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RISK FACTORS OF ANASTOMOTIC FISTULAS AFTER ESOPHAGEAL AND GASTRIC CANCER SURGERY: A RETROSPECTIVE STUDY

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RISK FACTORS OF ANASTOMOTIC FISTULAS AFTER ESOPHAGEAL AND GASTRIC CANCER SURGERY: A RETROSPECTIVE STUDY (Abstract): Anastomotic fistulas remain one of the most severe complications following esophageal and gastric cancer surgery, significantly impacting morbidity and mortality rates. **Materials and methods**: This retrospective study evaluates the risk factors associated with anastomotic fistula formation and assesses the efficacy and complications of esophageal stenting as a treatment modality. Data from 110 patients treated at the Surgery Clinic of "Sf. Maria" Hospital in Bucharest, between 2019 and 2023 were analyzed. The study population was divided into two groups: patients with postoperative anastomotic fistulas who underwent endoscopic esophageal stenting and those who did not develop fistulas. **Results:** Key findings indicate that advanced age, smoking, alcohol consumption, tumor size, TNM stage, hypertension, diabetes, and preoperative radiotherapy were significantly associated with an increased risk of fistula formation. Additionally, hypoalbuminemia, anemia, and impaired renal function emerged as critical predictors. While esophageal stenting proved to be an effective intervention, it was associated with specific complications requiring careful patient selection and monitoring. **Conclusions:** This study identifies multiple risk factors associated with the development of anastomotic fistulas after esophageal and gastric cancer surgery. Understanding these risk factors is crucial for identifying high-risk patients and implementing targeted perioperative strategies to improve surgical outcomes and reduce postoperative complications. **Keywords:** ANASTOMOTIC FISTULA, ESOPHAGEAL CANCER, GASTRIC CANCER, RISK FACTORS.

INTRODUCTION

Anastomotic fistulas are among the most serious postoperative complications following esophageal and gastric cancer surgery, significantly contributing to increased morbidity, prolonged hospitalization, and higher mortality rates. These fistulas result from impaired healing at the anastomotic site, leading to leakage, infection, and subsequent complications. Identifying risk factors associated with anastomotic fistula formation is crucial for optimizing surgical strategies and improving patient outcomes (1, 2).

Numerous factors have been implicated in the development of anastomotic fistulas, including patient-related parameters (age, comorbidities, nutritional status), tumor

characteristics (size, location, histopathology), and perioperative factors (neoadjuvant therapy, intraoperative technique). Despite advances in surgical techniques and perioperative management, the incidence of anastomotic fistulas remains significant, warranting further investigation into modifiable and non-modifiable risk factors (3-5).

The aim of this study is to evaluate the risk factors associated with the development of postoperative anastomotic fistulas in patients undergoing surgery for esophageal and gastric neoplasms. By comparing patients who developed fistulas with those who did not, we seek to identify key predictors that may contribute to an increased risk of fistula formation. A better understanding of these factors could support the development of preventive strategies and guide clinical decision-making in high-risk patients.

MATERIALS AND METHODS

This retrospective and observational study aimed to evaluate the efficacy and complications of esophageal stenting in the treatment of postoperative anastomotic fistulas in patients who underwent surgery for esophageal and gastric neoplasms. The analysis was conducted based on data from patients admitted to the Surgery Clinic of "Sf. Maria" Hospital in Bucharest, between 2019 and 2023. Data collection and processing were carried out during 2023-2024.

The studied population was divided into two groups:

- Study group: Patients who developed postoperative anastomotic fistulas and were treated with endoscopic esophageal stenting.
- Control group: Patients who underwent surgery for esophageal and gastric neoplasms but did not develop postoperative fistulas.

Patients aged ≥18 years with a histopathological confirmed diagnosis of esophageal or gastric neoplasm. The study group includes patients with imaging-confirmed anastomotic fistulas, while the control group consists of those without anastomotic fistulas. Patients with insufficient medical data are excluded.

The study was conducted in compliance with all national and international ethical research standards to ensure the integrity of the research process and patient protection. The study adhered to Law No. 206/2004 on good conduct in scientific research, technological development, and innovation, which defines ethical and integrity standards for research activities in Romania. The principles of the Declaration of Helsinki were implemented to uphold ethical research practices in human subjects. Fundamental ethical principles, such as confidentiality protection and respect for patient rights, were followed throughout the study.

RESULTS

Among the 110 patients included in the study, those without anastomotic fistulas had a mean age of 54.13 years (median: 54 years), with a standard deviation of 5.10 years. Patients who developed anastomotic fistulas had a higher mean age of 59.71 years (median: 58 years) and a larger standard deviation of 9.88 years. The t-test for the difference in means showed a statistically significant difference ($p < .001$) between the two groups. The mean difference was -5.58 years, with a standard error of 1.50 years.

Of the 42 female patients, 19 (45.24%) developed anastomotic fistulas, whereas 23 (54.76%) did not. Among the 68 male patients, 36 (52.94%) developed fistulas,

while 32 (47.06%) did not. The calculated odds ratio of 1.362 suggests a slightly higher risk for male patients; however, the 95% confidence intervals (0.629-2.947) include the value of 1, and Fisher's exact test ($p = 0.556$) indicates that the difference is not statistically significant.

Among the 43 smokers, 40 (93.02%) developed anastomotic fistulas, compared to only 15 cases (22.39%) among the 67 non-smokers. The odds ratio of 46.222 indicates a significantly increased risk of fistula development in smokers. The confidence intervals (95% CI: 12.518-170.680) and Fisher's exact test ($p < 0.001$) confirms statistical significance.

Regarding alcohol consumption, 33 of the 34 alcohol consumers (97.06%) developed fistulas, compared to only 22 cases (28.95%) among the 76 non-consumers. The odds ratio of 81 suggests an extremely high risk associated with alcohol consumption. Confidence intervals (95% CI: 10.425-629.371) and Fisher's exact test ($p < 0.001$) confirm the statistical significance.

Patients with smaller tumors (2 cm) developed anastomotic fistulas in only 26.09% of cases, compared to 94.44% of those with 4 cm tumors. The proportion of fistula development in intermediate-sized tumors (3 cm) was 45.59%. The chi-square test ($\chi^2 = 21.013$, $p < 0.001$) indicates a statistically significant association between tumor size and fistula occurrence.

The highest proportion of anastomotic fistulas was observed in patients with tumors located in the gastric mid-corporeal region, where 23 out of 38 patients (60.53%) developed fistulas. Subcardial tumors (Siewert III) were associated with a lower proportion of fistulas (37.93%). Junctional esophagogastric tumors (Siewert II), lower esophageal tumors (Siewert I), and mid-esophageal tumors exhibited similar fistula proportions (46.15%, 50%, and 50%, respectively). However, these differences were not statistically significant ($\chi^2 = 3.451$, $df = 4$, $p = 0.485$).

Patients with adenocarcinoma developed anastomotic fistulas in 53.49% of cases (46 out of 86), compared to 37.50% (9 out of 24) in those with squamous cell carcinoma. However, statistical analysis showed that the differences between histopathological types were not statistically significant ($\chi^2 = 1.919$, $p = 0.166$).

A progressive increase in the risk of anastomotic fistulas was observed with advancing TNM stage. No fistulas were detected in stage 1 patients, whereas the incidence was 35.71% in stage 2, 92.86% in stage 3, and 100% in stage 4. The significant association between TNM stage and fistula occurrence was confirmed ($\chi^2 = 38.286$, $p < 0.001$).

Among the 36 patients with arterial hypertension, 33 (91.67%) developed anastomotic fistulas, compared to only 22 out of 74 patients (29.73%) without hypertension. The odds ratio of 26 indicates an extremely high risk, confirmed by significant confidence intervals (7.209-93.768) and Fisher's exact test ($p < 0.001$).

Similarly, 14 out of 16 diabetic patients (87.50%) developed fistulas, compared to 41 out of 94 non-diabetic patients (43.62%). The odds ratio of 9.049 indicates an increased risk, with statistical significance ($p = 0.002$).

Preoperative radiotherapy was associated with a significantly increased risk of anastomotic fistulas, with an odds ratio of 3.514 ($p = 0.003$). In contrast, preoperative chemotherapy was associated with a slightly lower risk (OR = 0.588), but this difference was not statistically significant ($p =$

0.556).

Patients who developed anastomotic fistulas had significantly higher levels of serum creatinine (1.04 ± 0.15 mg/dL *vs.* 0.91 ± 0.14 mg/dL, $p < 0.001$), blood glucose (98.56 ± 25.65 mg/dL *vs.* 88.55 ± 13.70 mg/dL, $p = 0.012$), and lower levels of serum albumin (3.52 ± 0.17 g/dL *vs.* 3.72 ± 0.14 g/dL, $p < 0.001$). Furthermore, hemoglobin levels were significantly lower in patients who developed fistulas (10.49 ± 1.43 g/dL *vs.* 12.78 ± 0.45 g/dL, $p < 0.001$).

Patients with anastomotic fistulas had significantly lower body mass index (BMI) values compared to those without fistulas (22.77 ± 1.87 *vs.* 24.11 ± 1.42, $p < 0.001$), suggesting a relationship between lower BMI and an increased risk of fistula development (tab. I).

TABLE I.

Relationships between risk factors and the risk of fistula development

Risk Factor	No Fistula (Mean ± SD/%)	Fistula (Mean ± SD/%)	p-value
Age	54.13 ± 5.10 yrs.	59.71 ± 9.88 yrs.	< 0.001
Smoking	22.39%	93.02%	< 0.001
Alcohol Consumption	28.95%	97.06%	< 0.001
Tumor Size	2.0 cm (26.09%)	4.0 cm (94.44%)	< 0.001
TNM Stage	Stage 1 (0%)	Stage 4 (100%)	< 0.001
Hypertension	29.73%	91.67%	< 0.001
Diabetes Mellitus	43.62%	87.50%	0.002
Radiotherapy	37.88%	68.18%	0.003
Chemotherapy	61.54%	38.46%	0.556
Serum Creatinine	0.91 ± 0.14	1.04 ± 0.15	< 0.001
Blood Glucose	88.55 ± 13.70	98.56 ± 25.65	0.012
Serum Albumin	3.72 ± 0.14	3.52 ± 0.17	< 0.001
Hemoglobin	12.78 ± 0.45	10.49 ± 1.43	< 0.001
BMI	24.11 ± 1.42	22.77 ± 1.87	< 0.001

DISCUSSION

Anastomotic fistulas represent a major and frequent complication in gastroesophageal surgery, significantly impacting postoperative outcomes. In this study, the predominant localization of fistulas at the esophagojejunal anastomosis (61.82%) aligns with the existing literature, which reports a higher incidence in this segment due to technical complexity and vascularization challenges. Although esophagogastric fistulas (38.18%) were less frequent, they remain a significant cause of morbidity.

Contrast-enhanced CT scan was the primary diagnostic modality, used in 85.45% of cases, highlighting its role as the gold standard for detecting anastomotic fistulas due to its high sensitivity and specificity. The mean time to fistula onset was 7.44 days postoperatively, consistent with literature reports identifying this period as the critical window for fistula detection,

driven by inflammatory and scarring processes. The concentration of cases within the 7-8-day period suggests that mechanical tension and peak inflammatory responses contribute to anastomotic dehiscence at this stage (4, 5).

Advanced age was significantly associated with a higher risk of fistula formation, with affected patients having a mean age of 59.71 years compared to 54.13 years in the control group. Literature findings confirm that older patients are at greater risk due to slower tissue regeneration, multiple comorbidities, and reduced tissue resilience. These findings underscore the need for personalized management strategies in elderly patients, including optimized surgical techniques, closer postoperative monitoring, and targeted preventive measures (6, 7).

A slightly higher prevalence of fistulas was observed in male patients (52.94%) compared to female patients (45.24%). However, statistical analysis did not indicate a significant difference, suggesting that sex is not a major determinant of fistula formation (7).

The study found a strong association between smoking and anastomotic fistula formation, likely due to impaired wound healing, reduced tissue vascularization, collagen disruption, and increased inflammation and infection risk (8).

An even stronger correlation was observed with alcohol consumption, with an odds ratio of 81.000, emphasizing its detrimental effect on tissue regeneration. Alcohol consumption is known to inhibit angiogenesis, impair immune function, and exacerbate local inflammatory responses, thereby increasing the risk of fistula formation. These findings highlight the importance of preoperative cessation programs for smoking and alcohol consumption in high-risk patients (9).

A significant correlation was identified between tumor size and the risk of anastomotic fistulas. Larger tumors (>3 cm) were associated with higher fistula rates, likely due to vascular compromise, difficulty in achieving a tension-free anastomosis, and increased risk of dehiscence. In contrast, smaller tumors ($\leq$ 2 cm) had a significantly lower risk, reinforcing the hypothesis that tumor burden influences postoperative anastomotic integrity (10).

While gastric mid-body tumors (60.53%) were associated with a higher proportion of fistulas, statistical analysis did not identify a significant correlation between tumor location and fistula formation. Similarly, although adenocarcinoma (53.49%) had a higher rate of anastomotic fistulas than squamous cell carcinoma (37.50%), the difference was not statistically significant, suggesting that histopathology was not a decisive factor in fistula development in this cohort (11).

A progressive increase in fistula risk was observed with advancing TNM stage, with significant associations across T, N, and M components (12).

- T3-T4 tumors were associated with higher fistula rates, reflecting extensive local invasion and compromised tissue integrity, consistent with literature indicating that advanced local tumors increase anastomotic failure risk.
- All patients with distant metastases (M1) developed anastomotic fistulas, suggesting that systemic disease burden and poor overall physiological status contribute to impaired wound healing. These findings emphasize the importance of accurate preoperative staging and multidisciplinary interventions, including nutritional support

and perioperative optimization, to mitigate complication rates in advanced-stage patients.

A strong correlation was observed between hypertension and anastomotic fistula formation, indicating that compromised microvascular circulation and increased anastomotic tension may contribute to dehiscence (13,14).

Similarly, diabetes mellitus was associated with a higher fistula risk, likely due to microvascular dysfunction, chronic inflammation, and delayed wound healing. Given that diabetic patients are more prone to infections, strict perioperative glycemic control and wound surveillance are essential in reducing complications.

Preoperative radiotherapy was significantly associated with an increased risk of anastomotic fistulas, likely due to vascular damage and impaired tissue healing. Literature findings confirm that high radiation doses can compromise anastomotic integrity, particularly in advanced tumors (15).

In contrast, preoperative chemotherapy was not significantly associated with an increased fistula risk, suggesting that its impact on anastomotic healing is less pronounced than that of radiotherapy.

Altered biological parameters at hospital admission were strongly correlated with fistula development.

- Increased serum creatinine levels indicate renal dysfunction, which may impair tissue regeneration and stress response management.
- Hyperglycemia was associated with a higher risk of fistula formation, emphasizing the need for strict perioperative glucose control.
- Hypoalbuminemia, indicative of malnutrition, was a strong predictor of postoperative complications, reinforcing the importance of preoperative nutritional optimization.
- Anemia, reflected by lower hemoglobin levels, suggested tissue hypoxia and impaired healing capacity, highlighting the need for preoperative hematologic correction.

Patients with a lower BMI were more prone to anastomotic fistulas, likely due to malnutrition, reduced muscle mass, and lower energy reserves, all of which negatively impact wound healing. These findings emphasize the importance of preoperative nutritional assessment and correction, particularly in underweight patients. Nutritional interventions, including protein supplementation and enteral/parenteral support, may help reduce the risk of anastomotic fistulas and improve postoperative outcomes.

CONCLUSIONS

This study identifies multiple risk factors associated with the development of anastomotic fistulas after esophageal and gastric cancer surgery. Advanced age, smoking, alcohol consumption, large tumor size, advanced TNM stage, hypertension, diabetes, hypoalbuminemia, anemia, and preoperative radiotherapy were all strongly correlated with an increased risk of fistula formation. Understanding these risk factors is essential for identifying high-risk patients and implementing targeted perioperative interventions to improve surgical outcomes.

CONFLICT OF INTEREST AND FUNDING

The authors declare no conflicts of interests. The research did not receive external funding.

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