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Original Article

Clinicopathological Spectrum of Esophageal Lesions: A Retrospective Analysis of Biopsy Specimens from Shahid Sadoughi Hospital, Yazd, Iran

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A B S T R A C T

Introduction: Esophageal cancer is a highly lethal malignancy with marked geographic variation in incidence and histopathology, with squamous cell carcinoma predominating in high-risk regions such as Iran. Robust local epidemiological and pathological data are essential for early detection, effective management, and targeted prevention.

Materials and Methods: This retrospective, cross-sectional study analyzed all esophageal biopsy specimens submitted from 2016 to 2021. Demographic, clinical, anatomical, and histopathological data were collected. Statistical analysis was performed using SPSS v23, with chi-square tests for categorical variables and one-way ANOVA for continuous variables; $p < 0.05$ was considered significant.

Results: A total of 420 biopsies were analyzed (51% male; mean age 45.5 ± 25 years, range 1–90), with the highest frequency in patients aged 61–80 years (31%). Dysphagia was the most common symptom (51.9%), and the distal esophagus was the predominant site (75.2%). Malignant lesions accounted for 45.7% of cases, primarily squamous cell carcinoma (33.3%) and adenocarcinoma (9.5%) ,while benign lesions comprised 14.8%, most commonly squamous papilloma (5.7%) and esophagitis was present in 27.1% (mainly non-infectious) .Malignancies were more frequent in older patients, whereas benign and inflammatory findings predominated in younger individuals. Lesion type was unrelated to sex but significantly associated with location ($p = 0.001$). Dysphagia correlated significantly with malignant, inflammatory, and normal histology.

Conclusion: Malignant esophageal lesions, predominantly squamous cell carcinoma, mainly affect older adults and the distal esophagus in Yazd, Iran, whereas benign lesions are more common in younger patients. Despite dysphagia being the strongest predictor of malignancy, biopsy confirmation is still required.

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Introduction

Esophageal cancer is a highly lethal malignancy with poor overall survival, even with advances in diagnosis and treatment. It represents one of the most aggressive cancers of the gastrointestinal tract [1]. In the United States, esophageal cancer is the fifth most common gastrointestinal malignancy, with approximately 16,940 new cases annually, and it ranks as the sixth most common cancer worldwide [2]. Despite its relatively lower incidence compared to other gastrointestinal cancers, its high mortality underscores its significant clinical and public health burden [3].

Histopathology

The vast majority of esophageal cancers are classified into two main histological types: squamous cell carcinoma (SCC) and adenocarcinoma. Over the past three decades, the incidence of SCC has steadily declined to less than 30% in the United States, while the incidence of adenocarcinoma has risen to more than 60% [4]. Adenocarcinoma predominantly arises in the distal esophagus and the gastroesophageal junction largely driven by the increasing prevalence of Barrett's esophagus [5].

Etiology and risk factors

The etiology of esophageal cancer varies by histologic subtype and geographic region [5]. In the United States, nearly 90% of esophageal SCC cases are attributed to tobacco use, alcohol consumption, and diets low in fruits and vegetables [1]. In developing countries, additional risk factors include poor nutritional status, consumption of very hot beverages, and limited intake of fresh fruits and vegetables [6]. Human papillomavirus infection has been associated with SCC of the upper esophagus. Several pre-existing anatomical and genetic conditions increase the risk of SCC, including achalasia, caustic strictures, prior gastrectomy, atrophic gastritis, and synchronous or metachronous SCCs of the upper aerodigestive tract. Rare inherited syndromes such as tylosis (Howell–Evans syndrome), Bloom syndrome, and Fanconi anemia are also strongly associated with an increased risk of esophageal SCC [7]. Oral bisphosphonates have been linked to both SCC and adenocarcinoma of the esophagus.

In contrast, most esophageal adenocarcinomas in Western countries arise from Barrett's esophagus, with approximately 80% of cases associated with smoking, obesity, gastroesophageal reflux disease (GERD), and diets low in fruits and vegetables. Alcohol consumption does not appear to be a significant risk factor for adenocarcinoma [8]. Protective associations have been reported for diets rich in fruits, vegetables, antioxidants, folate, and vitamin C, as well as proton pump inhibitors and nonsteroidal anti-inflammatory drugs; however, none have been definitively proven to prevent progression to malignancy [8].

Epidemiology

Esophageal cancer demonstrates marked geographic variation. A high-risk region, known as the "esophageal cancer belt," extends from northern Iran through central Asia to northern China, where SCC accounts for approximately 90% of cases and esophageal

cancer ranks as the fourth most common malignancy. In contrast, the United States is considered a low-risk region, characterized by a rising incidence of adenocarcinoma related to increasing obesity and GERD, and a declining incidence of SCC due to reduced tobacco use [8]. Adenocarcinoma predominantly affects White males, whereas SCC is more common among black and Asian populations [9]. In Iran, a 2018 systematic review including 22 studies from different regions reported age-standardized incidence rates of esophageal cancer ranging from 22.93 to 25.05 per 100,000 in men, highlighting the continued importance of this disease within the country. Esophageal squamous cell carcinoma typically arises from dysplastic squamous epithelium and often presents as small polypoid lesions, plaques, or ulcerative tumors in the mid-esophagus [10]. Lugol's iodine staining may facilitate early detection by distinguishing normal glycogen-containing epithelium from neoplastic tissue. Advanced SCC lesions are frequently circumferential and ulcerative, with submucosal extension, longitudinal spread, and lymphatic metastasis to regional lymph nodes and distant organs, including the liver, lungs, and bone marrow [11]. Approximately 60% of distal esophageal and gastroesophageal junction adenocarcinomas arise from Barrett's esophagus [5]. Surveillance with upper endoscopy and biopsy is standard practice, as cancer risk increases significantly in the presence of dysplasia [12]. High-grade dysplasia requires aggressive management due to its strong association with malignant transformation. Molecular markers such as TP53 mutations and overexpression of human epidermal growth factor receptor 2 (HER2) (more common in adenocarcinoma than SCC) are associated with tumor invasion, lymph node metastasis, and poorer survival, and HER2 testing is recommended in all metastatic adenocarcinomas [13].

Clinical presentation and evaluation

Progressive dysphagia to solid foods is the most common presenting symptom of both SCC and adenocarcinoma, often indicating advanced disease. Dysphagia to liquids, weight loss, cachexia, chest discomfort, gastrointestinal bleeding, and anemia may occur as the disease progresses. Tracheobronchial invasion can result in cough, aspiration pneumonia, or vocal cord paralysis. Diagnostic evaluation includes a careful physical examination with attention to the supraclavicular and axillary lymph nodes [14]. Upper endoscopy with multiple biopsies remains the gold standard for diagnosis. Imaging studies, such as chest and abdominal computed tomography (CT), are used to assess tumor extent and distant metastases, while endoscopic ultrasound (EUS) provides superior accuracy for local staging and lymph node evaluation. Positron emission tomography combined with CT (PET/CT) plays a critical role in detecting occult metastatic disease and guiding treatment decisions [15].

Benign esophageal lesions and esophagitis

Benign esophageal lesions are rare, with a prevalence of less than 0.5%, though they account for up to 20% of esophageal neoplasms identified at autopsy [16]. These lesions are often asymptomatic and include epithelial and subepithelial tumors such as squamous

papilloma, leiomyoma, hemangioma, granular cell tumors, and heterotopic gastric mucosa. Advances in endoscopic and radiologic techniques have improved their detection and characterization. Esophagitis refers to inflammation or injury of the esophageal mucosa and presents with symptoms such as chest pain, heartburn, dysphagia, and odynophagia. Common causes include GERD, infections, radiation, medication-induced injury, eosinophilic esophagitis, and pill esophagitis. Oral bisphosphonates, certain antibiotics, nonsteroidal anti-inflammatory drugs, and iron supplements are well-recognized causes of medication-related esophagitis [17].

Given the rising incidence of gastrointestinal malignancies associated with unhealthy lifestyle factors such as smoking, alcohol consumption, obesity, and fast-food diets (particularly in developing countries) and considering the geographic significance of Iran as part of a high-risk region for esophageal cancer, accurate local data on esophageal lesions are essential. However, comprehensive, up-to-date information on the spectrum of esophageal lesions in Iran remains limited. Therefore, this study was conducted to evaluate histopathological findings of biopsies from various esophageal lesions referred to the pathology department at Shahid Sadoughi Hospital in Yazd. These findings provide valuable epidemiological and pathological insights that may contribute to improved diagnosis, management, and preventive strategies for esophageal diseases in the region.

Materials and Methods

Study design

This study was designed as a retrospective, descriptive cross-sectional investigation. The study population comprised all patients with esophageal lesions who had their biopsy specimens submitted to the Department of Pathology at Shahid Sadoughi Hospital, Yazd, Iran, between 2016 and 2021. A census sampling method was employed, whereby all esophageal biopsy specimens registered during the specified six-year period were included. The inclusion criterion was the availability of esophageal biopsy specimens within the defined timeframe, while biopsy reports with incomplete documentation or insufficient clinical or pathological information were excluded. Pathology records were reviewed, and relevant data were extracted using a pre-designed checklist. Collected variables included patient age, sex, clinical presentation, anatomical location of esophageal involvement, and histopathological diagnosis based on biopsy findings.

Statistical analysis

All collected data were entered into the Statistical Package for the Social Sciences (SPSS) software, version 23 (IBM Corp., Armonk, NY, USA), and analyzed using descriptive statistical methods. Chi-square tests were used to compare categorical variables where applicable, and one-way analysis of variance (ANOVA) was used for continuous variables. The primary limitation of this study was incomplete documentation of patients' clinical histories in some pathology

records, limiting the availability of certain clinical details.

Results

A total of 420 esophageal biopsy specimens obtained from patients with esophageal lesions referred to the Pathology Department of Shahid Sadoughi Hospital, Yazd, were included in this study. Of the patients, 214 (51%) were male and 206 (49%) were female, indicating an approximately equal sex distribution. The mean age of the patients was 45.5 ± 25 years, with a range from 1 to 90 years. The highest proportion of patients (31%) was in the 61–80-year age group.

Evaluation of clinical presentations showed that dysphagia was the most common presenting symptom, reported in 51.9% of patients. Other symptoms were considerably less frequent and included dyspepsia (8.3%), epigastric pain (7.6%), vomiting (7.6%), and cough (7%).

Regarding lesion location, analysis demonstrated that the distal esophagus was the most frequently involved site, accounting for 75.2% of all lesions. In contrast, involvement of the lower esophageal sphincter was rare and observed in only 1.4% of cases, making it the least common site of involvement.

Histopathological evaluation revealed that 45.7% of esophageal lesions were malignant, 27.1% were diagnosed as esophagitis, 14.8% were benign, and 11.4% showed normal pathology. Among malignant lesions, SCC was the most prevalent subtype (33.3%), followed by adenocarcinoma (9.5%). Less common malignant diagnoses included malignant round cell tumors (1.4%), adenosquamous carcinoma (1%), and lymphoma (0.5%). Among benign lesions, squamous papilloma (5.7%) was the most frequent, followed by hemangioma (2.8%), leiomyoma (1.9%), fibrovascular polyp (1%), fibroma (1%), granular cell tumor (1.4%), duplicated cyst (0.5%), and glycogenic acanthosis (0.5%). Esophagitis was predominantly non-infectious (23.8%), while infectious esophagitis, including candidiasis and cytomegalovirus infection, accounted for 3.3% of cases. Gastric heterotopia was identified in 1% of specimens.

Analysis of pathological findings by age group demonstrated a statistically significant association between age and lesion type (Chi-square test, $p = 0.001$). Malignant lesions were most frequent in patients aged 61–80 years, followed by those aged 41–60 years. In contrast, benign lesions, esophagitis, and normal histopathological findings were more commonly observed in patients aged 20 years or younger. Gastric heterotopia was rare and observed mainly in younger and middle-aged patients.

Further analysis of mean age across pathological diagnoses using one-way ANOVA revealed a significant difference between groups ($p = 0.001$). Patients with malignant lesions had the highest mean age (56.71 ± 16.2 years). Lower mean ages were observed in patients with benign lesions (44.37 ± 27.7 years), esophagitis (37.14 ± 27.8 years), gastric heterotopia (31 ± 30 years), and normal pathology (26.29 ± 27 years). These findings indicate that the probability of malignant

esophageal lesions increases with advancing age. Evaluation of pathological findings by gender showed no statistically significant association between sex and lesion type (chi-square test, p = 0.382). Malignant lesions were slightly more common in females, whereas benign lesions and esophagitis were more frequently observed in males. Normal findings were marginally more common in females, and gastric heterotopia was equally distributed between the two sexes.

Analysis of lesion location according to pathological diagnosis demonstrated a statistically significant association (chi-square test, p = 0.001). The majority of malignant, benign, inflammatory, and normal lesions were located in the distal esophagus. Lesions involving the proximal esophagus, middle third, upper esophageal sphincter, lower esophageal sphincter, or the entire esophagus were considerably less common.

Finally, assessment of clinical manifestations in relation to pathological diagnosis showed a significant association between presenting symptoms and lesion type (chi-square test, p = 0.001). Dysphagia was the predominant symptom among patients with malignant lesions, esophagitis, and normal pathology. In contrast, patients with benign lesions exhibited a more heterogeneous range of symptoms, with no single clinical presentation predominating.

Table 1. Pathological diagnosis of esophageal biopsy specimens

Pathological diagnosis	Frequency (n)	Percentage
Normal	48	11.4
Benign lesions (total)	62	14.8
Hemangioma	12	2.8
Leiomyoma	8	1.9
Fibrovascular polyp	4	1.0
Fibroma	4	1.0
Duplicated cyst	2	0.5
Glycogenic acanthosis	2	0.5
Granular cell tumor	6	1.4
Squamous papilloma	24	5.7
Malignant lesions (total)	192	45.7
Squamous cell carcinoma	140	33.3
Adenocarcinoma	40	9.5
Malignant round cell tumor	6	1.4
Adenosquamous carcinoma	4	1.0
Lymphoma	2	0.5
Esophagitis (total)	114	27.1
Infectious esophagitis	14	3.3
Non-infectious esophagitis	100	23.8
Gastric heterotopia	4	1.0
Total	420	100

Table 2. Distribution of pathological findings by lesion location

Lesion Type	Proximal (%)	Middle third (%)	Distal (%)	Upper sphincter (%)	Lower sphincter (%)	Entire esophagus (%)	Total	P-value
Malignant	34 (17.7)	20 (10.4)	116 (60.4)	4 (2.1)	2 (1)	16 (8.3)	192	
Benign	4 (6.5)	2 (3.2)	50 (80.6)	4 (6.5)	2 (3.2)	0	62	
Normal	2 (4.2)	0	46 (95.8)	0	0	0	48	
Esophagitis	6 (5.3)	0	100 (87.7)	2 (1.8)	2 (1.8)	4 (3.5)	114	0.001
Gastric heterotopia	0	0	4 (100)	0	0	0	4	
Total	46	22	316	10	6	20	420	

Table 3. Distribution of pathological findings by clinical presentation

Lesion Type	Dysphagia (%)	Dyspepsia (%)	Odynophagia (%)	Vomiting (%)	Epigastric pain (%)	Other (%)	Total	P-value
Malignant	132 (68.8)	6 (3.1)	4 (2.1)	2 (1)	6 (3.1)	42 (21.9)	192	
Benign	18 (29)	10 (16.1)	2 (3.2)	0	12 (19.4)	20 (32.3)	62	
Normal	20 (41.7)	6 (12.5)	0	8 (16.7)	10 (20.8)	4 (8.3)	48	
Esophagitis	48 (42.1)	12 (10.5)	8 (7)	20 (17.3)	4 (3.5)	22 (19.3)	114	0.000
Gastric heterotopia	0	0	0	2 (50)	0	2 (50)	4	
Total	218 (51.9)	34 (8.3)	14 (3.3)	32 (7.6)	32 (7.6)	90 (21.4)	420	

Discussion

Esophageal cancer remains one of the most serious malignancies worldwide, often associated with rapid progression and poor prognosis. In Iran, it is reported as the second and third most common malignancy among men and women, respectively, accounting for approximately 5,800 deaths annually. Various regional studies have highlighted differences in the demographic and clinicopathological patterns of esophageal lesions, emphasizing the importance of local epidemiological data for early diagnosis and management [10].

In the present study, we analyzed 420 esophageal biopsy specimens from Shahid Sadoughi Hospital, Yazd, representing a referral population from central and southern Iran. The mean age of patients was 45.5 ± 25 years, with a broad range of 1 to 90 years. The majority of patients were in the 61–80-year age group (31%), highlighting the increased risk of esophageal lesions with advancing age. Histopathological analysis confirmed a significant correlation between age and lesion type, with malignant lesions most prevalent among older patients (mean age 56.7 ± 16.2 years) and benign lesions, esophagitis, gastric heterotopia, and normal pathology predominating in younger patients. These findings are consistent with previous reports from Iran and Africa, which demonstrate that the incidence of esophageal malignancy increases with age [18, 19].

Gender distribution in our study was nearly equal (51% male, 49% female), and no statistically significant association between sex and lesion type was observed. Malignant lesions were slightly more common in females, whereas benign lesions and esophagitis were more frequent in males. These findings align with reports by Pindiga et

al. and Akbari et al. [19, 20], which found a gender distribution approximately equal. However, some studies in Tehran, Golestan, and Tanzania report a male predominance, potentially linked to higher tobacco and alcohol consumption among men [15, 18].

Clinically, dysphagia was the most common presenting symptom (51.9%), particularly among patients with malignant lesions, esophagitis, and normal histopathology. Other symptoms, including dyspepsia (8.3%), vomiting (7.6%), epigastric pain (7.6%), and cough (7%), were less frequent. The predominance of dysphagia in malignant cases aligns with prior studies, including Schlansky et al., where progressive dysphagia and weight loss were hallmark symptoms of esophageal cancer. In contrast, benign lesions exhibited more heterogeneous clinical presentations, without a single dominant symptom, emphasizing the limited specificity of clinical features for differentiating lesion type [21].

Regarding lesion location, the distal esophagus was the most frequently involved site across all lesion types, accounting for 75.2% of cases and 60.4% of malignant lesions. Involvement of the lower esophageal sphincter was rare (1.4%). These findings are consistent with prior studies in Iran, and internationally [18, 21], though some reports from Tanzania and other African countries observed a higher prevalence of tumors in the middle third of the esophagus. Anatomical differences in lesion distribution may reflect local etiologic factors, including dietary habits, reflux disease, and tobacco use [15, 18, 19, 21].

Histopathologically, malignant lesions accounted for 45.7% of all esophageal biopsies, with SCC as the most prevalent subtype (33.3%), followed by adenocarcinoma (9.5%). Less common malignancies included malignant round cell tumors (1.4%), adenosquamous carcinoma (1%), and lymphoma (0.5%). The predominance of SCC mirrors global patterns outside the United States, where it accounts for approximately 90% of esophageal cancers, and is consistent with studies from various regions of Iran [11, 18, 22]. Risk factors for SCC include tobacco, alcohol, and achalasia. Adenocarcinoma, although less common in this cohort, tended to occur in older patients and often involved the distal esophagus, reflecting its association with GERD and Barrett's esophagus.

Benign lesions accounted for 14.8% of biopsies, with squamous papilloma being the most common (5.7%), followed by hemangioma, leiomyoma, fibrovascular polyps, fibroma, granular cell tumor, duplicated cysts, and glycogenic acanthosis. These lesions were predominantly located in the distal esophagus. Although generally clinically insignificant, recognition of benign esophageal lesions is important to avoid overtreatment and to distinguish them from premalignant or malignant processes. Terada et al. similarly reported a predominance of benign esophageal lesions in the distal esophagus, including papillomas, leiomyomas, and granular cell tumors [11].

Esophagitis was diagnosed in 27.1% of cases, with non-infectious reflux-related esophagitis accounting for 23.8% and infectious

etiologies, including candidiasis and cytomegalovirus, representing 3.3%. The distal predilection of esophagitis is consistent with reflux-mediated injury. Notably, esophagitis was more frequent in younger patients (< 20 years), reflecting the increasing prevalence of pediatric and young adult GERD, as reported in multiple studies. Gastric heterotopia was rare (1%) and primarily observed in younger and middle-aged patients.

Comparison with other studies highlights several important epidemiologic and clinicopathologic patterns. Terada et al. analyzed 910 esophageal biopsies, reporting 23.8% malignant lesions and 76.2% normal or benign findings, with SCC predominating among malignancies. Similarly, Pedram et al. in northwest Iran reported a mean patient age of 61 years with a slight female predominance in SCC [11, 18]. Internationally, McHembe et al. observed SCC as the predominant histological type in Tanzania, with a male-to-female ratio of 2.2: 1 and a mean age of 47 years [15]. The consistency of these findings across diverse populations underscores the global predominance of SCC in esophageal malignancies, particularly in high-risk geographic regions.

The high proportion of malignant lesions in our study likely reflects the referral nature of Shahid Sadoughi Hospital, which receives cases from southern and central Iran, including advanced or previously undiagnosed cancers. This referral bias may explain why 45.7% of lesions were malignant, compared to lower rates in population-based studies such as Terada et al., where only 23.8% were malignant [11].

Conclusion

This study provides a comprehensive analysis of the clinicopathological spectrum of esophageal lesions in Yazd, Iran. Malignant lesions were frequent, predominantly SCC, and primarily involved the distal esophagus in older adults. Benign lesions and esophagitis were more common in younger patients and also mostly distal. These results are consistent with regional and international studies, emphasizing the need for targeted screening and early diagnosis, particularly among high-risk populations, to improve prognosis and survival in esophageal cancer.

Ethical Considerations

This study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran (IR.SSU.MEDICINE.REC. 1400.424). All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee. Verbal informed consent was obtained from all patients during follow-up telephone interviews.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare that they have no competing interests.

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Authors' Contributions

M.V: contributed to the study conception and design, pathology review, data analysis and interpretation, manuscript drafting and critical revision, and overall supervision of the study.

M.M: contributed to data collection, clinical data interpretation, and assistance in manuscript drafting.
M.H: (Corresponding Author) contributed to the study conception and design, pathology review, data analysis and interpretation, manuscript drafting and critical revision, and overall supervision of the study.
All authors read and approved the final manuscript.

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