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ORIGINAL ARTICLE

# ESOPHAGEAL TUMOR LENGTH – AN UNDERESTIMATED PREDICTOR OF SURVIVAL AFTER ESOPHAGEAL CANCER RESECTION

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***Abstract. Introduction.*** *Esophageal cancer is one of the most aggressive visceral tumors with increasing frequency and poor prognosis. Differences in survival between patients in the same clinical tumor stage necessitate searching for additional prognostic markers to help identify patients at high risk of recurrence, metastasis or death. The aim of the study was to assess prognostic significance of tumor length on survival after esophageal cancer resection in patients operated at a center for esophageal surgery.* ***Materials and methods.*** *This was a prospective cohort study including 117 patients who had undergone surgical resection with curative intent for esophageal cancer. The study was conducted at the First Surgical Clinic of UMHATEM "N. I. Pirogov", Sofia, Bulgaria. The inclusion period was between 1st January 2013 and 31st December 2015 and the patients were followed – up until 10 April 2022. The patients were divided into two groups according to the tumor length – under 3 cm (group 1) and over 3 cm (group 2). The prognostic impact of tumor length on survival was analyzed with Cox regression analysis. Overall survival was presented by the Kaplan-Meier method with log-rank tests.* ***Results.*** *The 5-year survival rate was 11.1%. Median survival rate was 26.0 months (95% CI 18.3-33.7 months) for the patients in the first group and 13.0 months (95% CI 10.3-15.7 months) for the second group patients. Tumor length over 3 cm was a negative prognostic factor (HR 2.36 95% CI 1.06-5.25; p = 0,03).* ***Conclusion.*** *Length of esophageal cancer is a powerful independent predictor of survival in addition to the TNM stage.*

***Key words:*** *esophageal carcinoma, tumor length, prognostic factor, survival*

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## INTRODUCTION

Epidemiological data on esophageal carcinoma worldwide have shown an increasing incidence over the past four decades, particularly for adenocarcinoma [1, 2].

According to the Bulgarian National Cancer Registry, the morbidity in Bulgarian patients during this period tripled in men and doubled in women [3]. At the same time, the five-year relative survival rate is low and, even with aggressive multimodal treatment, does not exceed 46% [4]. The five-year relative survival

reported for the period 2000–2007 is 5.8%, which is 6.4% lower than the European average (12-13%) [5].

Current treatment and prognosis of esophageal carcinoma are related to the stage at which the disease is diagnosed and treated. TNM system with its current 8th revision is the main classification system for staging of esophageal carcinoma [6]. Patients in the same esophageal carcinoma stage have been found to have different survival rates [7] which necessitates the search for additional prognostic markers to help identify patients at high risk of developing recurrence, metastasis, or death.

Tumor size, which is defined as maximum length of the tumor, is widely used in the staging of lung cancer and breast cancer [8, 9]. This parameter is easily measurable in esophageal carcinoma. Studies have shown that the tumor length is an independent prognostic factor and a longer tumor is associated with a worse survival [10, 11, 12, 13].

The aim of the study was to evaluate the prognostic value of the tumor length in terms of survival in patients operated for esophageal carcinoma at a high volume center for esophageal surgery.

## MATERIALS AND METHODS

### *Study design and population*

This was a prospective cohort study among patients who had undergone surgical resection for cancer of esophagus and gastro-esophageal junction with curative intent. The study was conducted at the First Surgical Clinic of UMHATEM “N. I. Pirogov”, Sofia, Bulgaria. The inclusion period was between 1st January 2013 and 31st December 2015 and the patients were followed – up until 10 April 2022.

In total, 129 patients were eligible to participate in the study, of which 12 were excluded due to the detection of advanced or metastatic carcinoma. The remaining 117 patients underwent curative esophageal resection and were included in the study. The type of esophageal resection was chosen according to the tumor localization and was one of the following: Ivor – Lewis, Mc Keown, Sweet, Orringer or transabdominal esophageal resection.

The patients were followed – up until death or the end of follow – up period (10 April 2022), whichever came first.

The patients were divided into two groups according to the length of the tumor – up to 3 cm and over 3 cm.

## ETHICS

Ethical permission was approved by the regional ethics committee.

### *Statistical analysis*

The effect of tumor length on survival was analyzed with Cox regression analysis. Median survival was analyzed by log rank test and presented with Kaplan-Meier curves.

Data were processed with IBM SPSS Statistics 28.0.0.0 statistical package utilizing a P value of < 0.05 for statistical significance.

## RESULTS

The main demographic, clinical and histo-pathological features of the patients are presented in Table 1.

**Table 1.** Baseline characteristics of patients operated for cancer of esophagus and gastro-esophageal junction at the First Surgical Clinic of UMHATEM “N. I. Pirogov”, Sofia, Bulgaria between 1st January 2013 and 31st December 2015

| | | |
|---|---|---|
| Gender | Male / Female | 97 (82.9%) / 20 (17.1%) |
| Age | Median<br>< 60 years<br>Male<br>Female<br>> 60 years<br>Male<br>Female | 59.0<br>66<br>55<br>11<br>51<br>42<br>9 |
| location | Upper third<br>Middle third<br>Lower third and cardia | 5(4.3%)<br>24 (20.5%)<br>88 (75.2%) |
| Pathological t stage | T1<br>T2<br>T3<br>T4<br>Tx or missing | 1 (0.9%)<br>23 (19.7%)<br>81 (69.2%)<br>8 (6.8 %)<br>4 (3.4 %) |
| Length | < 3 cm<br>> 3 см<br>Missing | 13 (11.1%)<br>92 (78.6%)<br>12 (10.3%) |
| Pathological N stage | N0<br>N1<br>N2<br>N3<br>Nx | 30 (25.6%)<br>28 (23.9%)<br>25 (21.4)<br>19 (16.2%)<br>12 (10.3%) |
| M stage | M0<br>M1 | 110 (94%)<br>7 (6%) |
| Radical resection | R0<br>R1<br>R2<br>Missing | 101 (86.3%)<br>12 (10.3%)<br>1 (0.8%)<br>3 (2.6%) |
| Histological subtype | Adenocarcinoma<br>Squamous cell carcinoma<br>Other | 72 (61.5%)<br>41 (35.1%)<br>4 (3.4%) |
| Grade of differentiation | Well differentiated (g1)<br>Moderately differentiated (g2)<br>Poorly differentiated (g3)<br>Missing | 14 (12%)<br>52 (44.4%)<br>47 (40.2%)<br>4 (4.4%) |

The majority of the patients were men, with ratio of 4:1. In terms of age, it is noticeable that almost half of the patients were of working age. The predominant histological subtype was adenocarcinoma.

Overall three year survival was 12.8% and five-year survival was 11.1%.

In the group with tumors under 3 cm, median survival was 26.0 months (95% CI 18.3-33.7 months). Patients with tumors over 3 cm had median survival 13.0 months (95% CI 10.3-15.7 months), p = 0.05 Table 2. Median survival is presented in Figure 1.

**Table 2.** Median survival according to the tumor length for patients, operated at UMHATEM "N. I. Pirogov", Sofia, Bulgaria

| Length of tumor | Survival in months | | |
|---|---|---|---|
| | Median | Lower Bound | Upper Bound |
| < 3 cm | 42.9 | 20.3 | 65.5 |
| > 3 cm | 22.1 | 15.7 | 28.6 |

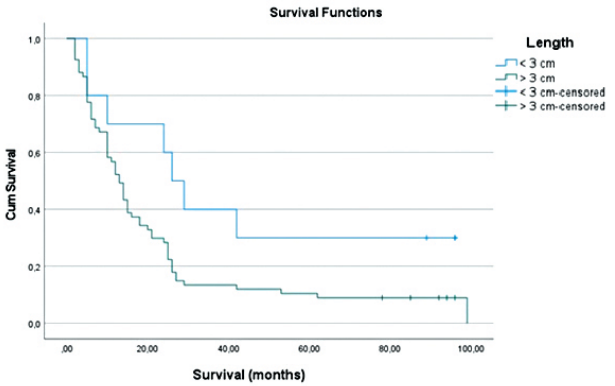



**Fig. 1.** Kaplan–Meier curve of overall survival according to the length of the tumor for patients operated at UMHATEM "N. I. Pirogov"

Data from regression analysis showed that tumor length greater than 3 cm was a negative prognostic factor (HR 2.36 95% CI 1.06-5.25, p = 0.03).

## DISCUSSION

In our study, the patients were divided into two groups according to the length of the tumor – up to 3 cm and over 3 cm. The results we obtained are statistically significant and show a decreasing survival with increasing tumor size. The survival rate for tumors over 3 cm is twice lower than that for tumors under 3 cm.

The negative predictive value of a tumor length of more than 3 cm was also proven by the performed regression analysis. In our analysis, tumor length was found to be a powerful prognostic criterion, more sensitive than tumor T stage.

This conclusion is confirmed by the publications of other authors. Song et al. found that in patients with esophageal carcinoma at the same stage, tumor length was an independent prognostic factor [14]. In their meta-analysis, Wang et al. reviewed 41 studies with a total of 28,973 patients and found that the critical value of tumor length varied in the different studies between 1.5 cm and 6 cm [15]. Eighteen studies examined the relationship between tumor length and prognosis in tumors ≥ 5 cm, while in the remaining twenty – three studies, tumors were less than 5 cm. The authors believe that tumor length is important in the prognosis of squamous-cell carcinoma and early adenocarcinoma [15, 16].

In addition to its prognostic value, this indicator has also an impact on the choice of surgical resection. For tumors longer than 5 cm, in order to achieve radical resection, a McKeown esophagectomy may be necessary, even for tumors in the distal part of the esophagus.

An interesting fact is that tumor length was a factor used to define T stage in the older versions of the AJCC TNM classification (3rd revision of 1982). Although in 1987 this indicator was replaced by the depth of tumor infiltration in the esophageal wall, tumor length is still considered by many authors as an indicator related to the extent of tumor invasion.

## CONCLUSION

Tumor length in esophageal carcinoma is a powerful independent predictor of survival in addition to TNM stage.

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## 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 May;71(3):209-249. doi: 10.3322/caac.21660. Epub 2021 Feb 4.
2. Castro C, Bosetti C, Malvezzi M, et al. Patterns and trends in esophageal cancer mortality and incidence in Europe (1980-2011) and predictions to 2015. Ann Oncol. 2014 Jan;25(1):283-90. doi: 10.1093/annonc/mdt486.

3. Valerianova Z, Atanasov T. (eds.) Cancer Incidence in Bulgaria, 2016 & 2017. University Specialized Hospital for Active Treatment in Oncology. Bulgarian National Cancer Registry. Paradigma Publ. Sofia, 2020.
4. Shapiro J, van Lanschot JJB, Hulshof MCCM, et al; CROSS study group. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015 Sep;16(9):1090-1098. doi: 10.1016/S1470-2045(15)00040-6. Epub 2015 Aug 5.
5. Anderson LA, Tavilla A, Brenner H, et al. Survival for oesophageal, stomach and small intestine cancers in Europe 1999-2007: Results from EUROCARE-5. Eur J Cancer 2015;51:2144-57.
6. MB Amin, SB Edge, FL Greene, et al. eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017.
7. Hsu PK, Chen HS, Liu CC, Wu SC. Application of the Eighth AJCC TNM Staging System in Patients With Esophageal Squamous Cell Carcinoma. Ann Thorac Surg. 2018 May;105(5):1516-1522. doi: 10.1016/j.athoracsur.2017.12.032. Epub 2018 Apr 5.
8. Nicholson AG, Chansky K, Crowley J, et al. Staging and Prognostic Factors Committee, Advisory Boards, and Participating Institutions; Staging and Prognostic Factors Committee Advisory Boards and Participating Institutions. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the Clinical and Pathologic Staging of Small Cell Lung Cancer in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016 Mar;11(3):300-11. doi: 10.1016/j.jtho.2015.10.008. Epub 2015 Dec 24.
9. Giuliano AE, Edge SB, Hortobagyi GN. Eighth Edition of the AJCC Cancer Staging Manual: Breast Cancer. Ann Surg Oncol. 2018 Jul;25(7):1783-1785. doi: 10.1245/s10434-018-6486-6. Epub 2018 Apr 18.
10. Zhang X, Wang Y, Jiang Y, et al. The prognostic impact of tumor length in esophageal cancer: Protocol for a systematic review and meta-analysis. Medicine (Baltimore). 2018 Oct;97(43):e12902. doi: 10.1097/MD.0000000000012902.
11. Zeybek A, Erdoğan A, Gülkesen KH, et al. Significance of tumor length as prognostic factor for esophageal cancer. Int Surg. 2013 Jul-Sep;98(3):234-40. doi: 10.9738/INTSURG-D-13-00075.1.
12. Yendamuri S, Swisher SG, Correa AM, et al. Esophageal tumor length is independently associated with long-term survival. Cancer. 2009 Feb 1;115(3):508-16. doi: 10.1002/cncr.24062. PMID: 19117343.
13. Yang J, Liu Y, Li B, et al. Prognostic significance of tumor length in patients with esophageal cancer undergoing radical resection: A PRISMA-compliant meta-analysis. Medicine (Baltimore). 2019 Apr;98(14):e15029. doi: 10.1097/MD.0000000000015029.
14. Song Z, Wang J, Lin B, Zhang Y. Analysis of the tumor length and other prognosis factors in pT1-2 node-negative esophageal squamous cell carcinoma in a Chinese population. World J Surg Oncol. 2012 Dec 18;10:273. doi: 10.1186/1477-7819-10-273.
15. Wang ZY, Jiang YZ, Xiao W, et al. Prognostic impact of tumor length in esophageal Cancer: a systematic review and Meta-analysis. BMC Cancer. 2021 Sep 3;21(1):988. doi: 10.1186/s12885-021-08728-1.
16. Yordanov YP, Shef A. Hypertrophic Scars and Keloids – Contemporary Concepts and Treatment Options. Acta Medica Bulgarica 2014; 41(1): 57-74.