

The oesophagus lies close to central lung tumours and mediastinal nodal stations. Esophageal irradiation is therefore often unavoidable in stage III disease, particularly with paratracheal, subcarinal or bulky nodal involvement. The severity of injury depends on the radiation dose distribution, concurrent systemic therapy, disease geometry, nutritional reserve, baseline swallowing function and the timeliness of supportive care.

Mean oesophageal dose is a practical planning measure and is commonly constrained to below 34 Gy when feasible [3,4]. However, a mean dose can conceal a focal region receiving near-prescription dose. D2cc, V50 and V60 are useful complementary summaries of high-dose exposure, and multi-institutional and pooled analyses suggest that high-dose parameters are particularly relevant to clinically significant or severe oesophagitis [5,6]. This prospective study examined these relationships in patients treated with a uniform definitive IMRT prescription at a public-sector tertiary oncology centre in India.

MATERIALS AND METHODS

Study design and eligibility

This prospective single-centre observational study was conducted in the Department of Radiation Oncology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai, from July 2024 to November 2025. Thirty consecutive patients aged 18–70 years with histologically proven stage I–III NSCLC, ECOG performance status 0–3 and an intention to receive definitive IMRT were included. Patients with metastatic disease, prior thoracic radiotherapy, pre-existing oesophagitis, prior oesophageal surgery or stricture, or inability to undergo serial assessment were excluded.

Simulation, planning and treatment

CT simulation was performed with the patient supine, arms elevated and thoracic immobilisation either using VacLock or Thoracic mould. The oesophagus was contoured as a solid structure, including lumen and wall, from the lower border of the cricoid cartilage to the gastro-oesophageal junction. Plans were generated in Eclipse version 15.6 with Acuros XB for final dose calculation, and IMRT was delivered on a Varian TrueBeam linear accelerator. All patients received 60 Gy in 30 fractions. Dmean, D2cc, V50 and V60 were extracted from the planned dose–volume histogram (DVH); V50 and V60 were recorded as absolute volumes (cm^3).

Outcome assessment

Acute oesophagitis was graded using the RTOG acute radiation morbidity criteria [7] at baseline, weekly during treatment and 4 weeks after completion. The highest observed grade was used for the primary analysis. Dysphagia was assessed with the DSQ at the same visits.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) and categorical variables as number and percentage. Spearman rank correlation was used to assess the association between each DVH metric and the ordinal peak RTOG grade. ROC analysis was used to derive exploratory cut-offs for grade 3 oesophagitis using the Youden index. Analyses were performed in SPSS version 25.0 (IBM Corp., Armonk, NY, USA), and $p < 0.05$ was considered statistically significant.

RESULTS

Patient and treatment characteristics

Stage II, IIIA and IIIB disease was present in 5 (16.7%), 16 (53.3%) and 9 (30.0%) patients, respectively. Twenty-five patients (83.3%) received concurrent chemotherapy and five (16.7%) received Radical RT alone [Table 1].

Acute oesophagitis

Any-grade oesophagitis occurred in 27 patients (90.0%). Peak grades 0, 1, 2 and 3 were recorded in 3, 6, 15 and 6 patients, respectively [Figure 1]. Grade ≥ 2 oesophagitis occurred in 21 patients (70.0%), and no grade 4 events occurred. All grade ≥ 2 events were observed in the concurrent-chemotherapy group; this unadjusted finding cannot separate the effect of chemotherapy from disease extent or target-volume factors.

Dose–toxicity relationship

Cohort mean Dmean was 25.1 ± 8.0 Gy, D2cc 57.6 ± 12.6 Gy, V50 9.6 ± 6.0 cm^3 and V60 4.0 ± 2.6 cm^3. Each metric rose progressively with increasing peak RTOG grade [Table 2, Figure 2]. Patients with grade 3 toxicity had a mean Dmean of 35.5 Gy and a mean D2cc of 73.0 Gy. When grouped, patients with grade 2–3 toxicity had higher mean values than those with grade 0–1 for all four metrics [Figure 3].

Correlation and ROC analysis

All four metrics correlated strongly with peak RTOG grade [Table 3]. D2cc had the highest correlation (r_s = 0.894), although the coefficients were close in magnitude (0.880–0.894), indicating that the metrics are interrelated rather than independent markers. In exploratory ROC analysis, each metric showed an apparent AUC of 0.958 for grade 3 oesophagitis, with sensitivity of 100.0% and specificity of 91.7% at the study-derived cut-offs [Table 4].

DISCUSSION

Principal findings

This prospective cohort shows a consistent dose–response relationship between oesophageal dose and acute radiation

Table 1: Patient and treatment characteristics (n = 30).

Characteristic	n (%)
AJCC stage II	5 (16.7)
AJCC stage IIIA	16 (53.3)
AJCC stage IIIB	9 (30.0)
Concurrent chemotherapy	25 (83.3)
IMRT alone	5 (16.7)
Prescription	60 Gy in 30 fractions (all patients)

AJCC, American Joint Committee on Cancer; IMRT, intensity-modulated radiotherapy.

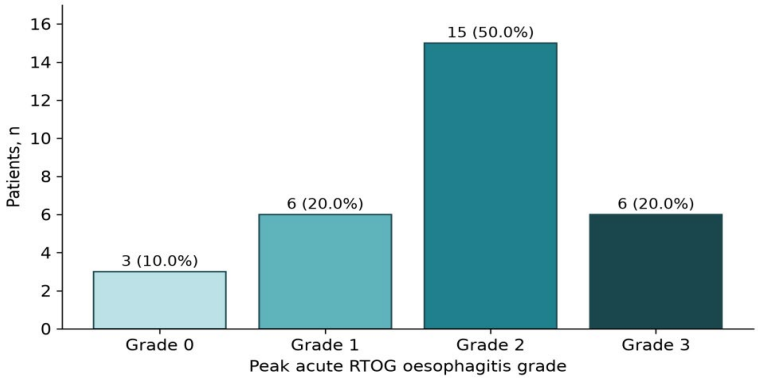


Figure 1: Distribution of peak acute RTOG oesophagitis grade (n = 30).

Table 2: Oesophageal dose–volume metrics by peak RTOG grade (mean ± SD).

Peak RTOG grade	Dmean (Gy)	D2cc (Gy)	V50 (cm³)	V60 (cm³)
0 (n = 3)	12.7 ± 3.1	36.7 ± 4.2	2.2 ± 1.3	0.6 ± 0.4
1 (n = 6)	17.9 ± 2.9	45.3 ± 4.4	4.3 ± 1.6	1.6 ± 0.8
2 (n = 15)	26.4 ± 4.3	60.6 ± 6.3	9.7 ± 3.2	4.3 ± 1.4
3 (n = 6)	35.5 ± 4.1	73.0 ± 4.6	18.2 ± 4.9	7.5 ± 1.8
All patients (n = 30)	25.1 ± 8.0	57.6 ± 12.6	9.6 ± 6.0	4.0 ± 2.6

SD, standard deviation; D2cc, minimum dose to the most exposed 2 cm³; V50/V60, absolute oesophageal volume receiving ≥ 50/60 Gy.

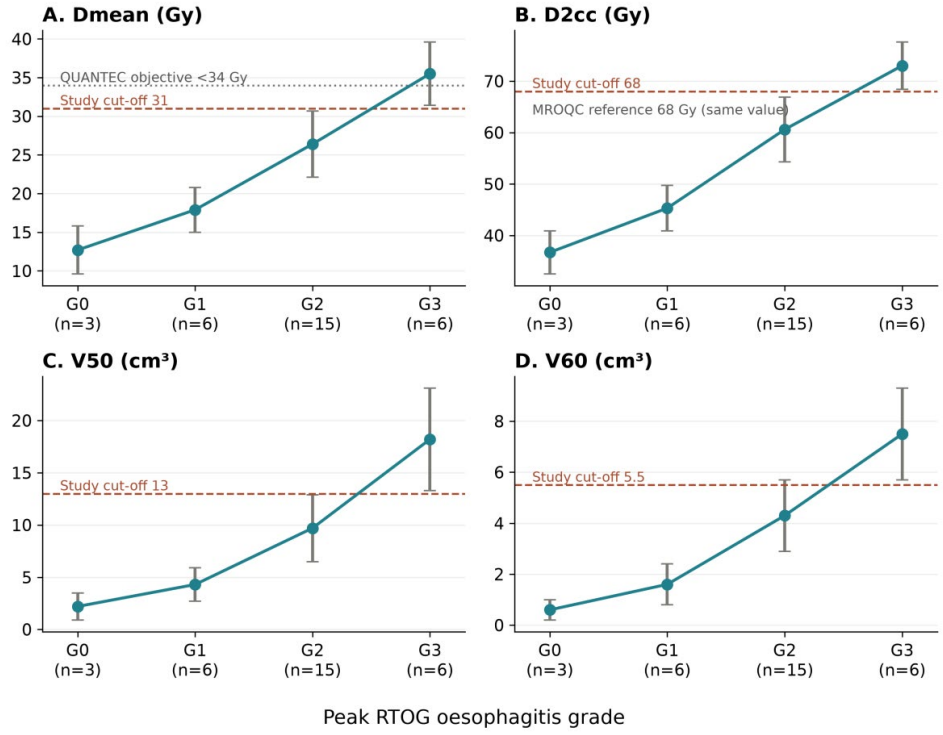


Figure 2: Oesophageal dose–volume metrics across peak RTOG grades (mean ± SD). Dashed lines show study-derived exploratory cut-offs for grade 3 oesophagitis; the dotted line in panel A shows the QUANTEC-informed Dmean objective of < 34 Gy. The study D2cc cut-off (68 Gy) coincides with the MROQC reference value.

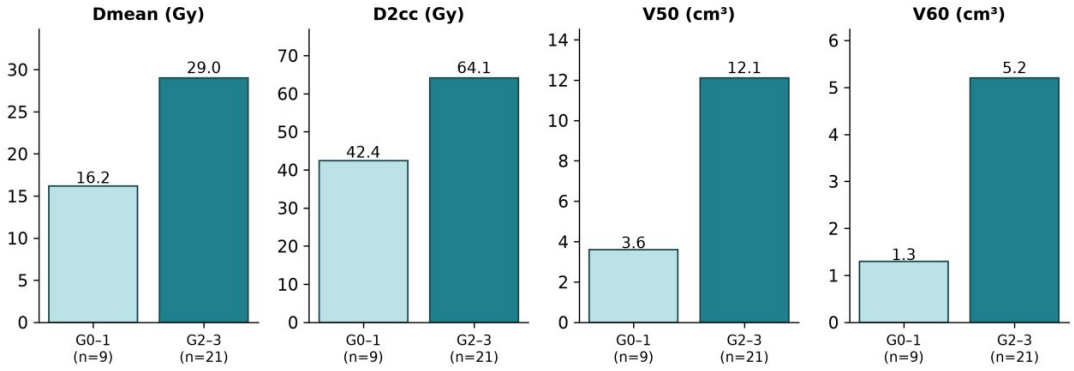


Figure 3: Mean dose–volume metrics in patients with grade 0–1 (n = 9) versus grade 2–3 (n = 21) oesophagitis. Group values were derived from grade-specific means weighted by patient number.

Table 3: Spearman correlation between oesophageal DVH metrics and peak RTOG grade.

Parameter	Spearman r_s	p value
Dmean	0.882	< 0.001
D2cc	0.894	< 0.001
V50	0.88	< 0.001
V60	0.885	< 0.001

Table 4: Exploratory ROC analysis for grade 3 oesophagitis.

Parameter	Endpoint	AUC	Cut-off	Sensitivity	Specificity
Dmean	Grade 3	0.958	31.0 Gy	100.00%	91.70%
D2cc	Grade 3	0.958	68.0 Gy	100.00%	91.70%
V50	Grade 3	0.958	13.0 cm^3	100.00%	91.70%
V60	Grade 3	0.958	5.5 cm^3	100.00%	91.70%

AUC, area under the receiver operating characteristic curve. Cut-offs were derived and tested in the same cohort (six grade 3 events) and are therefore subject to optimism.

oesophagitis in patients with stage I–III NSCLC treated with definitive IMRT. Any-grade oesophagitis occurred in 90.0% of patients, grade ≥ 2 in 70.0% and grade 3 in 20.0%. This high rate of clinically relevant toxicity shows that oesophageal morbidity remains important despite contemporary conformal techniques, particularly when most patients receive concurrent chemotherapy.

All four prespecified metrics rose progressively with peak RTOG grade, and Spearman correlations were uniformly high (r_s 0.880–0.894). D2cc had the strongest observed correlation, but the difference from the other metrics was modest and D2cc should not be regarded as categorically superior in this small dataset. Its prominence is nevertheless biologically plausible. The oesophagus behaves largely as a serial organ, so injury to a short high-dose segment can produce disproportionate dysphagia or odynophagia. D2cc also summarises dose to a small but clinically meaningful volume and is less sensitive than a point maximum to a single voxel or contouring irregularity. V60 adds related information by quantifying how much oesophagus receives near-prescription dose.

Comparison with existing evidence

The association with Dmean is consistent with QUANTEC, which identifies mean oesophageal dose as a useful predictor of acute toxicity and supports an objective below approximately 34 Gy where target coverage permits.3,4 In our cohort the overall mean Dmean was 25.1 Gy, but it was 35.5 Gy among patients with grade 3 toxicity. This supports continued use of mean dose, while showing that an acceptable cohort mean does not guarantee low risk for every individual plan.

The relationship of V60 with severe toxicity agrees with the international individual-patient meta-analysis by Palma and colleagues, in which V60 emerged as an important predictor of oesophagitis after chemoradiotherapy.6 Similarly, the prospective Michigan Radiation Oncology Quality Consortium (MROQC) study identified high-dose metrics, including D2cc and gEUD, as the strongest predictors of severe oesophagitis and reported a D2cc of 68 Gy as the value limiting the estimated grade ≥ 3 risk to about 5%.5 Our exploratory D2cc cut-off of 68 Gy is numerically identical.

Even so, these thresholds should not be read as confirmed constraints. With only six grade 3 events and cut-offs generated and tested in the same cohort, the apparent AUC of 0.958 and 100% sensitivity are susceptible to optimism. The near-identical AUCs for all four metrics also reflect strong collinearity: in thoracic plans, Dmean, D2cc, V50 and V60 may represent a shared pattern of difficult target–oesophagus geometry rather than four independent predictors. External validation is essential before adoption.

Implications for IMRT planning

The main planning implication is to avoid relying on a single metric. Mean dose remains a useful global measure but should be reviewed together with D2cc, V50 and V60. A plan that meets a mean-dose objective may still expose a short oesophageal segment to near-prescription dose; conversely, a modestly higher mean dose may be acceptable when focal high-dose exposure is limited and target coverage would otherwise suffer.

Consistent contouring is fundamental. Variability in oesophageal delineation can materially change Dmean and high-dose volumes, particularly in the upper mediastinum and at air–soft tissue interfaces. Absolute-volume metrics reduce dependence on total contoured length but do not remove the need for a contouring protocol and peer review.

When oesophageal exposure is high, options include re-evaluating beam arrangement, inverse-planning priorities and avoidance objectives, and reducing high-dose spill while maintaining planning target volume coverage. Oesophageal sparing must not compromise coverage of gross disease. With central tumours or bulky subcarinal and paratracheal nodes, high oesophageal dose may be anatomically unavoidable; the appropriate response is to document the trade-off, minimise dose where safely possible and plan proactive supportive care.

Concurrent chemotherapy and confounding

All grade ≥ 2 events occurred in patients receiving concurrent chemotherapy, consistent with the radiosensitising and mucosa-injuring effects reported in landmark chemoradiotherapy trials.1,2 However, chemotherapy allocation was not random and may have been related to performance status, stage, target volume, tumour location and fitness. Larger mediastinal targets may both increase oesophageal dose and favour selection for concurrent therapy, so chemotherapy, disease burden and dose are likely interrelated. The small sample precluded credible multivariable adjustment, and these results should be interpreted as associations rather than causal effects. Baseline dysphagia, body mass index, weight loss, nutritional intake, smoking, reflux disease, candidal infection, chemotherapy regimen, treatment breaks and supportive-care intensity were not fully captured and should be collected systematically in future studies.

Patient-centred relevance and supportive care

Acute oesophagitis can rapidly turn adequate oral intake into pain-limited swallowing, dehydration and significant weight loss, threatening chemotherapy delivery and uninterrupted radiotherapy. Combining physician-graded RTOG toxicity

with serial DSQ assessment acknowledges that dysphagia has functional, nutritional and quality-of-life consequences that physician grading alone may underestimate. Early symptoms in weeks 2–3 can identify patients who need intensified support before severe toxicity develops.

A pragmatic pathway for patients with high D2cc or V60, early swallowing symptoms or concurrent chemoradiotherapy should include:

- baseline and weekly weight review, with early dietitian referral;
- high-calorie, high-protein oral supplements;
- optimised oral and topical analgesia and hydration assessment;
- evaluation for candidiasis or reflux where indicated;
- timely assessment for enteral feeding when oral intake remains inadequate.

Such measures do not change the delivered dose but can reduce the clinical consequences of toxicity.

Strengths and limitations

Strengths include the prospective design with serial assessment during treatment and at 4 weeks, a uniform 60 Gy/30-fraction prescription on a single IMRT platform, planned DVH extraction, and the use of a patient-reported dysphagia measure.

Several limitations must be acknowledged. The study was single-centre with 30 patients and only six grade 3 events, limiting precision, generalisability and the reliability of ROC-derived thresholds; confidence intervals, internal resampling and external validation are needed. Stable multivariable modelling was not possible. The endpoint was peak physician-graded acute toxicity, which may not capture symptom duration, hospitalisation, feeding support or treatment compliance, and follow-up ended 4 weeks after radiotherapy, so persistent dysphagia, stricture and fistula were not assessed. gEUD, oesophageal subsegments, dose-surface metrics, accumulated delivered dose and normal-tissue complication probability modelling were not analysed.

A multicentre prospective validation study with harmonised contouring, standardised toxicity and patient-reported outcome collection, detailed nutritional assessment and prespecified modelling is the logical next step. Such a study should report calibration as well as discrimination and test whether dose-based risk stratification improves supportive care or reduces clinically significant oesophagitis without compromising target coverage.

CONCLUSIONS

Higher oesophageal Dmean, D2cc, V50 and V60 were strongly associated with the severity of acute radiation oesophagitis in stage I–III NSCLC treated with definitive IMRT. Routine plan review should consider mean oesophageal dose together with focal high-dose metrics, particularly D2cc and V60. The study-specific thresholds are exploratory and should be used only for risk awareness and supportive-care planning, alongside careful contouring, structured DVH review and transparent documentation of unavoidable target–organ-at-risk trade-offs, until validated in larger multicentre prospective datasets.

DECLARATIONS

Ethics approval and consent to participate: Ethical approval was obtained from the Institutional Scientific Committee and Institutional Ethics Committee of Madras Medical College before enrolment [IEC-MMC/APPROVAL/57042025]. Written informed consent was obtained from all participants.

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Competing interests: The authors declare no competing interests.

Data availability: De-identified data are available from the corresponding author on reasonable request, subject to ethics approval and institutional policy.

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