Risk Factors for Esophageal Fistula in Esophageal Cancer Patients Treated with Radiotherapy: A Systematic Review and Meta-Analysis

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Keywords

Risk factors · Esophageal fistula · Radiotherapy · Meta-analysis

Abstract

Objective: Esophageal fistula is a critical and fatal complication of esophageal cancer. The aim of this meta-analysis was to explore the risk factors for esophageal perforation in esophageal cancer patients treated with radiotherapy.

Methods: Data from the PubMed and Embase databases were retrieved for clinical research published between 1990 and 2018. The Newcastle-Ottawa Scale was used to evaluate the quality of the articles. A meta-analysis was performed using the RevMan 5.3 software provided by the Cochrane Collaboration Network. **Results:** Seventeen articles were eligible for the meta-analysis. In these articles, over 35 risk factors for esophageal fistula formation were described and 17 risk factors were analyzed. Significant differences in the odds of developing an esophageal perforation were found with regard to age (OR 2.34, 95% CI 1.08–5.03, $p = 0.001$), ulcerative type (OR 2.72, 95% CI 1.43–5.16, $p = 0.002$), histology (OR 4.16, 95% CI 1.14–15.12, $p = 0.03$), T stage (OR 2.66, 95% CI 1.44–4.91, $p = 0.002$), short-term response (OR 2.21, 95% CI 1.06–4.62, $p = 0.03$), chemotherapy regimen (OR 2.80, 95% CI 1.38–5.68, $p = 0.005$), and stenosis (OR 2.00, 95% CI 1.03–3.89, $p = 0.04$). **Conclusions:** An age of <60–65 years, ulcerative type, squamous cell cancer, T4 stage, incomplete response, fluorouracil-based regimen, and stenosis were associated with an increased risk of esophageal fistula during or

after radiotherapy. However, further, large-scale prospective studies are needed to establish the validity of this association.

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Introduction

Esophageal cancer is one of the most common malignant tumors in China and its outcome is poor, even though extensive research has been conducted and treatment implemented [1]. The majority of patients have no opportunity for surgical resection because of the tumor's position or disease development, or they undergo comprehensive treatment based on radiation therapy [2]. Esophageal perforation is a disastrous complication of esophageal cancer after radiotherapy or during radiotherapy [3]. The incidence of esophageal perforation among patients with esophageal cancer treated with radiotherapy is around 5.6–33% [4–17].

The causes of esophageal fistula in esophageal cancer patients are complicated. Esophageal cancer may become perforating during natural development, mainly because of tumor invasion, thinning of the esophageal wall, and increased intraluminal pressure during swallowing or severe coughing [18]. Treatment of esophageal cancer such as radiotherapy, chemotherapy, and brachytherapy may also cause esophageal fistula, owing to the imbalance between tumor shrinkage and normal tissue repair [19]. The prognosis of esophageal perforation is poor and the death

Table 1. Characteristics of the studies included in the meta-analysis

First author	Year	Location	Study design	Patients (fistula/all), <i>n</i>	Treatment	Period of treatment	Study quality, NOS score	Ref.
Zhang	2018	China	Prospective	22/212	Chemoradiotherapy	2014–2016	6	[5]
Tsushima	2016	Japan	Retrospective	31/140	Chemoradiotherapy	2004–2009	6	[10]
Chen	2014	China	Retrospective	18/322	Chemoradiotherapy/radiotherapy	2007–2011	6	[14]
Kawakami	2018	Japan	Retrospective	28/116	Chemoradiotherapy	2004–2015	6	[15]
Taniguchi	2011	Japan	Retrospective	7/48	Chemoradiotherapy	2002–2009	6	[16]
Lingrong	2018	China	Retrospective	22/336	Chemoradiotherapy/radiotherapy	2012–2015	7	[6]
Kim	2018	Japan	Retrospective	4/62	Chemoradiotherapy/radiotherapy	2001–2015	7	[4]
Kim	2012	Japan	Retrospective	3/10	Chemoradiotherapy/radiotherapy	2007–2011	5	[11]
Zhou	2015	China	Retrospective	11/55	Radiotherapy	2003–2012	5	[13]
Yamaguchi	2011	Japan	Retrospective	4/31	Chemoradiotherapy/radiotherapy	1996–2008	7	[17]
Gaspar	2000	America	Prospective	6/49	Chemoradiotherapy/radiotherapy/brachytherapy	1992–1995	5	[7]
Taal	1996	The Netherlands	Prospective	6/74	Radiotherapy/brachytherapy	1991–1994	5	[9]
Grazziotin Reisner	2015	Brazil	Retrospective	8/115	Chemoradiotherapy/radiotherapy/brachytherapy	2001–2011	6	[29]
Sun	2016	China	Retrospective	17/179	Chemoradiotherapy	2009–2014	8	[8]
Hama	2002	Japan	Retrospective	3/6	Radiotherapy/brachytherapy	1996–1997	4	[28]
Ohtsu	1999	Japan	Prospective	5/54	Chemoradiotherapy	1992–1997	5	[30]
Kaneko	2003	Japan	Retrospective	3/57	Chemoradiotherapy	1996–2000	5	[31]

rate is high [20]. Patients with esophageal perforation are prone to develop secondary uncontrolled mediastinitis or lung infection, which leads to systemic infection and even to toxic shock and death [21]. At present, there are no satisfactory treatments [22–24]; therefore, the prevention of esophageal fistula should be taken seriously. However, no definitive risk factors for esophageal perforation have been identified. We performed this meta-analysis to provide comprehensive and systematic data on the topic. To the best of our knowledge, this is the first meta-analysis of risk factors for esophageal fistula relevant to esophageal cancer patients on radiation therapy.

Methods

Information Sources and Search Parameters

A systemic bibliographic search on PubMed and Embase was performed using the terms “esophagus cancer [MeSH]” and “tracheoesophageal fistula,” “esophagorespiratory fistula” or “esophageal fistula” or “esophageal perforation” and “radiotherapy” or “radiation therapy” or “chemoradiotherapy.” A total of 779 articles published between 1990 and 2018 were found. After a thorough search, 120 duplicates were removed and the remaining articles were screened by title and abstract; thereafter, the full texts were examined as potential articles for analysis. A search through the references in the available articles was also conducted to retrieve missing articles.

Eligibility Criteria and Exclusion Criteria

Studies which met the following criteria were included: (1) all subjects were definitely diagnosed with esophageal cancer; (2) data regarding esophageal perforation or fistula were presented; and (3) all patients were treated with radiation therapy. Studies meeting the following criteria were excluded: (1) studies other than clinical trials (case reports, reviews, questionnaires, editorial notes, etc.);

(2) there were fewer than 3 cases of esophageal perforation; (3) studies failing to provide sufficient data; (4) articles neither in English nor in Chinese; and (5) studies related to postoperative complications of esophageal cancer or indistinguishable. The first author's name, country, year of publication, study type, clinical patient information, and risk factors for fistula were extracted from the articles for analysis (Table 1).

Quality Assessment

We used the Newcastle-Ottawa Quality Assessment Scale (NOS) [25] to evaluate the methodological quality of the eligible studies. The NOS checklist is applicable to case-control studies or cohort studies. The assessment was carried out regarding three aspects: subject choice (4 scores in total), comparability between groups (2 scores in total), and exposure assessment (3 scores in total). A score of more than 5 points is considered to represent high quality.

Two independent reviewers screened the retrieved articles, extracted the data, and evaluated the quality of the included studies. Discrepancies were settled by consensus or submitted to a third reviewer for assistance.

Statistical Analysis

The meta-analysis was conducted by synthesizing the outcomes of the studies in which potential risk factors for esophageal fistula were presented. Microsoft Excel was used for data entry and RevMan 5.3 was used for the meta-analysis. We used the Mantel-Haenszel method to calculate odds ratios (ORs) and 95% confidence interval (CIs).

Heterogeneity was assessed by inconsistency statistics (I^2) and the χ^2 test [26]. I^2 values <25%, <50%, and >50% were considered to represent low, moderate, and severe heterogeneity, respectively [26]. In the presence of low heterogeneity, the fixed-effects model was used to pool the primary outcomes. The random-effects model was utilized for the other two conditions. A p value <0.05 indicated statistical significance. Assessment of publication bias was conducted by funnel plot when there were more than 10 studies [27]. The robustness and reliability of the pooled outcomes were assessed by sensitivity analysis.

Fig. 1. Flowchart of the study selection process.

Results

Study Selection and Characteristics of the Eligible Articles

After data retrieval from the databases and eliminating duplicates, 677 articles were obtained. After reading the titles and abstracts, 599 articles were removed, and the remaining 78 studies were reviewed in full text. Based on the eligibility and exclusion criteria, a total of 17 studies, including 1,866 patients, were included in the meta-analysis (Fig. 1). The included studies consisted of 4 prospective studies and 13 retrospective studies. Fourteen of the studies were carried out in East Asian countries including China and Japan (82.4%); 1 was carried out in the USA, 1 in Brazil, and 1 in the Netherlands. The sample size ranged from 6 to 322. The characteristics of the studies eligible for meta-analysis are shown in Table 1.

Risk Factors

In the 17 articles, over 35 risk factors for esophageal fistula formation were described. Meta-analyses were performed for those risk factors that were presented in more than one article (Fig. 2). The examined risk factors and relevant studies are listed in Table 2.

Effect of Patient Status on Fistula Formation

Gender

Eight articles [4–6, 10, 11, 14–16] reported on gender ($n = 1,246$). The meta-analysis demonstrated no difference between males and females in the risk of esophageal fistula (OR 1.31, 95% CI 0.73–2.36, $p = 0.36$). Slight heterogeneity was found ($I^2 = 8\%$, $p = 0.37$).

Age

Age was reported in 8 articles [4–6, 10, 11, 14–16], but 3 of them [10, 15, 16] were excluded because of insufficient data. The meta-analysis found a significant differ-

Fig. 2. Meta-analysis of the risk factors for esophageal fistula in esophageal cancer patients treated with radiotherapy.

Table 2. Risk factors for esophageal fistula formation in esophageal cancer patients receiving radiotherapy

Patients' status [Ref.]	Tumor	Treatment	Others
Gender [4–6, 10, 11, 14–16]	Ulcerative tumor [5, 8, 10]	Concurrent chemoradiotherapy [5, 11, 14, 17]	Stenosis [4, 5, 10, 15]
Age [4–6, 11, 14]	Tumor location [5, 9–11, 16, 28, 29]	Treatment response [4, 6, 9, 11]	
KPS/PS [5, 10, 11, 14–16]	T4 [4–8, 10, 11, 14, 30, 31]	Chemotherapy regimen [5, 8]	
Albumin [10, 15]	Histology [6, 9]	Re-radiotherapy [6, 13, 14]	
Hemoglobin [10, 15]	Tumor length [15, 16]		
BMI [5, 16]	Tumor size [7, 28]		

KPS, Karnofsky Performance Status; PS, performance status; BMI, body mass index.

ence between the group older than 60–65 years and the group younger than 60–65 years. The patients younger than 60–65 years had a greater risk of developing esophageal fistula than the patients older than 60–65 years (OR 2.34, 95% CI 1.08–5.03, $p = 0.03$). Moderate heterogeneity was found ($I^2 = 41\%$, $p = 0.15$).

Karnofsky Performance Status/Performance Status

Six clinical studies [5, 10, 11, 14–16] ($n = 526$) examined the role of the Karnofsky Performance Status/performance status (KPS/PS) on fistula formation, and the meta-analysis showed no significant difference in the risk of developing esophageal fistula (OR 0.76, 95% CI 0.30–1.93, $p = 0.56$). However, a remarkably high heterogeneity was found ($I^2 = 73\%$, $p = 0.002$). A moderator analysis was carried out. After removal of the study by Chen et al. [14], a decrease in heterogeneity was found ($I^2 = 56\%$, $p = 0.06$), but there still was no significant difference between groups (OR 1.09, 95% CI 0.49–2.42, $p = 0.84$).

Hemoglobin, Albumin, and Body Mass Index

Two articles reported on hemoglobin [10, 15], and there was no significant difference between patients with normal/high hemoglobin levels and patients with low hemoglobin levels (OR 2.21, 95% CI 0.88–5.50, $p = 0.09$; heterogeneity: $I^2 = 47\%$, $p = 0.17$). We also determined no effect of body mass index (BMI) [5, 16] (>20 –24 vs. <20 –24; OR 0.88, 95% CI 0.33–2.36, $p = 0.80$; heterogeneity: $I^2 = 56\%$, $p = 0.13$) and albumin [10, 15] (>3.5 vs. <3.5 g/dL; OR 0.46, 95% CI 0.16–1.27, $p = 0.13$; heterogeneity: $I^2 = 36\%$, $p = 0.21$) on esophageal fistula formation. However, these results should be treated with caution owing to the small number of included studies.

Tumor-Related Risk Factors

Location

Seven studies [5, 9–11, 16, 28, 29] included this factor ($n = 605$). The meta-analysis demonstrated no significant difference between patients with cervical/upper disease and

those with middle/lower disease with regard to the development of esophageal fistula (OR 0.92, 95% CI 0.53–1.58, $p = 0.75$). No heterogeneity was found ($I^2 = 0\%$, $p = 0.96$).

T Stage

This risk factor was examined in 10 articles [4–8, 10, 11, 14, 30, 31] ($n = 1,291$). Overall, a significant difference in the odds for the development of esophageal fistula was found (OR 2.66, 95% CI 1.44–4.91, $p = 0.002$). The patients with T4 disease were more likely to have a fistula than the patients with non-T4 disease. Heterogeneity was moderate ($I^2 = 30\%$, $p = 0.17$). The funnel plot showed asymmetry, suggesting that publication bias may have existed (Fig. 3).

Ulcerative Type

The risk factor “ulcerative type” was discussed in 3 studies [5, 8, 10] ($n = 531$). A significant difference in the odds for fistula formation was seen between patients with and those without ulcerative-type disease (OR 2.72, 95% CI 1.43–5.16, $p = 0.002$). The patients with ulcerative disease had a higher risk of developing esophageal fistula. No heterogeneity was found ($I^2 = 0\%$, $p = 0.41$).

Histology

Two articles [6, 9] ($n = 410$) offered sufficient data on histology for a meta-analysis. Patients with squamous cell cancer had a higher risk of having esophageal fistula (OR 4.16, 95% CI 1.14–15.12, $p = 0.03$). Slight heterogeneity was found ($I^2 = 23\%$, $p = 0.25$).

We also performed meta analyses to determine the effect of tumor size [7, 28] and tumor length [15, 16] on the risk of fistula formation. However, no statistically significant difference was found for tumor size (OR 1.65, 95% CI 0.76–3.61, $p = 0.10$; heterogeneity: $I^2 = 0\%$, $p = 0.37$) and tumor length (OR 0.61, 95% CI 0.28–1.32, $p = 0.21$; heterogeneity: $I^2 = 0\%$, $p = 0.62$).

Tumor-Related Factors

Short-Term Response

This risk factor was discussed in 4 articles [4, 6, 9, 11] ($n = 482$). Among patients without complete remission (CR), the probability of esophageal fistula formation was increased (OR 2.21, 95% CI 1.06–4.62, $p = 0.03$), and no heterogeneity could be observed ($I^2 = 0\%$, $p = 0.42$).

Chemotherapy Regimen

A chemotherapy regimen with fluorouracil plus cisplatin (FP) versus taxane plus cisplatin (TP) was studied in 2 articles [5, 8] ($n = 391$). The meta-analysis showed that the odds for developing fistula among subjects undergoing the fluorouracil-plus-cisplatin regimen were higher than among those receiving the taxane-plus-cisplatin regimen (OR 2.80, 95% CI 1.38–5.68, $p = 0.005$).

Fig. 3. Publication bias tested by funnel plot for T stage.

No heterogeneity was found ($I^2 = 0\%$, $p = 0.78$). Due to the small number of cases, this result should be interpreted with caution.

Four articles reported on concurrent chemotherapy [5, 11, 14, 17] ($n = 575$). The meta-analysis did not lead to a significant difference between patients with and those without concurrent chemotherapy (OR 1.59, 95% CI 0.55–4.80, $p = 0.40$). Heterogeneity was high ($I^2 = 49\%$, $p = 0.12$). We performed a moderator analysis after removal of the study by Chen et al. [14]; no heterogeneity was found ($I^2 = 0\%$, $p = 0.74$), nor did the analysis have an influence on the odds ratio (OR 0.95, 95% CI 0.41–2.19, $p = 0.9$).

Three articles [6, 13, 14] ($n = 772$) presented sufficient data on re-radiation as a risk factor. No significant difference between groups was observed (OR 2.73, 95% CI 0.65–11.52, $p = 0.17$). High heterogeneity was observed ($I^2 = 68\%$, $p = 0.04$). After removal of the study by Chen et al. [14], no heterogeneity was found ($I^2 = 0\%$, $p = 0.83$), nor did the analysis have an influence on the odds ratio (OR 1.31, 95% CI 0.52–3.31, $p = 0.57$).

Other Risk Factors

Stenosis

Stenosis was reported as a factor in 4 articles [4, 5, 10, 15] ($n = 530$). The meta-analysis showed that the odds for fistula formation were 2.00 times higher in the group with stenosis (OR 2.00, 95% CI 1.03–3.89, $p = 0.04$). Moderate heterogeneity was found ($I^2 = 34\%$, $p = 0.21$).

Discussion

Esophageal perforation is one of the most serious complications of esophageal cancer; most patients will die of it within 3 months [20]. Therefore, the prevention of fis-

tula formation is very important for an individualized cancer treatment. The purpose of this meta-analysis was to identify risk factors for esophageal perforation in esophageal cancer patients treated with radiotherapy.

A total of 17 articles reporting over 35 risk factors were included, and we carried out a meta-analysis for 17 risk factors. Seven of the 17 examined factors (age, ulcerative type, histology, T stage, short-term response, chemotherapy regimen, and stenosis) were related to the formation of esophageal perforation. The 10 remaining factors (gender, hemoglobin, KPS/PS, albumin, BMI, tumor location, tumor length, tumor size, re-radiotherapy, and concurrent chemoradiotherapy) had no significant correlation with esophageal fistula formation.

Our study showed that stenosis was a strong predictor of esophageal perforation; the odds for developing esophageal fistula were 2.00 times higher in this group. The mechanism of this phenomenon is not yet completely understood. It may be associated with food friction or increased intraesophageal pressure caused by swallowing and severe cough [5]. Clinicians should be alerted to the risk of esophageal perforation in patients with esophageal stenosis during or after radiotherapy. However, there is a limitation, since the diagnosis of stenosis was not performed according to the same standards in the different studies, or it was not clearly described. Thus, to unify the evaluation system for the diagnosis of stenosis with patients' symptoms and/or imaging manifestations is quite important.

T4 stage is another significant prognostic factor. The risk of esophageal fistula in patients with stage T4 cancer is 2.66 times higher than that in T1–3 stage cancer patients. Anatomically, the esophagus is surrounded by the trachea, large vessels, and the lung. Cancer of the T4 stage means that tumor tissue infiltrates the whole layer of the esophagus into the surrounding tissues. It is easy for a fistula to form when the rate of tumor regression is faster than that of normal tissue repair. In addition, if the tumor is residual after treatment, esophageal perforation may occur if the disease progresses [6]. The risk of esophageal perforation in patients who did not reach CR after treatment was 2.21 times higher than that in CR patients.

Patients with the ulcerative type maybe have a higher risk of developing esophageal fistula. One of the reasons is that the injured mucosa is prone to fungal infection, which can affect the subepithelial venous plexus to cause mucous edema and circulatory disorder [32]. However, Tsushima et al. [10] insisted that ulcers should not be counted as a risk factor, because all ulcers will occur before perforation.

Esophageal perforation was more frequent with fluorouracil than with taxane administration. An explanation for this might be that fluorouracil increases the risk of mucositis, leading to a higher probability of perforation [33].

The patients younger than 60–65 years were found to have a higher risk of fistula formation. This may be owing to the more intensive treatment regimen used in this group, which may accelerate contraction of the tumor but inhibit repair of the normal tissue [14].

Whether re-radiation can increase the risk of perforation cannot be definitely determined. The salvage measures for esophageal cancer recurrence after radiotherapy are surgery, re-radiotherapy, chemotherapy, brachytherapy, and so on [34–36]. The data on re-radiation were scarce [37]. On the one hand, re-radiation can control the progression of local tumors; on the other hand, re-irradiation may cause more serious damage to the tissues damaged by radiotherapy [14]. The incidence of esophageal fistula among re-radiation patients was as high as 12–33% [11–13, 17]. However, no significant results have been obtained in our study.

There are several limitations to our study. Firstly, all the included studies came from published literature, which is why there is the possibility of publishing bias. Secondly, the majority of the subjects studied were East Asian, with relatively few Caucasians enrolled. Some indicators were reported in few studies; therefore, an effective subgroup analysis could not be carried out in the presence of heterogeneity, which may have had a certain impact on the results. Finally, for the risk factors of age, BMI, and KPS, the cutoffs were intervals, which is because the cutoffs provided in the literature were not uniform.

In conclusion, our study showed risk factors for esophageal fistula or perforation in patients with esophageal cancer undergoing radiotherapy. The factors age <60–65 years, ulcerative type, squamous cell cancer, T4 stage, non-CR, fluorouracil-based regimen, and stenosis were associated with an increased risk of esophageal fistula formation.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

All authors declare no conflict of interest.

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