Obstructive Esophageal Cancers at Endoscopy Are Associated with Reduced Survival and Poor Outcome

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ABSTRACT **Background:** Esophageal cancer is comprised of adenocarcinoma and squamous cell carcinoma and is the sixth leading cause of cancer-related mortality worldwide. Upper endoscopy may reveal a partially or completely lumen-occluding mass at diagnosis, yet the prognostic significance of such a presentation is not clear.

Objectives: To investigate whether endoscopic obstructing lesions have a meaning regarding patient prognosis.

Methods: We reviewed upper gastrointestinal endoscopic studies performed over a 20-year period (2000–2020). We compared overall survival, disease stage, histologic criteria, and anatomic location of the lesions in esophagus lumen-obstructing and non-obstructing tumors. Differences between the two groups were statistically evaluated.

Results: Sixty-nine patients were diagnosed with histologically confirmed esophageal cancer. As assessed through endoscopy, 32/69 (46%) patients had obstructive and 37/69 (54%) had non-obstructive cancers. Median survival was significantly shorter in the lumen-obstructing lesions compared with the non-obstructing lesions (4 months vs. 14 months, $P = 0.001$). Female median survival displayed a trend toward shorter survival compared to males (3.5 months vs. 10 months, $P = 0.059$). There was no statistically significant difference in the percentages of advanced, stage IV disease in the obstructive group and the non-obstructive group (11/32 [34.3%] and 14/37 [37.8%], respectively $P = 0.80$).

Conclusions: Obstructive esophageal cancers predict shorter median overall survival compared with non-obstructive cancers, without any correlation between obstruction of the lesion and tumor metastatic stage.

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KEY WORDS: esophageal cancer, survival, luminal obstruction, endoscopy

Esophageal cancer (EC) is a devastating disease. It is the eighth most common cancer worldwide and the sixth leading cause of cancer-related mortality, with a dismal 18% overall 5-year survival rate [1-3]. Esophageal cancer can develop from squamous epithelium, commonly found in the middle-lower esophagus, giving rise to squamous cell carcinoma (SCC), or from glandular epithelium, commonly found in the distal esophagus, giving rise to esophageal adenocarcinoma (EAC). The cervical esophagus is an uncommon site of the disease [2]. SCC risk factors include smoking, red-meat consumption, low intake of fruits and vegetables, and low socioeconomic status with poor oral hygiene. EAC arises in the context of Barret's esophagus, with risk factors that include male gender, obesity, cigarette smoking, and long-standing gastroesophageal reflux. Esophageal cancer prognosis greatly depends on the extent of local invasion as well as lymphatic and hematogenous spread to local and distant structures [2-4]. Unfortunately, esophageal cancer is often asymptomatic in its early stages, while advanced disease presents with dysphagia to solids first, followed by liquids as the mass enlarges, unintentional weight loss, odynophagia, new-onset dyspepsia, heartburn, chest pain, or signs of blood loss [5]. Diagnosis is made by upper endoscopy with mucosal biopsy for histologic confirmation. Staging relies on imaging, mainly computer tomography (CT) for distant metastases, and endoscopic ultrasonography for local lymphovascular and intramural depth of invasion [6-9]. Global trends in esophageal cancer subtypes have shown a change in the ratio of SCC to EAC, with a decrease from 4.7:1 in 1975 to 0.43:1 in 1998 in Western countries, probably due to the increased burden of obesity and its consequences, expressed by reflux esophagitis [10,11]. Esophageal cancer screening programs in Asia, along with surveillance protocols for Barrett's esophagus, have led to the diagnosis of earlier stages where T1 tumors that are limited to the submucosa are still amenable for endoscopic resection. Esophagectomy is advised for lesions invading the muscularis propria (T2 and above) or superficial lesions with high risk of lymph node metastases [12-15]. Lumen obstructing lesions are common at index endoscopy and further challenge the therapeutic possibilities. We investigated whether endoscopic obstructing lesions have a meaning regarding patient prognosis.

PATIENTS AND METHODS

This retrospective cohort study reviewed upper gastrointestinal endoscopic examinations performed over a 20-year period (2000–2020) in the gastroenterology and liver disease department at the Hillel Yaffe Medical Center, a university-affiliated

hospital in Israel, and searched for reports of patients identified with a diagnosis of esophageal cancer. Patients were excluded if they had an additional advanced malignancy or if a full dataset was not obtained. Patient characteristics (age, sex, ethnic origin, and date of diagnostic procedure) and endoscopic details that included morphologic description of the lesion (obstructive or not), location within the esophagus and gastric cardia involvement were recorded. Histologic characteristics included type of cancer (EAC vs. SCC), histological grade, and degree of differentiation. We studied the prognosis and mortality difference between obstructing lesions (described as lumen blocking or obstructive) and non-obstructing lesions (described as ulcerative or infiltrative by the performing endoscopist). Ethnic origin, patient sex, anatomic location, and histologic type of the tumor were evaluated as prognostic factors. The local institutional Helsinki ethics committee approved the study.

STATISTICAL ANALYSIS

Descriptive statistics in terms of mean values, standard deviation, percentages, and ranges were performed for all parameters in the study. The differences between the two groups (obstructive vs. non-obstructive) for the quantitative parameters were demonstrated by *t*-test.

RESULTS

The study comprised 85 patients suspected for esophageal malignancy in upper endoscopies performed at our institution between 2000 and 2020. Twelve (14.1%) were excluded since histologic analysis found inflammatory features only. An additional four (4.7%) cases were excluded due to pre-cancerous findings (atypia or dysplasia) on histology. Sixty-nine patients found to have malignant esophageal disease were included in the final analysis. Demographic and lesion characteristics are shown in Table 1. Among the cases included in the final analysis, 41 were males (59%) and 28 were female (41%). The average age at the index endoscopy, in which the malignancy was found, was 72.1 years. Death occurred on average 8 months after the index endoscopy. Thirty-eight patients (55%) presented with adenocarcinoma (EAC) and 29 (42%) with squamous cell carcinoma (SCC). In total, 75% of the tumors were located in the lower esophagus, while the rest were distributed in the mid and upper parts of the esophagus.

Of the 69 patients included in the study, 32 (46%) had obstructing lesions and 37 (54%) had non-obstructing lesions. Patient distribution according to obstructing and non-obstructing tumors are shown in Table 2. Among the obstructive tumors, the leading indication for upper endoscopy was dysphagia, followed by weight loss, abdominal pain, and pathologic imaging study. Eight (25%) of the obstructing tumors prevented endoscope passage and were defined as total lumen-blocking lesions.

Table 1. Main demographics and lesion characteristics found at index endoscopy

Characteristic	Value, n (%)
Sex	
Male	41 (59%)
Female	28 (41%)
Age at test in years, mean ± (range)	72.1 ± 11.3 (48–92)
Average survival, months (range) Total: 0–72	8.0 (2.5–16.5)
Ethnic origin	
Russia and the Former Soviet Union	24 (35%)
Israel	25 (36%)
Romania	6 (8%)
Other	14 (21%)
Histologic type	
EAC	38 (55%)
SCC	29 (42%)
HGD BE	1
CA (unknown histology)	1
Location	
Lower esophagus	52 (75%)
Middle esophagus	12 (17%)
Upper esophagus	5 (7%)
Gastric cardia involvement	
No	39 (56.5%)
Yes	30 (43.5%)
Morphology	
Obstructing	32 (46%)
Non-obstructing	37 (54%)

SD = standard deviation

OVERALL SURVIVAL

Obstructing esophageal cancers were significantly associated with decreased median survival compared with non-obstructing esophageal cancers (4 months vs. 14 months, P = 0.001). The survival model curve is shown in Figure 1. The average tumor survival for total-lumen obstructing lesions was 6.5 months while the average survival for the partially lumen obstructing lesion was 14.1 months.

Survival: By sex

Among all esophageal tumors, obstructing and non-obstructing, female median survival displayed a trend toward shorter overall survival than males (3.5 months vs. 10 months $P = 0.059$).

Table 2. Main characteristics of obstructing and non-obstructing esophageal tumors

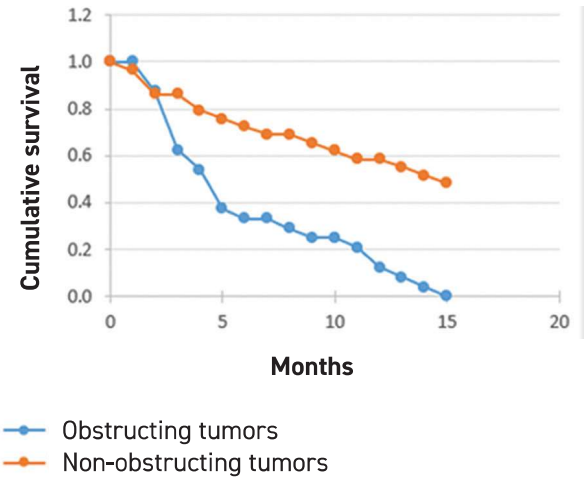
Characteristics	Obstructive cancer (n=32)	Non-obstructive (n=37)	*P*-Value
Age (year)	73.4	70.9	**NS**
Sex			
Male	53.1%	64.8%	
Female	46.8%	35.1%	
Histological type			
SCC	46.8%	37.8%	
EAC	46.8%	62.1%	
N/A	3.1%	–	
Esophageal location			
Upper	6.2%	8.1%	
Middle	21.8%	13.5%	
Lower	71.8%	78.3%	
Histologic grade			
Well-differentiated	–	1 (2.70%)	
Mod-well differentiated	2 (6.25%)	3 (8.10%)	
Moderately differentiated	5 (15.62%)	8 (21.62%)	
Poorly-mod differentiated	6 (18.75%)	8 (21.62%)	
Poorly differentiated	11 (34.37%)	8 (21.62%)	
Unknown differentiation	7 (21.87%)	7 (18.91%)	
High grade dysplasia BE	1 (3.12%)	–	
Intramucosal carcinoma	–	1 (2.70%)	
Foci suspicious of SCC	–	1 (2.70%)	
Stage IV disease: metastases by computed tomography scan	(34.3%) 11	(37.8%) 14	0.80
Median survival, months	4	14	0.001

Survival: By staging

There was no statistically significant difference in the percentages of stage IV disease in the obstructive group and the non-obstructive group (11/32 [34.3%] and 14/37 [37.8%], respectively P = 0.80). Lower stage disease (≤ stage IIa) was more common in the obstructive cancer group (15.6%) compared with the non-obstructing group (5.4%).

Analysis showed that median survival was shorter for SCC compared with EAC (4 months and 8.5 months, respectively), although these differences did not reach statistical significance

Figure 1. Survival model for obstructive and non-obstructive esophageal tumors



($P = 0.44$). Gastric cardia involvement did not show a difference in survival compared to other esophageal locations.

DISCUSSION

Esophageal cancer is a malignant disease with a diversity in tumor presentation, location, histology, and prognosis. Esophageal cancers are less studied than the more common gastric and colonic malignancies. It appears that although the histologic type of esophageal cancer has shifted from SCC to EAC, the overall survival rate has not changed significantly in the past few decades [16]. Although it seems reasonable that obstructing lesions are more deadly, tumor staging according to the TNM classification does not take into consideration intraluminal expansion, but it does consider the depth of the tumor (T stage) [8,13-14]. We searched for reports of tumors that were described as lumen obstructive in contrast to infiltrating or ulcerative without an obstruction of the esophageal lumen.

Patients with obstructive tumors had a significantly shorter survival time compared with those with tumors described as non-obstructive (4 months vs. 14 months, $P = 0.001$), although higher stages of cancers were seen with the non-obstructing (infiltrating, ulcerative) cancer group.

We think that the obstructive lesions were at a lower TNM stage because their phenotype was a one of expansion into the lumen, while not necessarily involving the invasion of esophageal wall and its subsequent local lymph node metastases. To some extent, even the wall-infiltrating tumors can cause dysphagia because of local edema and inflammation, which impair esophageal function.

Our findings may be due to later diagnosis, increased chances of aspiration pneumonia, or earlier development of

malnutrition and sarcopenia in cases of obstructing tumors [17]. As a group, obstructing tumors showed more advanced histology than non-obstructing tumors. While most of the obstructing tumors were poorly differentiated or with unknown differentiation (34.1% and 21.8%, respectively), non-obstructing tumors showed fewer poorly differentiated tumors (21.6%) and more moderately and well differentiated tumors [Table 2]. The average age at diagnosis was higher in obstructive cancers compared to non-obstructing cancers (73.4 and 70.9, respectively). These findings could support the idea that obstructing cancers are diagnosed later, while already more advanced. As the field of endoscopic treatment of esophageal tumor progresses, we believe that these findings can influence therapeutic options [12-15].

This study supports the Western world trend that has shown increased incidence of esophageal adenocarcinoma rather than squamous cell carcinoma [1,5,11]. This trend is attributed to the increased obesity pandemic associated with the increased incidence of reflux esophagitis and subsequent neoplastic progression. Female sex has displayed a trend toward shorter survival compared to males ($P = 0.059$); however, esophageal cancer was more common in males (59%).

Although it is assumed that polypoid or exophytic tumors have a better prognosis than ulcerating or infiltrating lesions [18], a recent investigation showed that obstructive colon cancers found at endoscopy are associated with a more advanced stage and worse outcome [19], as we found with our study. This finding could indicate a similar case with esophageal tumors.

Limitations of this study include its relatively small sample size and its lack of full tumor staging analysis due to lack of imaging studies, which in some cases could not be retrieved. Esophageal tumors tend to be diagnosed in older patients, most commonly in populations with dementia who are deemed unfit for surgical or chemotherapeutic treatment. Full TNM staging with endoscopic ultrasound (EUS) is seldom performed. In addition, the practice of EUS staging of gastrointestinal malignancies was not performed routinely at the years these tumors were diagnosed. Imaging studies can be used to define distant metastatic disease. Among the 69 patients in study, imaging studies with CT or 18F-fluorodeoxyglucose positron-emission tomography/computed tomography scans were found for 27 patients (39.1%). EUS staging was performed on 13 patients (18.8%), and a few others had intraoperative staging. For 14 patients (20.2%), no staging data could be found. This lack of data, however, still enabled us to make a crude division of the tumors into low stage and advanced/metastatic stage disease.

Another limitation of the study is the fact that the degree of obstruction could not be determined mathematically but rather only through the description of the endoscopy-performing physician.

CONCLUSIONS

Esophageal tumors are associated with significantly shorter survival when presenting as lumen obstructing lesions with no relation to tumor stage or metastasis compared to non-obstructive esophageal tumors.

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References

1. Malhotra G, Yanala U, Ravipati A, Follet M, Vijayakumar M, Chandrakanth A. Global trends in esophageal cancer. *J Surg Oncol* 2017; 115: 564-79.
2. Enzinger P, Mayer R. Esophageal cancer. *N Engl J Med* 2003; 349: 2241-52.
3. Zhang Y. Epidemiology of esophageal cancer. *World J Gastroenterol* 2013; 19(34): 5598-606.
4. Domper Arnai M, Ferrandez Arenas A, Lanas Arbeloa A. *World J Gastroenterol* 2015; 21 (26): 7933-43.
5. Gibbs J, Rajput A, Chadha K, et al. The changing profile of esophageal cancer presentation and its implication for diagnosis. *J Natl Med Assoc* 2007; 99: 620-6.
6. Short M, Burgers K and Fry V. Esophageal cancer. *Am Fam Physician* 2017; 95 (1): 22-8.
7. Lordick F, Mariette C, Haustermans K, Obermannova R, Arnold D. Oesophageal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016; 27 (Suppl. 5): 50-7.
8. Rice T, Ishwaran H, Blackstone E, Hofstetter W, Kelsen D, Apperson-Hansen C. Recommendations for clinical staging (cTNM) of cancer of the esophagus and esophagogastric junction for the 8th edition of AJCC/UICC staging manuals. *Dis Esophagus* 2016; 29: 913-19.
9. Quint LE, Hepburn L, Franois I, Whyte R, Orringer M. Incidence and distribution of distant metastases from newly diagnosed esophageal carcinoma. *Cancer* 1995; 76 (7): 1120-5.
10. Hongo M, Nagasaki Y, Shoji T. Epidemiology of esophageal cancer: orient to occident. Effects of chronology, geography and ethnicity. *J Gastroenterol Hepatol* 2009; 24: 729-735.
11. Thrift, A. The epidemic of oesophageal carcinoma: Where are we now? *Cancer Epidemiol* 2016; 41: 88-95.
12. Barret, M, Prat F. Diagnosis and treatment of superficial esophageal cancer. *Ann Gastroenterol* 2018; 31(3): 256-65.
13. Naveed M, Kubiliun N. Endoscopic treatment of early-stage esophageal cancer. *Curr Oncol Rep* 2018; 20: 1-10.
14. Manner H, Pech O, Heldmann Y, et al. Efficacy, safety and long-term results of endoscopic treatment for early stage adenocarcinoma of the esophagus with low-risk sm1 invasion. *Clin Gastroenterol Hepatol* 2013; 11: 630-5.
15. Fujita H, Sueyoshi S, Yamana H, et al. Optimum treatment strategy for superficial esophageal cancer: endoscopic mucosal resection versus radical esophagectomy. *World J. Surg* 2001; 25: 424-31.
16. 16: Njei B. McCarty T and Birk J. Trends in esophageal cancer survival in united states adults from 1973 to 2009: a SEER database analysis. . *J Gastroenterol Hepatol* 2016; 31: 1141-6.
17. Ida S, Watanabe M, Yoshida N, et al. Sarcopenia is a predictor of postoperative respiratory complications in patients with esophageal cancer. *Ann Surg Oncol* 2015; 22: 4432-7.
18. Bresalier RS. Sleisenger and Fordtran's Gastrointestinal and Liver Disease *Colorectal Cancer* 2020; 127: 2108-2152.
19. Abu Baker F, Taher R, Ganayem M, Mari A, Oren G, Kopelman Y. Obstructive colon cancers at endoscopy are associated with advanced tumor stage and poor patient outcome. A retrospective study on 398 patients. *Eur J Gastroenterol Hepatol2021*; 33 (1): 50-3.