American Journal of Aging Science and Research

Bollschweiler et al., Am J Aging Sci Res. 2024;4(1):22-27.

Commentary

Impact of sex on premature mortality for elderly patients with early adenocarcinoma of the esophagus or stomach

Elfriede Bollschweiler[1,*], Arnulf H Hölscher[2]

[1]Medical Faculty, University of Cologne, Cologne, Germany

[2]Center for Esophageal Diseases, Elisabeth-Krankenhaus Essen, Germany

*Author for correspondence: Email: ebollsch@uni-koeln.de

Received date: July 31, 2024
Accepted date: August 28, 2024

Citation: Bollschweiler E, Hölscher AH. Impact of sex on premature mortality for elderly patients with early adenocarcinoma of the esophagus or stomach. Am J Aging Sci Res. 2024;4(1):22-27.

Abstract

Background: In a recent study, it was shown that patients with pT1 adenocarcinoma of the esophagus or stomach have a shorter survival time compared to an age- and gender-matched group from the normal population despite curative therapy. The reasons for the loss of expected life years (YLL) can only be discussed. The aim of the present evaluation is to analyze the influence of the patients' gender on the results.

Methods: The data from the aforementioned study was used for this purpose.

Results: Of the 214 patients, 112 had pT1 carcinoma of the esophagus and 102 had gastric carcinoma. The male (m):female (f) ratio was significantly ($p<0.0001$) different between esophageal (m:f=10:1) and gastric (m:f=3:2) tumors. Women (n=48) were significantly older at the time of treatment with a median age of 69.0 (min:42.0, max:84.7) years than male patients (n=166) with a median age of 62.2 (min:18.5, max: 80.7) years ($p<0.001$). Tumor characteristics, postoperative course, 5-year survival rate and the rate of YLL were not significantly different between men and women. The analysis of the group of older patients (60 years or older) shows a relevant lower loss of expected life years for women compared to male patients.

Conclusion: Women are significantly less likely to develop adenocarcinoma of the esophagus or stomach compared to men. Although the average age of onset is significantly higher for women than for men, the prognosis is the same for both groups. In contrast, women in the group of older patients lose no or only a small number of expected years of life (EYL).

Keywords: Esophageal neoplasm, Stomach neoplasm, Esophagus mucosa, Gastric mucosa, Adenocarcinoma, Lymph node metastasis, Cancer survivors, Years of life lost

Abbreviations: AC: Adenocarcinoma; CI: Confidence Interval; EAC: Adenocarcinoma of the Esophagus; EYL: Expected Years of Life; F: Female; GAC: Adenocarcinoma of the Stomach; GI: Gastrointestinal; H.R.: Hazard-Ratio; LNM: Lymph Node Metastasis; M0: No distant Metastasis; M: Male; Max: Maximum; Min: Minimum; N: Number; N.S: No Significance; p: Level of Significance; pN0: No Tumor Infiltration in Regional lymph Nodes after Lymphadenectomy; pN+: Tumor Infiltration in One or More Regional Lymph Nodes after Lymphadenectomy; pT1: Maximal Depth of Tumor Infiltration into the Mucosa or Submucosa according to Histopathologic Report; pT1a: Maximal Depth of Tumor Infiltration into the Mucosa according to Histopathologic Report; pT1b: Maximal Depth of Tumor Infiltration into the Submucosa according to Histopathologic Report; SEER-Program: The Surveillance, Epidemiology, and End Results (SEER) Program ;Y: Year; YLL: Years of Life Lost

Introduction

Carcinomas of the upper gastrointestinal (GI) tract are not among the most common tumors in Germany. Gastric carcinoma ranks 10th in the frequency of malignant diseases for both men and women. Carcinomas of the esophagus are in 13th place for men and 22nd place for women [1]. The incidence differs significantly between men and women for both gastric carcinoma and esophageal

tumors. In 2020, the number of new cases of gastric tumors was around 1.7 times higher for men compared to women and 3.4 times higher for esophageal carcinomas. Both diseases occur at an older age, but here too there are differences between the sexes. In general, the severity of the tumor disease is assessed based on the short and long-term prognosis. In Germany, relative 5-year survival rates are currently around 37% for women with gastric cancer and 34% for men [1]. Although the survival prospects have improved recently, they remain rather unfavorable compared to other cancers. This is because in most cases the disease is diagnosed at an advanced tumor stage. The situation is different for early cancers, where the 5-year survival rate for these tumors is 77% [2]. For most people, it makes a big difference whether someone dies young, around the age of 35, or at an advanced age, around 70 [3]. If one respects this view, from the perspective of healthcare system planning, a distinction must be made as to whether a disease typically only causes death in old age or at a younger age. The concept of Years of Life Lost (YLL) takes this into account. This concept does not simply count deaths, but hypothetically determines how much life is lost because of these deaths.

In a recent study, we investigated whether patients with a curatively treated early carcinoma of the upper GI tract have the same life expectancy as the normal population [2]. The results showed that despite total removal of the primary tumor and any metastases in the adjacent lymphatic vessels, the life expectancy of these patients was reduced compared to a sex- and age-matched population.

Studies on the question of whether sex has an influence on the prognosis of patients with these tumors show varying results [4-7]. Benign and malignant diseases of the upper GI tract show gender-specific differences. The frequent gastroesophageal reflux disease is a prime example: men have an erosive reflux disease more often than women and are also younger at the time of onset [8]. The female hormone status influences the localization and histopathology of adenocarcinoma of the esophagogastric junction and gastric carcinoma [9]. Liatsou *et al.* performed a systematic review about the role of sex disparities in survival of patients who underwent esophagectomy for esophageal cancer [10]. The results showed a tendency for better survival in women. The authors conclude that more studies are necessary for better understanding the role of sex in these tumor entities.

The aim of this study is to describe the influence of sex on life expectancy, taking into account the patient's age at the time of treatment. The data from the above-mentioned study are used for this purpose [2].

Patients and Methods

Patients

A total of 214 patients with pT1 adenocarcinoma of the stomach (GAC) or esophagus (EAC) were included in the study. A detailed description of the patient population can be found in the above-mentioned publication [2].

Therapy

All patients were treated surgically. Patients with GAC (n=102) underwent either total gastrectomy or subtotal gastrectomy with corresponding lymphadenectomy. For patients with EAC (n=112), the treatment of choice was esophagectomy with reconstruction through the raised stomach.

Statistics

Frequency distributions were tested for significance using the Chi-square test or Fisher's Exact test. The Kruskal-Wallis test was used to compare continuous variables. Univariate survival analysis was conducted according to the Kaplan-Meier method, and survival curves were compared with the log rank test. Multivariate analysis was performed with the Cox-regression method. Prognosis was analyzed including postoperative mortality (90-day mortality). The patients of the study group with early cancer and complete resection had the very best prerequisites for a curative approach, which means long-term freedom of cancer. This encourages the comparison to the life expectancy of the age-and gender-adapted normal population (control group). To evaluate the number of years of life, a person loses as consequences of dying early (YLL), we documented the number of expected years of life (EYL) for each patient. The EYL calculation was based on data from the Federal Statistical Office of Germany (Destatis) GENESIS V3.1. 2020 [11]. The EYL was calculated for the date of surgical therapy according to the age and sex of each patient and then registered. We used the average life expectancy (period life table) by years, sex, and completed age based on the year 2020. Details of calculation of this estimation are described in GENESIS [11].

Results

Demography and histopathology

The study included 214 patients with a median age of 63.4 (min:18.5, max: 84.7) years. Women (n=48) were significantly older at the time of treatment with a median age of 69.0 (min:42.0, max:84.7) years than the male patients (n=166) with a median age of 62.2 (min:18.5, max: 80.7) years ($p<0.001$). Patients with GAC (n=102) were significantly older with a median age of 65.5 (min:21.9, max:84.7) years compared to EAC patients (n=112) with 61.3 (min:18.5, max:80.7) years ($p=0.031$). Analyzing the age and sex relation for the different tumor locations, the median age for male patients with GAC (n=64) was 64.2 (min:21.9, max:78.4) years and for female patients with GAC (n=38) was 69.6 (min:41.9, max:84.7) years ($p=0.032$). The median age for male patients with EAC (n=102) was 60.2 (min:18.5, max:80.7) years and for female patients with EAC (n=10) was 68.0 (min:49.3, max:80.1) years ($p=0.044$). The later age of onset of the disease in women particularly affected the group of older patients (≥ 60 years). **Figure 1** shows the differences between men and women in the age groups. The most important tumor characteristics are listed in **(Table 1)**. Women are significantly less frequently affected by these tumors compared to men. This applies both to EAC with a sex ratio of male:female= 10:1 and to GAC with male:female=3:2.

Prognosis

The short- and long-term results did not differ significantly between the sexes **(Table 2)**. The 90-day postoperative mortality was 3.3%. The median survival for all patients was 12.3 (95%CI = 10.9-13.9) years. Multivariate analysis of prognosis including the factors' location (GAC vs. EAC), age groups (<60 vs. 60 years or older), sex (male vs. female), pT-category (pT1a vs. pT1b), and pN-category (pN0 vs. pN+) showed that patient age and pN+ significantly influenced the total prognosis (age <60 vs. ≥60y: H.R. = 2.58, 95%CI = 1.78-3.91, $p < 0.0001$; pN0 vs. pN+: H.R. = 1.73, 5%CI = 0.46-0.94, p = 0.024).

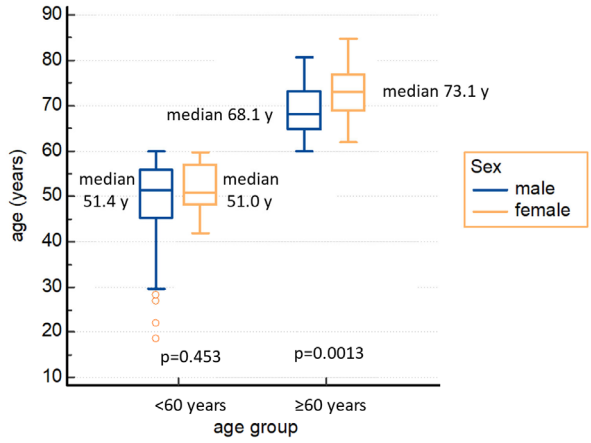

Figure 1. Comparison of age for 214 patients at the date of surgical therapy for early adenocarcinoma of the esophagus or stomach between males (n=166) and females (n=48) for older and younger patients. (y: Years; p: Value of significance).

Table 1. Tumor characteristics of 214 patients with early adenocarcinoma of esophagus or stomach comparing males and females.

	n	Males n (%)	Females n (%)	Significance p
All patients	214	166 (77.6%)	48 (22.4%)	-
Tumor location EAC GAC	 112 102	 102 (91.1%) 64 (62.7%)	 10 (8.9%) 38 (37.3%)	<0.0001
pT-category pT1 mucosa pTb submucosa	 90 124	 75 (83.3%) 91 (73.4%)	 15 (16.7%) 33 (26.6%)	n.s.
pN-category pN0 pN+	 181 33	 138 (76.2%) 28 (84.8%)	 43 (23.8%) 5 (15.2%)	n.s.

EAC: Adenocarcinoma of the Esophagus; GAC: Gastric Adenocarcinoma; p: Value of significance; n.s.: Non significance

Table 2. Postoperative course of 214 patients with early adenocarcinoma of the esophagus or stomach comparing males and females.

	All patients	Males	Females	Significance p
n	214	166 (77.6%)	48 (22.4%)	-
90-day mortality	n=7 (3.3%)	n=6 (3.6%)	n=1 (2.1%)	n.s.
2-year survival rate	89.7%	89.8%	87.5%	n.s.
5-year survival rate	76.6%	76.5%	77.1%	n.s.
	Patients died during follow-up			
n	145	102 (70.3%)	43 (29.7%)	
YLL Median and 25% - 75% PC	8.0 years 2.0 – 13.0 years	8.1 years 3.2 -14.5 years	7.0 years -0.6 – 13.0 years	n.s.

YLL: Years of Life Lost; PC: Percentile; p: Value of significance; n.s.: Non significance

Years of life lost (YLL)

Overall, 145 patients (68%) of the study cohort died during the follow-up period. For each patient of this subgroup, we calculated the YLL as the number of life years lost as a consequence of dying earlier compared to the life expectancy of the normal population. The median YLL for this group was 8.0 (95%CI = 6.0-9.1) years. A comparison between men and women shows that women have a lower number of YLL overall. However, the difference is not significant **(Table 2).** In the group of older patients (60 years or older), there is a considerably lower loss of expected life years for women compared to men. A more detailed look at the individual age groups shows that the advantage for women increases with age **(Figure 2)**. Thus, in the age group of 70 years or older, for women is no loss of life years to be expected, while men live a median of 5.4 years shorter than expected.

Discussion

The results of the present evaluation show that women who are diagnosed with early cancer of the upper GI tract late in life can expect little or no loss of life years. The number of YLL is quite different compared to men of the same age. This raises the question of the importance of this result.

It is known that women are significantly less likely to develop AC of the esophagus or stomach than men [12]. The search for the causes of these differences is the subject of current research. Adenocarcinomas in the gastrointestinal junction (AEG tumors) are among the carcinomas with increasing incidence in western industrialized nations [13-15]. Due to the lack of screening programs in Western countries, these carcinomas are mostly diagnosed at an advanced stage. The data for Germany show a proportion of early carcinomas of the esophagus of around 13% and of the stomach of 20% for both men and women [1]. The gender ratio in the group of patients with early carcinoma does not differ either in the data of the cancer registry or in the cohort studied here. It can therefore be assumed that the selection of the patient population - early carcinomas - does not significantly influence the difference in YLL between the sexes.

Early carcinoma for this tumor entity is defined according to the extent of the primary tumor and the detection of any metastases based on the UICC/AJCC TNM criteria [16]. In our study the diagnosis of early EAC or GAC means that a tumor has been diagnosed with pT1a or 1b, N0 or N+, M0). This assessment was made after removal of the primary tumor including an adequate lymphadenectomy and histopathological examination of the specimen, with the prefix p marked.

A distinction was made between tumors infiltrating the mucosa (pT1a) and those infiltrating the submucosa (pT1b). All patients included in this study had an indication for surgical therapy and the tumor and regional lymph nodes could be removed accordingly - R0 resection. It follows that the results could also apply primarily to this group of patients. However, various studies have shown that the long-term results for these pT1 carcinomas after adequate indication for endoscopic or surgical treatment do not differ between the forms of treatment [17,18]. The number of YLL for this tumor entity has been little studied to date. A study from Sweden was able to show that life expectancy was also reduced for patients who were still alive 5 years after successful tumor therapy due to a tumor of the esophagus [19]. This effect was much more pronounced for men than for women. However, all tumor stages were included in this study and not just early carcinomas.

In our study, we assumed that after successful tumor removal and without further stressful tumor therapy, the life expectancy for these patients should not differ from the corresponding normal population. Based on the actual study results, there appear to be other factors that can influence life expectancy. These are either parameters that have already led to the tumor disease or influences that are caused by the therapy. In the present evaluation, we particularly analyzed the role of gender in this tumor disease. For both tumor entities, women are less likely to develop the disease than men. Some studies show a better prognosis for women with gastric or esophageal carcinoma compared to men [4,5,7,20]. However, all tumor stages were usually included in these studies. In a recent Japanese study, patients were analyzed separately according to early and advanced stage and the results showed a significantly better 5-year survival rate

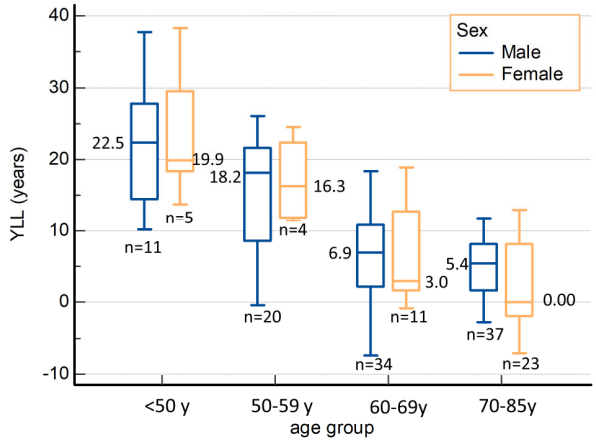

Figure 2. Comparison of years of life lost (YLL) for 145 patients dying during follow-up after surgical therapy for early adenocarcinoma of the upper GI-tract between males (n=102) and females (n=43) for different age groups. (y=years).

for women with "localized tumor without LNM" compared to male patients [20]. Hormonal influences of e.g. estrogens in the different stages of life are cited as possible reasons for such differences [21]. The data from Asian countries are not always easily comparable with the treatment results from Western industrialized nations due to differences in tumor pathology or the existence of screening programs, different treatment options and the like [22].

Our analysis shows that the late age of onset in women in particular prevents patients from losing EYL. In an analysis of the Surveillance, Epidemiology, and End Results (SEER) database of early gastric cancers, it was shown that the risk of lymph node metastasis (LNM) decreases with increasing age and that women have a lower overall risk of LNM compared to men [23]. In the patient population we examined, the rate of LNM was also lower in women (10%) than in men (17%), which was not significant due to the small number of cases. The influence of age on the frequency of LNM could not be demonstrated in these patients. Only young patients <50 years of age were diagnosed with LNM more frequently than older patients [2].

The advantage that older female patients with adenocarcinoma in the upper GI tract have due to the small loss of potential years of life can only be tried to explain. Women generally pay more attention to their health. AC in the esophagus or stomach can be caused by an unhealthy diet or lifestyle which may differ between the sexes. And when symptoms occur, women are more likely to see a doctor. A population-based study showed that women with heartburn were more likely to see a doctor and take appropriate medication than men suffering from the same symptoms [24].

The results discussed here are based on a small number of patients and may therefore lead in the wrong direction. Studies with larger numbers of cases are therefore necessary in order to better assess possible influencing factors.

Conclusion

The available data show that older female patients with early adenocarcinoma of the esophagus or stomach have little or no loss of expected life years. Men of the same age with this diagnosis lose a median of 5.4 years of life expectancy. The high rate of YLL should lead to considerations as to what meaningful prevention could look like, especially for men. For older women diagnosed with early carcinoma of the upper GI tract, information about the low loss of life expectancy is better information than the tumor-specific probability of survival.

Acknowledgements

This study did not receive financial or other support from any organizations or other people not listed as authors.

Conflict of Interest

All authors declare that there is no conflict of interest.

Author Contribution Statement

Elfriede Bollschweiler participated in research design, performance of research, data analysis and writing the paper.

Arnulf H. Hölscher participated in surgical therapy, research design, performance of research and writing the paper.

References

1. Krebs in Deutschland für 2019/2020. 14. Ausgabe. . Berlin: Robert Koch-Institut (Hrsg) und die Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. (Hrsg). ; 2023.
2. Bollschweiler E, Hölscher AH, Markar SR, Alakus H, Drebber U, Mönig SP, et al. Premature mortality for patients after completely resected early adenocarcinoma of the esophagus or stomach. Cancer Med. 2024 May;13(10):e7223.
3. Wengler A, Rommel A, Plaß D, Gruhl H, Leddin J, Ziese T, et al ; BURDEN 2020 Study Group. Years of Life Lost to Death—A Comprehensive Analysis of Mortality in Germany Conducted as Part of the BURDEN 2020 Project. Dtsch Arztebl Int. 2021 Mar 5;118(9):137-144.
4. Quaas A, Pamuk A, Klein S, Quantius J, Rehkaemper J, Barutcu AG, et al. Sex-specific prognostic effect of CD66b-positive tumor-infiltrating neutrophils (TANs) in gastric and esophageal adenocarcinoma. Gastric Cancer. 2021 Nov;24(6):1213-1226.
5. Bozzetti F, Bonfanti G, Morabito A, Bufalino R, Menotti V, et al. A multifactorial approach for the prognosis of patients with carcinoma of the stomach after curative resection. Surg Gynecol Obstet. 1986 Mar;162(3):229-34.
6. Chandanos E, Lagergren J. Oestrogen and the enigmatic male predominance of gastric cancer. Eur J Cancer. 2008 Nov;44(16):2397-403.
7. Mantziari S, Elliott JA, Markar SR, Klevebro F, Goense L, Johar A, et al; ENSURE Study Group. Sex-related differences in oncologic outcomes, operative complications and health-related quality of life after curative-intent oesophageal cancer treatment: multicentre retrospective analysis. BJS Open. 2024 Mar 1;8(2):zrae026.
8. Plum PS, Monig SP, Gockel I, Keller G, Ott K. [Gender medicine in diseases of the upper gastrointestinal tract]. Chirurgie (Heidelb). 2024;95(9):685-95.
9. Baxter MA, Spender LC, Walsh S, Bray S, Skinner G, King S, et al, On Behalf Of The Go Investigators. Female Sex but Not Oestrogen Receptor Expression Predicts Survival in Advanced Gastroesophageal Adenocarcinoma-A Post-hoc Analysis of the GO2 Trial. Cancers (Basel). 2023 May 3;15(9):2591.
10. Liatsou E, Bellos I, Katsaros I, Michailidou S, Karela NR, Mantziari S, et al. Sex differences in survival following surgery for esophageal cancer: A systematic review and meta-analysis. Dis Esophagus. 2024 Aug 14:doae063
11. Durchschnittliche Lebenserwartung in Deutschland [Internet]. Statistisches Bundesamt Germany. 2020. Available from: https://www-genesis.destatis.de/genesis/online.
12. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, 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.
13. Bollschweiler E, Wolfgarten E, Gutschow C, Hölscher AH. Demographic variations in the rising incidence of esophageal adenocarcinoma in white males. Cancer. 2001 Aug 1;92(3):549-55.
14. Radkiewicz C, Asplund J, Lagergren J. Incidence Trends and Survival in Early-Onset Esophagogastric Adenocarcinoma: A Swedish Population-Based Cohort Study. Cancer Epidemiol Biomarkers Prev. 2023 May 24:OF1-OF8.
15. Abdulkarim D, Mattsson F, Lagergren J. Recent incidence trends of oesophago-gastric cancer in Sweden. Acta Oncol. 2022 Dec;61(12):1490-1498.

16. Brierley J, Gospodarowicz M, Wittekind C. TNM Classification of Malignant Tumours, 8th edition. Brierley J, Gospodarowicz M, Wittekind C, editors: Wiley-Blackwell; 2016.

17. Pech O, Bollschweiler E, Manner H, Leers J, Ell C, Hölscher AH. Comparison between endoscopic and surgical resection of mucosal esophageal adenocarcinoma in Barrett's esophagus at two high-volume centers. Ann Surg. 2011 Jul;254(1):67-72.

18. Lu W, Li P, Wen W, Jian Y. Comparison of Long-Term Survival Between cT1N0 Stage Esophageal Cancer Patients Receiving Endoscopic Dissection and Esophagectomy: A Meta-Analysis. Front Surg. 2022 May 6;9:917689.

19. Lundberg E, Lagergren P, Mattsson F, Lagergren J. Life Expectancy in Survivors of Esophageal Cancer Compared with the Background Population. Ann Surg Oncol. 2022 May;29(5):2805-2811.

20. Xing Y, Hosaka H, Moki F, Tomaru S, Itoi Y, Sato K, et al. Gender Differences in Patients with Gastric Adenocarcinoma. J Clin Med. 2024 Apr 25;13(9):2524.

21. Liu Z, Zhang Y, Lagergren J, Li S, Li J, Zhou Z, et al. Circulating Sex Hormone Levels and Risk of Gastrointestinal Cancer: Systematic Review and Meta-Analysis of Prospective Studies. Cancer Epidemiol Biomarkers Prev. 2023 Jul 5;32(7):936-946.

22. Bollschweiler E, Plum PS. Prediction of Lymphatic Invasion for Patients with Early Gastric Cancer: A Review. AME Clin Trials Rev 2024;2:43

23. Pang S, Wang W, Zhou J, Jiang X, Lin R. Inverse association between age and risk of lymph node metastasis in patients with early gastric cancer: a surveillance, epidemiology, and end results analysis. J Cancer. 2024 Mar 25;15(9):2829-2836.

24. Bollschweiler E, Knoppe K, Wolfgarten E, Hölscher AH. Prevalence of reflux symptoms in the general population of Cologne. Zeitschrift fur Gastroenterologie. 2007 Feb 1;45(2):177-81.