International Journal of General Medicine Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Risk Factors of Esophageal Fistula Associated with Volumetric Modulated Arc Therapy for Esophageal Squamous Cell Cancer

Jinyun Wang, Xiaowei Wu, Ge Hu

Hefei Cancer Hospital, Chinese Academy of Sciences, Hefei 230031, People's Republic of China

Correspondence: Ge Hu, Email 937408831@qq.com

Purpose: To investigate risk factors for esophageal fistula in esophageal squamous cell cancer (ESCC) patients who treated with volumetric modulated arc therapy (VMAT).

Patients and Methods: A retrospective analysis was performed on 171 ESCC patients treated with VMAT at Hefei Cancer Hospital, Chinese Academy of Sciences, from February 2017 to February 2021. Clinical and dosimetric parameters, including age, gender, feeding channel, tumor location, T stage, ulcerative tumor, were recorded. Univariate and multivariate logistic regression were used to determine risk factors for esophageal fistula. The predictive accuracy of the constructed nomogram was assessed using a receiver operating characteristic (ROC) curve and calibration curves.

Results: Esophageal fistula occurred in 12.87% (22/171) of all the patients. Univariate analysis showed that gender, age, diabetes, T4 stage, ulcerative tumor, total radiation dose, maximum gross tumor volume (GTV) diameter, and GTV length correlated with the incidence of esophageal fistula. Multivariable analysis highlighted gender, age, diabetes, T4 stage, and total radiation dose as significant predictors. A predictive nomogram including these five factors was developed and showed an AUC of 0.876 (95% CI 0.807–0.946), a C-index of 0.847, and a corrected C-index of 0.833.

Conclusion: Gender, age, diabetes, T4 stage, and total radiation dose emerged as significant risk factors for esophageal fistula in ESCC patients undergoing VMAT. The developed nomogram provides a reliable tool to predict the risk of esophageal fistula risk in this cohort.

Keywords: ESCC, VMAT, esophageal fistula, risk factor, nomogram

Introduction

In 2020, esophageal cancer accounted for 604,000 new cases worldwide, resulting in 544,000 deaths.[1,2] Of note, approximately 320,000 new cases were reported in China, making esophageal cancer as the fourth leading cause of cancer-related deaths in the country.[3] The primary subtype of esophageal cancer in China is ESCC, which is characterized by high morbidity and mortality rates with marked geographical variations.[4] ESCC often presents with non-specific symptoms, and most patients are diagnosed at an advanced stage or with multiple metastases.[5,6] Radiation therapy is a way to treat ESCC, relieving symptoms of dysphagia, improving the patient's nutritional status, and preparing the patient for systemic therapy.

A common complication of radiotherapy is radiation-induced esophageal injury, the most severe of which is oesophageal fistula. [7,8] Types of esophageal fistula include esophageal-mediastinum fistula (EMF), esophagus-respiratory fistula (ERF), and aorto-esophageal fistula (AEF).[9,10] The anatomy of the esophagus is unique, being a muscular tube without a layer of serosa, lacking a barrier to loco-regional spread, and local extension of tumor to adjacent structures such as the pericardium, trachea and mediastinum is common. The development of an oesophageal fistula can be attributed to tumor invasion or radiotherapy induced tissue damage.[11–13] Radiotherapy has a dual effect: it can damage the esophageal walls and neighboring organs, and it can cause an imbalance between tumor regression and

Received: 7 August 2024
Accepted: 24 November 2024
Published: 17 December 2024

normal tissue repair, leading to esophageal fistula. The development of esophageal fistula poses is significant clinical challenge, potentially delaying or interrupting radiotherapy and adversely affecting tumor control, long-term survival, and overall patient quality of life. Tragically, most epatients with oesophageal fistula die within 3–4 months due to cachexia, excessive bleeding, or severe infection.

Previous studies have reported esophageal fistula incidence rates ranging of 6–22% in ESCC patients undergoing radiotherapy.[8,14] VMAT is a new radiotherapy technique developed based on conventional intensity-modulated radiotherapy techniques, in which dose distributions are highly conformal to the target volume by dynamically and simultaneously varying the dose rate, gantry rotation speed, and multi leaf collimator aperture shape in one or more arcs. VMAT can significantly reduce radiation dose to normal organs at risk (OARs) in the vicinity of the target area, while allowing dose escalation to the tumor and regional lymph nodes, thereby significantly reducing the incidence of gastrointestinal, urinary, and hematological toxicities.

However, reliable tools for predicting esophageal fistula are lacking in clinical practice. Our research has carefully identified and analyzed several esophageal fistula-associated parameters to predict the risk of esophageal fistula in ESCC patients receiving VMAT.

Materials and Methods

Study Design

We conducted a retrospective analysis of 171 ESCC patients treated with VMAT at the Hefei Cancer Hospital, Chinese Academy of Sciences, between February 2017 and February 2021. These patients had either declined surgery or were not candidates for surgery. Inclusion criteria: 1. Pathologically confirmed squamous cell carcinoma; 2. Assessment by endoscopic ultrasound, bronchoscopy, glucose analogue (18) F-fluorodeoxyglucose-positron emission computed tomography, or contrast-enhanced computed tomography scan before treatment, staged as II–IV according to the American Joint Committee on Cancer (8th edition); 3. Karnofsky performance status score of 70 or higher; 4. Received VMAT treatment; 5. Absence of other severe medical conditions; 6. Absence of esophageal fistula prior to VMAT; 7. Comprehensive clinical records. Exclusion criteria: 1. Previous esophageal surgery; 2. Previous esophageal radiotherapy; 3. Lost to follow-up.

This study was approved by the Institutional Research Ethics Committee of Hefei Cancer Hospital, Chinese Academy of Sciences, and the data obtained do not contain patient identifiers. Informed consent was waived due to the retrospective nature of the study and was supported by the Ethics Review Committee of Hefei Cancer Hospital, Chinese Academy of Sciences.This study conforms to the Declaration of Helsinki.

Radiotherapy

All patients in this study received esophageal radiotherapy using VMAT (Infinity LINAC, Elekta Ltd., Sweden) at doses ranging of 1.8–2.2Gy per fraction, administered five days a week. During radiotherapy sessions, patients were stabilized using body vacuum bags or head and neck thermoplastic molds. Scanning covered a region starting from the cricoid cartilage to 5 cm below the base of the lung, with image slices of 5mm thickness. Acquired CT images (Philips Medical System, Cleveland, OH, USA) were processed using the Monaco planning system to define the target regions and the surrounding organs at risk. GTV was constrained based on esophageal barium meal assessments supplemented by computed tomography, or PET-CT. The GTV of metastatic lymph nodes (GTVnd) was specified as nodes greater than 10mm in short diameter. The clinical target volume (CTV) comprised the GTV, associated subclinical lesions, and zones of high-risk lymphatic drainage. The planned target volume (PTV) was derived by expanding the CTV radially by 0.5–0.8 cm, with additional extensions of 1.0–2.0 cm cranially and caudally. For GTVnd, an omnidirectional extension of 0.5 cm was applied. A 6 MV X-ray source was used for radiation delivery. The dose distribution was optimized to ensure that the therapeutic dose enveloped 95% of the PTV. Established dose thresholds for organs at risk were: V20<25% and V5<50% for bilateral lungs with an a mean dose threshold of <20Gy, a peak dose to the spinal cord of ≤40Gy, and an mean dose constraint to the heart of <30Gy. Most patients received chemotherapy regimens containing cisplatin,

paclitaxel, or fluorouracil. Targeted therapies included nimotuzumab, apatinib, and anlotinib, while the immunotherapeutic agents used were camrelizumab, pembrolizumab, and nourizumab.

Diagnostic Criteria of Esophageal Fistula

Esophagography with barium contrast and esophagoscopy are standards for diagnosis of oesophageal fistula. Computed tomography remains a key diagnostic tool for esophageal fistula. Established diagnostic criteria include: iodinated contrast has been observed to leak from the fistula or into the patient's chest/mediastinum, or CT scan shows mediastinal air around the esophagus, adjacent to the esophagus in the pleural space, pleural esophageal fistula fusion, pneumothorax, and subdiaphragmatic air.

Data Collection

The study is retrospective and single-centre. Clinical characteristics, laboratory results, and therapeutic measures were extracted from electronic health records. Clinical parameters included demographics (age and gender), lifestyle factors (history of smoking and alcohol consumption), diabetes, family history of gastrointestinal malignancies, need for feeding tube, tumour characteristics (location, T stage, and presence of ulcerative ESCC), systemic therapeutic interventions, and radiological metrics (maximum and longitudinal of GTV, and radiation field length). Therapeutic metrics also included fractional and cumulative radiation doses.

Follow-Up

Patients underwent evaluations every three months for the first two years and then every six months until the development of an esophageal fistula. Investigations included clinical examination, contrast-enhanced CT of the neck, chest, and abdomen, and barium esophagography. The final follow-up was in February 2023, as determined by medical records, outpatient records, and telephone consultations.

Statistical Analysis

Analyses were performed using SPSS (version 23). Variables were assessed by univariate analysis using logistic regression. Subsequently, variables deemed significant ($p < 0.1$) in the univariate model were subjected to multivariate analysis to identify influential risk determinants. Both univariate and multivariate regression models were employed to compute odds ratios (OR) and their 95% confidence intervals (CIs). A p-value threshold of < 0.05 was set for statistical significance in the multivariate model.

Results

Patient Characteristics

From February 2017 to February 2021, 198 patients were evaluated. Of these, 27 were omitted due to exclusion criteria, leaving in 171 patients for analysis, as detailed in Table 1. The median age was 70.73 years, ranging from 41 to 88 years. The cohort comprised 128 males (74.85%) and 43 females (25.15%), giving a male to female ratio of 2.98:1. The distribution by site was as follows: cervical (20 patients, 11.70%), upper thoracic (40 patients, 23.39%), middle thoracic (67 patients, 39.18%), and lower thoracic (44 patients, 25.73%). Other clinical details included: 25 patients with T4 stage ESCC (14.62%), 30 with ulcerative ESCC (17.54%), 8 with diabetes (4.68%), and 22 patients had a feeding tube before the end of VMAT (12.87%). Esophageal fistula was present in 22 patients (20 males, 2 females), with an incidence rate of 12.87%. Specifically, 3 patients developed an esophageal fistula during VMAT and 19 patients developed an esophageal fistula after VMAT. The median time between the start of VMAT and the detection of an esophageal fistula was 155.53 days, ranging from 63 to 364 days. Notably, there was no evidence of esophageal tumor progression prior to esophageal fistula in these cases. The esophageal fistula breakdown includes esophagomediastinal fistula (16 cases), esophagotracheal fistula (5 cases), and one patient with esophagomediastinal fistula and esophagotracheal fistula. Treatment approaches for esophageal fistula included: feeding tube (13 cases, 59.09%), esophageal stents (2 cases, 9.09%), and parenteral nutrition (7 cases, 31.81%).

Table 1 The Characteristics of ESCC Patients

Characteristics	No-Esophageal Fistula Patients (N=149)	Esophageal Fistula Patients (N=22)
Gender		
Female	41(27.52%)	2(9.09%)
Male	108(72.48%)	20(90.91%)
Age (years)		
<70	49(32.89%)	6(27.28%)
≥70	100(67.11%)	16(72.72%)
Smoking		
No	80(53.69%)	13(59.09%)
Yes	69(46.31%)	9(40.91%)
Drinking		
No	101(67.79%)	14(63.64%)
Yes	48(32.21%)	8(36.36%)
Diabetes		
No	145(97.31%)	18(81.81%)
Yes	4(2.69%)	4(18.19%)
Nutrition canal		
No	129(86.58%)	20(90.9%)
Yes	20(13.42%)	2(9.1%)
Location of primary tumor		
Cervical section	17(11.41%)	3(13.64%)
Upper thoracic	32(21.48%)	8(36.36%)
Mid thoracic	59(39.59%)	8(36.36%)
Lower thoracic	41(27.52%)	3(13.64%)
T stage		
T4	14(9.40%)	11(50%)
Non-T4	135(90.60%)	11(50%)
Total radiation dose (Gy)		
<60	47(31.54%)	11(50%)
≥60	102(68.46%)	11(50%)
Fraction dose (Gy)		
<2	18(12.08%)	1(4.55%)
≥2	131(87.92%)	21(95.45%)
Ulcerative tumor		
No	126(84.56%)	15(68.18%)
Yes	23(15.44%)	7(31.82%)
The length of GTV		
Range (cm)	2.57–21.66	4.23–23.65
The maximum diameter of the GTV (range) (cm)	1.2–8.53	2.98–8.77
RT field length (range) (cm)	7.41–25	10.65–25.06

Risk Factors for Esophageal Fistula

Univariate analysis identified gender, age, diabetes, ulcerative tumor, T stage, total radiation dose, GTV length, and GTV maximum diameter as significant factors for esophageal fistula ($p < 0.1$). These results, summarised in Table 2, were then used for multivariate analysis. The advanced evaluation revealed that T4, gender, age, diabetes, and total radiation dose retained significance ($p < 0.05$), highlighting them as independent risk determinants for esophageal fistula in ESCC patients undergoing VMAT (Table 3).

Table 2 Univariate Analysis for the Incidence of Esophageal Fistula

Characteristics	No-Esophageal Fistula Patients (N=149)	Esophageal Fistula Patients (N=22)	OR	95% CI	*p*
Gender					
Female	41	2			
Male	108	20	3.98	1.04–24.44	0.081
Age (years)					
<70	49	6			
≥70	100	16	0.89	0.85–0.94	0.0001
Smoking					
No	80	13			
Yes	69	9	0.78	0.31–1.92	0.595
Drinking					
No	101	14			
Yes	48	8	1.20	0.45–3.01	0.699
Diabetes					
No	145	18			
Yes	4	4	8.06	1.77–36.86	0.005
Nutrition canal					
No	129	20			
Yes	20	2	0.65	0.10–2.45	0.574
Location of primary tumor					
Cervical section	17	3	1.23	0.27–4.10	0.762
Upper thoracic	32	8	2.90	0.78–5.33	0.13
Mid thoracic	59	8	0.87	0.33–2.17	0.772
Lower thoracic	41	3	0.42	0.09–1.30	0.176
T stage					
T4	14	11			
Non-T4	135	11	7.39	2.72–20.22	0.0001
Total radiation dose (Gy)					
<60	47	11			
≥60	102	11	0.48	0.19–1.18	0.097
Fraction dose (Gy)					
<2	18	1			
≥2	131	21	2.89	0.55–53.23	0.315
Ulcerative tumor					
No	126	15			
Yes	23	8	3.13	1.18 to 8.31	0.071
The length of GTV					
Range (cm)	2.57–21.66	4.23–23.65	1.17	1.03–1.33	0.015
The maximum diameter of the GTV (range) (cm)	1.2–8.53	2.98–8.77	1.65	1.19–2.26	0.003
RT field length (range) (cm)	7.41–25	10.65–25.06	1.09	0.97–1.22	0.146

Predictive Nomogram for Esophageal Fistula

In the light of the multivariate results, we created a nomogram that summarises five critical risk facets for the prediction of esophageal fistula (Figure 1A). The collective score integrates data from the T4, gender, age, diabetes, and total radiation dose. Each variable on the score axis has its own score. The cumulative score is derived by summing individual scores, allowing us to deduce esophageal fistula probability through the aggregate score.

Our subsequent evaluation validated the accuracy of the nomogram. It showed strong discrimination with an AUC of 0.876 (95% CI 0.807–0.946) (Figure 1B). The calibration plot showed close agreement between predicted and actual

Table 3 Multivariate Analysis for the Incidence of Esophageal Fistula

Characteristics	OR	95% CI	*p*
Gender			
Female			
Male	7.43	1.32–72.30	0.043
Age (years)			
<70			
≥70	0.92	0.86–0.98	0.018
History of diabetes			
No			
Yes	24.80	1.77–36.86	0.005
T stage			
T4			
Non-T4	7.39	3.49–193.39	0.001
Total radiation dose (Gy)			
<60			
≥60	0.23	0.06–0.84	0.03
Ulcerative tumor			
No			
Yes	3.07	0.78–12.58	0.107
The length of GTV			
Range (cm)	0.91	0.70–1.17	0.461
The maximum diameter of the tumor (range) (cm)	1.18	0.67–2.03	0.558

esophageal fistula probabilities. Furthermore, the unadjusted concordance index (C-index) registered was 0.847, while internal validation yielded a corrected C-index of 0.833 (Figure 1C).

Discussion

In our evaluation of 171 patients with ESCC who underwent VMAT, 12.87% developed an esophageal fistula. Notably, 3 patients developed an esophageal fistula during VMAT and 19 patients developed an oesophageal fistula after VMAT. Our comprehensive evaluation of the parameters of gender, age, diabetes, T4 stage and total radiation dose associated with esophageal fistula revealed several novel independent risk factors by multivariate analysis.

Several factors research our study apart from previous research. First, our cohort consisted exclusively of patients who had undergone primary radiotherapy, deliberately excluding those who had undergone secondary radiotherapy. This distinction is important because re-radiotherapy for esophageal cancer is reported to result in a significantly increased incidence of oesophageal fistula. As only a minority of patients with oesophageal cancer receive re-radiotherapy in clinical practice, it is more pragmatic to focus on the correlation between primary radiotherapy and oesophageal fistula. Furthermore, our participants underwent VMAT only, whereas previous studies may have included different radiotherapy modalities. As a result, the risk factors in our study differed from those reported in some previous papers.[15–19]

Esophageal fistula is a serious complication following radiotherapy for esophageal cancer,[13,16,20,21] potentially resulting in systemic infection, massive bleeding, and a poor prognosis.[8,11] Numerous studies have demonstrated a median survival time of only 2–3 months after diagnosis of oesophageal fistula,emphasizing the urgency of its early detection. Given the seriousness of esophageal fistula and its consequences, patients with esophageal fistula risk factors require vigilant monitoring and treatment plans should be tailored the occurrence of oesophageal fistula.

The prevalence of esophageal fistula in our study is consistent with the 6–22% range documented in the literature,[17,20,22] suggesting that VMAT does not necessarily reduce the incidence of esophageal fistula compared to other radiation modalities.[23] Hu et al found that radiation dose was not associated with the occurrence of oesophageal

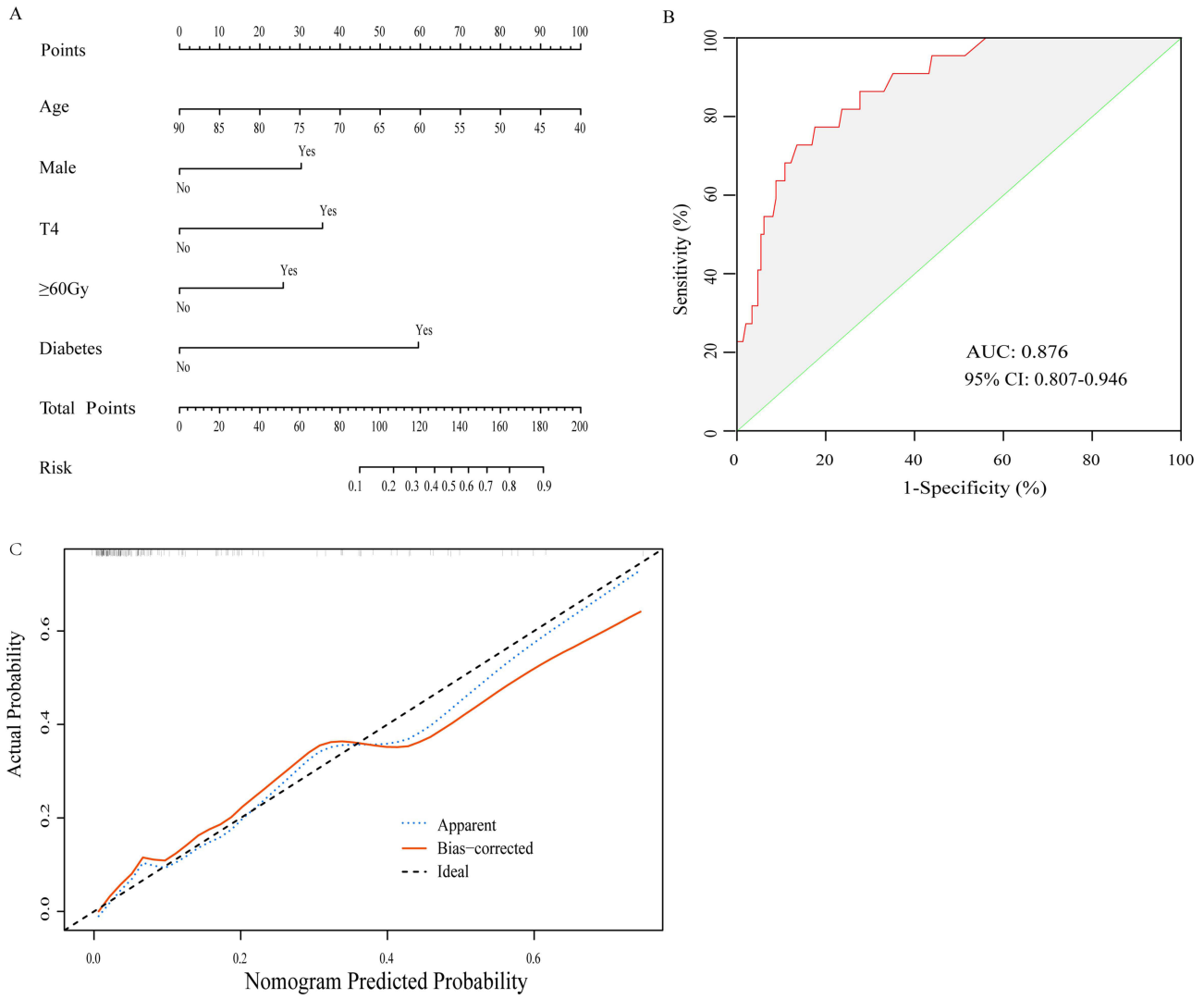

Figure 1 Nomogram for the individualized prediction of esophageal fistula in ESCC patients. (**A**) Nomogram for the individualized prediction of radiation-related esophageal fistula in esophageal cancer patients. (**B**). ROC curve for the prediction nomogram. (**C**). Calibration curve showing nomogram-predicted esophageal fistula probabilities compared with the actual esophageal fistula.

fistula, possibly because 70% of patients received a radiation dose of 60±7Gy. As re-irradiation is a strong risk factor for oesophageal fistula, 54 of the patients included in the study were patients who had received re-irradiation, so some of the patients with a total dose of <60 Gy were oesophageal cancer patients who had received re-irradiation. The RTOG90-12 trial showed that dose escalation did not confer a survival benefit and may increase treatment-related mortality compared with standard radiotherapy. The ESMO guidelines also recommend a dose of 50.4 Gy for radical radiotherapy for oesophageal cancer and up to 60 Gy for oesophageal squamous cell carcinoma, with the support of advanced radiotherapy techniques such as intensity-modulated radiotherapy (IMRT). Escalation is associated with increased toxicity with no apparent survival benefit. However, the pathological types and biological behaviour of oesophageal cancer in China are very different from those in Western countries, and the dose of radical radiotherapy is still preferred to 60 Gy. Our findings highlight that doses ≥60 Gy may increase the risk of oesophageal fistula, and therefore vigilance for oesophageal fistula is required in patients with oesophageal cancer treated with VMAT at a total dose greater than 60 Gy.

According to the 8th edition of the AJCC TNM staging system, T4 refers to esophageal carcinoma that invades adjacent structures such as the pleura, pericardium, azygos vein, diaphragm, peritoneum, aorta, vertebral body and airway.[24] This invasive nature implies the potential development of fistulas between the esophagus and these adjacent

structures, especially if the tumors are rapidly eradicated by chemoradiotherapy without allowing for sufficient tissue repair. This scenario makes fistula formation between the esophagus and the mediastinum highly plausible.[25] Chen et al reported an incidence of esophageal fistula of 30.1% in patients with T4b esophageal cancer. Similarly,[16] Tomoko et al studied 59 patients with T4-stage esophageal cancer before receiving either definitive or palliative chemoradiotherapy, fistula was evident in 18 patients, translating to an incidence of 31%. Our study reported an increased esophageal fistula incidence of 44% in T4 ESCC patients. Although our data showed an association between tumor length and maximum tumor diameter with esophageal fistula in the univariate analysis, multivariate analysis did not support these findings as significant.

It is worth noting that diabetes has been consistently associated with increased complications of esophageal fistulafects from various cancer treatments, including oesophageal cancer. However, prior to our study, there was a lack of research explicitly looking at the incidence of esophageal fistula in diabetic ESCC patients receiving VMAT.[26–28] Our results identified pre-existing diabetes as an independent risk factor for the development of esophageal fistula in ESCC patients receiving VMAT. A plausible explanation for this association is the systemic inflammatory response syndrome often observed in diabetic patients and their reduced tissue repair capacity. It may be related to the low cellular immunity of diabetics, and the patients are in a state of hyperdecomposition, reduction of collagen synthesis in the body, reduction of wound healing ability and susceptibility to secondary infections.

Another notable finding was the high susceptibility of the male gender to esophageal fistula after VMAT for ESCC. In China, the proportion of men who drink alcohol is significantly higher than that of women, susceptibility may be due to prolonged heavy alcohol consumption. Alcohol consumption may induce chronic inflammation by prolonged agitation of the esophageal mucosa. Interestingly, our study did not find a direct link between a history of alcohol consumption and esophageal fistula. This may suggest that the degree of esophageal irritation depends not only on the act of drinking, but also on the duration and intensity of alcohol consumption. It's worth noting that our study did not look at quantifying the duration or amount of alcohol consumption, which points to an area for further research.

This study had several limitations. First, the data collected were all from the same centre of Hefei Cancer Hospital, Chinese Academy of Sciences, and the number of samples was limited. Further research in different populations with a larger cohort of patients is needed to validate our findings. Second, although the robustness of our nomogram is extensively validated by internal validation using bootstrapping, external validation cannot be performed. This nomogram needs to be externally validated in a larger multicentre patient cohort.

Conclusion

We were the first to report parameters predicting the risk of esophageal fistula in ESCC patients undergoing VMAT, our comprehensive evaluation of the parameters of gender, age, diabetes, T4 stage and total radiation dose associated with esophageal fistula, and after external validation, the identified parameters can be used as parameters to predict esophageal fistula.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
2. Cao W, Chen HD, Yu YW, et al. Changing profiles of cancer burden worldwide and in China: a secondary analysis of the global cancer statistics 2020. *Chin Med J*. 2021;134(7):783–791. doi:10.1097/CM9.0000000000001474
3. He Z, Ke Y. Precision screening for esophageal squamous cell carcinoma in China. *Chin J Cancer Res*. 2020;32(6):673–682. doi:10.21147/j.issn.1000-9604.2020.06.01
4. Hoshino I, Gunji H, Kuwayama N, et al. Efficacy of thoracotomy and thoracoscopic-assisted esophageal surgery in conversion and salvage surgeries: a retrospective study. *World J Surg Oncol*. 2022;20(1):16. doi:10.1186/s12957-022-02637-8
5. Gao X, Tsai PC, Chuang KH, et al. Neoadjuvant carboplatin/paclitaxel versus 5-fluorouracil/cisplatin in combination with radiotherapy for locally advanced esophageal squamous cell carcinoma: a multicenter comparative study. *Cancers*. 2022;14(11):2610. doi:10.3390/cancers14112610

6. Yun Y, Zhang Y, Xu Q, et al. SOX17-mediated MALAT1-miR-199a-HIF1α axis confers sensitivity in esophageal squamous cell carcinoma cells to radiotherapy. *Cell Death Discov*. 2022;8(1):270. doi:10.1038/s41420-022-01012-6
7. Ahn SJ, Kahn D, Zhou S, et al. Dosimetric and clinical predictors for radiation-induced esophageal injury. *Int J Radiat Oncol Biol Phys*. 2005;61(2):335–347. doi:10.1016/j.ijrobp.2004.06.014
8. Guan X, Liu C, Zhou T, et al. Survival and prognostic factors of patients with esophageal fistula in advanced esophageal squamous cell carcinoma. *Biosci Rep*. 2020;40(1):BSR20193379. doi:10.1042/BSR20193379
9. Yoshida N, Morito A, Nagai Y, et al. Clinical importance of sputum in the respiratory tract as a predictive marker of postoperative morbidity after esophagectomy for esophageal cancer. *Ann Surg Oncol*. 2019;26(8):2580–2586. doi:10.1245/s10434-019-07477-7
10. Petrov RV, Su S, Bakhos CT, et al. Surgical anatomy of paraesophageal hernias. *Thorac Surg Clin*. 2019;29(4):359–368. doi:10.1016/j.thorsurg.2019.07.008
11. Zhang Y, Li Z, Zhang W, et al. Risk factors for esophageal fistula in patients with locally advanced esophageal carcinoma receiving chemoradiotherapy. *Onco Targets Ther*. 2018;11:2311–2317. doi:10.2147/OTT.S161803
12. Kawakami T, Tsushima T, Omae K, et al. Risk factors for esophageal fistula in thoracic esophageal squamous cell carcinoma invading adjacent organs treated with definitive chemoradiotherapy: a monocentric case-control study. *BMC Cancer*. 2018;18(1):573. doi:10.1186/s12885-018-4486-3
13. Pao TH, Chen YY, Chang WL, et al. Esophageal fistula after definitive concurrent chemotherapy and intensity modulated radiotherapy for esophageal squamous cell carcinoma. *PLoS One*. 2021;16(5):e0251811. doi:10.1371/journal.pone.0251811
14. Zhu C, Ding J, Wang S, et al. Development and validation of a prognostic nomogram for malignant esophageal fistula based on radiomics and clinical factors. *Thorac Cancer*. 2021;12(23):3110–3120. doi:10.1111/1759-7714.14115
15. Chen HY, Ma XM, Ye M, et al. Esophageal perforation during or after conformal radiotherapy for esophageal carcinoma. *J Radiat Res*. 2014;55(5):940–947. doi:10.1093/jrr/rru031
16. Taniyama TK, Tsuda T, Miyakawa K, et al. Analysis of fistula formation of T4 esophageal cancer patients treated by chemoradiotherapy. *Esophagus*. 2020;17(1):67–73. doi:10.1007/s10388-019-00691-y
17. Balazs A, Kupcsulik PK, Galambos Z. Esophagorespiratory fistulas of tumorous origin. non-operative management of 264 cases in a 20-year period. *Eur J Cardiothorac Surg*. 2008;34(5):1103–1107. doi:10.1016/j.ejcts.2008.06.025
18. Tsushima T, Mizusawa J, Sudo K, et al. Risk factors for esophageal fistula associated with chemoradiotherapy for locally advanced unresectable esophageal cancer: a supplementary analysis of JCOG0303. *Medicine*. 2016;95(20):e3699. doi:10.1097/MD.0000000000003699
19. Wang X, Hu B, Chen J, et al. Risk factors of esophageal fistula induced by re-radiotherapy for recurrent esophageal cancer with local primary site. *BMC Cancer*. 2022;22(1):207. doi:10.1186/s12885-022-09319-4
20. Li K, Ni X, Lin D, Li J. Incorporation of PET metabolic parameters with clinical features into a predictive model for radiotherapy-related esophageal fistula in esophageal squamous cell carcinoma. *Front Oncol*. 2022;12:812707. doi:10.3389/fonc.2022.812707
21. Wu R, Geng LD, Zhao ZH, et al. Clinical application of oral meglumine diatrizoate esophagogram in screening for esophageal fistula during radiotherapy or chemoradiotherapy for esophageal cancer. *Front Oncol*. 2020;10:562147. doi:10.3389/fonc.2020.562147
22. Zhu C, Wang HP, You YH, et al. Risk factors for esophageal fistula in esophageal cancer patients treated with radiotherapy: a systematic review and meta-analysis. *Oncol Res Treat*. 2020;43:34–40. doi:10.1159/000503754
23. Hu B, Jia F, Zhou H, et al. Risk factors associated with esophageal fistula after radiotherapy for esophageal squamous cell carcinoma. *J Cancer*. 2020;11(12):3693–3700. doi:10.7150/jca.39033
24. Daiko H, Kato K. Updates in the 8th edition of the TNM staging system for esophagus and esophagogastric junction cancer. *Jpn J Clin Oncol*. 2020;50(8):847–851. doi:10.1093/jjco/hyaa082
25. Chen B, Deng M, Yang C, et al. High incidence of esophageal fistula on patients with clinical T4b esophageal squamous cell carcinoma who received chemoradiotherapy: a retrospective analysis. *Radiother Oncol*. 2021;158:191–199. doi:10.1016/j.radonc.2021.02.031
26. Wang JB, Zheng CH, Li P, et al. esophageal fistulafect of comorbidities on postoperative complications in patients with gastric cancer after laparoscopy-assisted total gastrectomy: results from an 8-year experience at a large-scale single center. *Surg Endosc*. 2017;31(6):2651–2660. doi:10.1007/s00464-016-5279-x
27. Li Y, Tan B, Fan L, et al. Clinicopathologic characteristics of elderly with gastric cancer, and the risk factors of postoperative complications. *J Invest Surg*. 2017;30(6):394–400. doi:10.1080/08941939.2016.1265617
28. Hayashi M, Yoshikawa T, Yura M, et al. Predictive value of the surgical Apgar score on postoperative complications in advanced gastric cancer patients treated with neoadjuvant chemotherapy followed by radical gastrectomy: a single-center retrospective study. *BMC Surg*. 2020;20(1):150. doi:10.1186/s12893-020-00813-9
29. Huang W, Huang Y, Sun J, et al. Atlas of the thoracic lymph nodal delineation and recommendations for lymph nodal CTV of esophageal squamous cell cancer in radiation therapy from China. *Radiother Oncol*. 2015;116(1):100–106. doi:10.1016/j.radonc.2015.06.024