

Original Article



Identifying Predictors of Radiation-Induced Esophagitis in Head and Neck Cancers: A Logistic Regression-Based Study

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BRIEF TEXT

Background and Objective

Radiation-induced esophagitis is an important acute toxicity of radiotherapy for head and neck cancers and may compromise swallowing, nutritional status, quality of life, and treatment continuity. Head and neck cancers remain a major global health problem, while advances in intensity-modulated radiotherapy (IMRT) have improved target coverage but have not eliminated radiation-related normal-tissue toxicity [1-4]. The esophagus may receive clinically relevant radiation doses when lower cervical and adjacent treatment fields are used. Previous studies have suggested that esophageal dose-volume parameters, particularly mean dose and selected volumetric indices, are associated with esophagitis, whereas demographic and clinical predictors have shown less consistent effects [5]. ... [6, 7]...[8, 9]...[1,5,10,11]. Because prediction models may support treatment planning and individualized toxicity assessment, the present prospective study aimed to identify independent predictors of grade ≥ 1 radiation-induced esophagitis in patients with head and neck cancers using binary logistic regression.

Materials and Methods

This prospective study was conducted at the Radiotherapy Department of Seyed-o-Shohada Hospital, Isfahan, Iran, during 2024–2025. A total of 50 consecutive patients aged >18 years with pathologically confirmed head and neck cancer who required IMRT and provided written informed consent were enrolled. Patients with previous head and neck radiotherapy, pre-existing swallowing disorders, esophageal invasion or metastasis, previous esophageal surgery, incomplete three-month follow-up, death during follow-up, or withdrawal were excluded. Patients had tumors involving the oral cavity, pharynx (including oropharynx, hypopharynx, and nasopharynx), or larynx. All patients were treated using an Accuray Radixact/Tomotherapy system with IMRT, five fractions per week, 2 Gy per fraction, and a prescribed total dose of 60 Gy. Dosimetric variables were extracted from dose-volume histograms and included mean, minimum, and maximum esophageal dose, prescribed dose, number of fractions, and V20, V30, and V50. A radiation oncologist assessed esophagitis one week before radiotherapy, at treatment completion, and three months after radiotherapy, and graded it from 0 to 4 according to Radiation Therapy Oncology Group criteria [12]. Descriptive statistics were calculated as mean $\pm$ standard deviation or frequency and percentage. Associations with grade ≥ 1 esophagitis were examined using chi-square/Fisher's exact tests and independent-samples t-tests. Variables meeting the predefined univariate screening criterion were considered for multivariable modeling. Pearson correlation coefficients were used to identify multicollinearity; correlations >0.75 were considered important, and redundant variables were removed according to clinical and statistical relevance. The final binary logistic regression model was reported using odds ratios (ORs), 95% confidence intervals (CIs), β coefficients, standard errors, and Wald statistics. Model fit was evaluated using the Hosmer–Lemeshow test, and discrimination was assessed by the area under the receiver operating characteristic curve. Statistical analyses were performed in SPSS (version 26), with $P < 0.05$ considered statistically significant.

Results

Among the 50 patients, 28 (56%) were women, and 22 (44%) were men. The mean age was 53.44 ± 14.22 years (range, 32–81 years), and the mean body mass index was 27.43 ± 6.13 kg/m². Twenty-six patients (52%) had a history of

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smoking, 22 (44%) received concurrent chemotherapy, 24 (48%) had comorbidities, and 28 (56%) reported a positive family history of cancer. Tumor stage was II in 16 patients (32%), III in 18 (36%), and IV in 16 (32%) (Table 1). During the three-month follow-up, 22 patients (44%) remained free of clinical esophagitis (grade 0), whereas 28 (56%) developed grade ≥ 1 esophagitis. Grade 1 occurred in 9 patients (18%), grade 2 in 10 (20%), grade 3 in 7 (14%), and grade 4 in 2 (4%). Thus, 9 patients (18%) experienced severe or life-threatening toxicity (grade ≥ 3). In univariate logistic regression, three variables were significantly associated with grade ≥ 1 esophagitis: mean esophageal dose ($P = 0.002$), disease stage ($P = 0.008$), and maximum esophageal dose ($P = 0.022$). Age, sex, body mass index (BMI), smoking, comorbidities, family history, education, socioeconomic status, concurrent chemotherapy, V20, V30, and V50 were not significant. Pearson correlation analysis identified strong relationships between weight and BMI ($r = 0.845$), mean and maximum esophageal dose ($r = 0.925$), V20 and V30 ($r = 0.970$), V20 and V50 ($r = 0.925$), and V30 and V50 ($r = 0.948$) (Table 2). Redundant variables were removed before multivariable modeling. The final model included mean esophageal dose and disease stage; VIF values for the retained continuous variables were all below 1.5 (Table 3). Mean esophageal dose was the only independent predictor of grade ≥ 1 esophagitis ($\beta = 0.104$, SE = 0.039, Wald = 7.326, $P = 0.007$; OR = 1.11, 95% CI: 1.03–1.20). Thus, each 1-Gy increase in mean esophageal dose was associated with an 11% increase in the odds of esophagitis. Disease stage was no longer significant after adjustment ($\beta = 0.296$, SE = 0.399, Wald = 0.552, $P = 0.457$; OR = 1.34, 95% CI: 0.62–2.94) (Table 4). The model showed acceptable fit (Hosmer–Lemeshow $\chi^2 = 6.59$, $P = 0.581$), explained 24.2% of the variance according to Nagelkerke R^2 , and demonstrated acceptable discrimination (area under the curve [AUC] = 0.746, 95% CI: 0.61–0.89).

Discussion

More than half of the patients in this cohort developed radiation-induced esophagitis, confirming that esophageal toxicity remains clinically relevant in head and neck radiotherapy. The overall frequency was consistent with previous reports, including Ozgen et al., which identified mean esophageal radiation dose as an important predictor of acute esophagitis [13]. The central finding of the present study was that mean esophageal dose remained the sole independent predictor after adjustment for disease stage. The observed 11% increase in odds per 1 Gy is biologically plausible because increasing radiation exposure to the esophageal mucosa can promote epithelial injury, inflammation, edema, and swallowing dysfunction [14]. This finding is also consistent with systematic evidence showing an important relationship between esophageal dose-volume parameters and esophagitis risk [15], as well as with studies in cervicothoracic and head-and-neck/thoracic tumors demonstrating the greater predictive contribution of dosimetric variables compared with demographic factors [16]. Disease stage was significant in univariate analysis but not after adjustment for mean esophageal dose. More advanced tumors may require larger treatment fields and may consequently expose adjacent structures to higher doses, suggesting that the apparent stage effect may be mediated partly by esophageal dose [17]. The lack of significant associations for age, sex, BMI, smoking, comorbidities, socioeconomic status, education, and concurrent chemotherapy should be interpreted cautiously. In particular, the absence of a chemotherapy effect differs from the frequent identification of concurrent chemotherapy as a risk modifier in previous literature [15, 16]. The small sample, heterogeneous chemotherapy regimens, and potential overlap between chemotherapy and dosimetric exposure may have reduced the ability to detect independent effects. The non-significance of V20, V30, and V50 also differs from reports in thoracic malignancies in which multiple dose-volume parameters predicted acute or severe esophagitis [18, 19]. Its AUC of 0.746 indicates acceptable discrimination, but the small single-center sample, potential overfitting, short follow-up, and absence of internal validation limit generalizability.

Conclusion

Radiation-induced esophagitis affected 56% of patients with head and neck cancer in this prospective IMRT cohort, with 18% developing grade ≥ 3 toxicity. Mean esophageal dose was the only independent predictor of grade ≥ 1 esophagitis, with an 11% increase in odds for each 1-Gy increase. These findings support careful consideration of esophageal dose constraints during treatment planning.

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Table 1. Demographic and Clinical Characteristics of the Study Population (n = 50)

Variable	No /Mean	%
Age (y)	53.44 ± 14.22	—
Body mass index (kg/m ²)	27.43 ± 6.13	—
Sex: Female	28	56
Sex: Male	22	44
Smoking: Yes	26	52
Smoking: No	24	48
Concurrent chemotherapy: Yes	22	44
Concurrent chemotherapy: No	28	56
Comorbidity: Yes	24	48
Comorbidity: No	26	52
Positive family history of cancer: Yes	28	56
Positive family history of cancer: No	22	44
Education: Below diploma	7	14
Education: Diploma	17	34
Education: Bachelor's	13	26
Education: Master's or higher	13	26
Socioeconomic status: Low	20	40
Socioeconomic status: Moderate	15	30
Socioeconomic status: High	15	30
Disease stage: II	16	32
Disease stage: III	18	36
Disease stage: IV	16	32

Table 2. Pearson Correlation Matrix for Selected Continuous Variables and Assessment of Multicollinearity

Variable 1	Variable 2	Pearson r
Body mass index	Weight	0.845
Mean esophageal dose	Maximum esophageal dose	0.925
V20	V30	0.970
V20	V50	0.925
V30	V50	0.948

Table 3. VIF Values for the Final Continuous Variables After Removal of Highly Collinear Variables

Continuous variable	VIF
Age	1.31
Weight	1.17
Tumor size	1.14
Prescribed dose	1.11
Number of fractions	1.29
Mean esophageal dose	1.21
Minimum esophageal dose	1.08
V20	1.24

Abbreviations: VIF, variance inflation factor.

Table 4. Multivariable Binary Logistic Regression Model for Grade ≥1 Radiation-Induced Esophagitis

Variable	β	SE	Wald	OR	95% CI	Pvalue
Mean esophageal dose (Gy)	0.104	0.039	7.326	1.11	1.03–1.20	0.007
Disease stage	0.296	0.399	0.552	1.34	0.62–2.94	0.457

Abbreviations: SE, standard error; OR, odds ratio; CI, confidence interval.