ACTA ONCOLOGICA
2023, VOL. 62, NO. 5, 438–443
https://doi.org/10.1080/0284186X.2023.2214681

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ORIGINAL ARTICLE

Use of 5α-reductase inhibitors and survival of oesophageal and gastric cancer in a nationwide Swedish cohort study

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ABSTRACT

Background: We hypothesised that the use of the anti-androgenic drug 5α-reductase inhibitors (5-ARIs) improves survival in patients with oesophago-gastric cancer.

Methods: This nationwide Swedish population-based cohort study included men who underwent surgery for oesophageal or gastric cancer between 2006-2015, with follow-up until the end of 2020. Multivariable Cox regression estimated hazard ratios (HR) for associations between 5-ARIs use and 5-year all-cause mortality (main outcome) and 5-year disease-specific mortality (secondary outcome). The HR was adjusted for age, comorbidity, education, calendar year, neoadjuvant chemo(radio)therapy, tumour stage, and resection margin status.

Results: Among 1769 patients with oesophago-gastric cancer, 64 (3.6%) were users of 5-ARIs. Compared to non-users, users of 5-ARIs were not at any decreased risk of 5-year all-cause mortality (adjusted HR 1.13, 95% CI 0.79-1.63) or 5-year disease-specific mortality (adjusted HR 1.10, 95% CI 0.79-1.52). Use of 5-ARIs was not associated with any decreased risk of 5-year all-cause mortality in subgroup analyses stratified by categories of age, comorbidity, tumour stage, or tumour subtype (oesophageal or cardia adenocarcinoma, non-cardia gastric adenocarcinoma, or oesophageal squamous cell carcinoma).

Conclusion: This study did not support the hypothesis of improved survival among users of 5-ARIs after curatively intended treatment for oesophago-gastric cancer.

ARTICLE HISTORY
Received 27 February 2023
Accepted 11 May 2023

KEYWORDS
Stomach neoplasms; oesophageal neoplasms; 5-alpha reductase inhibitors; gonadal steroid hormones; prognosis

Introduction

Oesophago-gastric cancer carries a poor prognosis (<30% 5-year survival) and has a high incidence, accounting for 1,315,000 deaths globally in 2020 (13.2% of all cancer-related deaths) [1–3]. There is a great need for novel treatments that can improve survival in these aggressive tumours, and sex-hormonal therapy may be an interesting target in this respect.

Oesophago-gastric cancer is characterised by an unexplained male predominance and poorer survival among men than in women [4–10]. The sex distribution of risk factors and prognostic factors for these tumours do not explain these differences [6,11–15]. A growing number of studies have indicated that sex hormones may be associated with both incidence and survival in oesophago-gastric cancer, particularly in oesophageal adenocarcinoma [6,16–22].

Medication with 5α-reductase inhibitors (5-ARIs) is used against benign prostatic hyperplasia and acts by inhibiting the 5α-reductase enzyme, a protein that converts testosterone to the more potent androgen dihydrotestosterone [23,24]. Thus, 5-ARIs have strong anti-androgenic properties, and patients medicating with 5-ARIs have on average 70% reduced serum levels of dihydrotestosterone and thereby less activation of androgen receptors [25]. Some previous studies have shown that higher levels of androgen receptor expression are associated with poorer prognosis among oesophageal cancer patients [16], and possibly also among patients with gastric cancer [26].

This study set out to be the first to examine the hypothesis that the use of 5-ARIs improves survival in patients with oesophago-gastric cancer.

Methods

Design

This was a Swedish population-based cohort study of patients who received curatively intended treatment for oesophago-gastric cancer between 1 July 2006 and 31 December 2015, with follow-up until the end of 2020. Data were retrieved from medical records and national Swedish registries. All data were interlinked for each patient by using the unique personal identity number given to every person

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residing in Sweden. Ethical approval was obtained from the Regional Ethical Review Board in Stockholm (2017/141-31/2).

Cohort

The cohort included patients who underwent resectional surgery for either of three subtypes of oesophago-gastric cancer: oesophageal or cardia adenocarcinoma, non-cardia gastric adenocarcinoma and oesophageal squamous cell carcinoma. A cohort of patients with oesophageal cancer and another with gastric cancer were combined for this study, and these cohorts have been described in detail elsewhere [15,27,28]. In brief, patients with oesophago-gastric cancer were identified in the Swedish Cancer Register. Those who underwent resectional surgery for these tumours were identified in the Swedish Patient Registry. The final cohort was determined after a thorough review of the medical records of all patients. The completeness of oesophageal and gastric cancer diagnoses in the Swedish Cancer Register is 98%, and the data on tumour staging for oesophageal cancer has been validated in separate studies to have 98% completeness [29–32]. The Patient Registry has a positive predictive value of 99.6% on surgery for oesophageal cancer [33].

Exposure

The study exposure was defined as at least 2 records of the 5-ARIs finasteride or dutasteride dispensed within 1 year before surgery. The earliest possible date of exposure to 5-ARIs was July 1st 2005 because the study period began 1 July 2006. Records on dispensed medication were obtained from the Swedish Prescribed Drug Registry, which started 1 July 2005 and uses the Anatomical Therapeutic Chemical Classification (ATC) codes for defining finasteride (ATC-code G04CB01) and dutasteride (ATC-code G04CB02). The Swedish Prescribed Drug Registry has nationwide coverage and high accuracy and completeness for the recording of all prescribed medications because all dispensed prescriptions in all Swedish pharmacies are automatically transferred to this registry.

Outcomes

The follow-up started at the date of surgery and ended at 5 years of follow-up, death or end of the study period, whichever occurred first. The primary outcome was 5-year all-cause mortality, i.e., death within 5 years of surgery regardless of the cause, with follow-up data available throughout 2020. The secondary outcome was 5-year disease-specific mortality, i.e., with oesophago-gastric cancer as a main or contributing cause of death, with follow-up data available until the end of 2019. The date and cause of death were obtained from the Swedish Cause of Death Register, which is 100% complete for the date of death and over 96% complete for the cause of death [34].

Covariates

The Swedish National Patient Register provided data on surgery for oesophago-gastric cancer, age at surgery and comorbidity [33,35]. Comorbidities were converted into the most updated version of the well-validated Charlson Comorbidity Index, which was designed to assess how comorbidity influences survival after surgery [36,37]. Data on surgical details, neoadjuvant chemo(radio)therapy, pathological tumour stage and resection margin status were obtained by reviewing the medical records of all participating patients. Education level was obtained from the Swedish Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) [38].

Statistical analysis

Kaplan-Meier plots were used to illustrate the survival trends within 5 years of surgery among users and non-users of 5-ARIs. Multivariable Cox proportional hazards regression estimated hazard ratios (HR) with 95% confidence intervals (CI) of the 5-year mortality outcomes, comparing the risk of death between users and non-users of 5-ARIs. Both a crude and adjusted model was applied, and the adjusted model included the following covariates: (1) age (continuous), (2) comorbidity (Charlson Comorbidity Index score 0, 1, or $\geq$2), (3) education level ($<$9, 9–12 or $>$12 years), (4) calendar year (continuous), (5) neoadjuvant chemo(radio)therapy (yes or no), (6) tumour stage (0-I, II, or III-IV) and (7) resection margin status (no tumour involvement [R0] or tumour involvement [R1/R2]). Use of 5-ARIs and risk of 5-year all-cause mortality was stratified by the following variables: (1) age (below or equal to the median, or above median), (2) comorbidity (Charlson Comorbidity Index score 0 or $\geq$1), (3) tumour stage (0-II, or III-IV), and (4) tumour subtypes (oesophageal or cardia adenocarcinoma, non-cardia gastric adenocarcinoma, or oesophageal squamous cell carcinoma). An interaction term for each of these variables was added to the adjusted model to derive HR for each stratum of each variable. We adhered to complete-case analysis and thus excluded patients with any missing data supposed to be included in the analysis. Two sensitivity analyses were performed to assess the robustness of the results: One also included participants with 2 dispensed records of 5-ARIs within 1 year after surgery, i.e., in an adjuvant setting, and another excluding participants with any prior cancer diagnoses other than oesophagogastric cancer or non-malignant melanoma.

A study protocol was enacted before the initiation of analyses, and the data management and analyses were performed accordingly by the first author (SR) using Stata (Release 17, StataCorp, College Station, TX) and validated by an experienced statistician (FM) using SAS (Version 9.4, SAS Institute Inc., Cary, NC, USA).

Results

Patients

A total of 1877 patients had undergone surgery for oesophago-gastric cancer between 1 July 2006 and 31 December 2015 in Sweden. After excluding 108 patients (6%) with missing data on variables supposed to be included in the

analyses, 1769 patients remained for the final complete case analysis. Of these participants, 64 (3.6%) were exposed to 5-ARIs and 1,705 (96.4%) were unexposed. The median follow-up was 3.1 years (interquartile range 0.8–5.0 years) among 5-ARIs users and 2.7 years (interquartile range 1.0–5.0 years) for non-users. Characteristics of the study participants are presented in Table 1. The mean age at diagnosis was higher in the 5-ARIs group (74 years, standard deviation 6 years) than in the unexposed group (67 years, standard deviation 10 years), and the non-users of 5-ARIs more frequently had advanced tumour stage and neoadjuvant chemo(radio)therapy compared to users. Other characteristics were similar between the users and non-users of 5-ARIs (Table 1).

Table 1. Characteristics of users and non-users of 5α-reductase inhibitors (5-ARIs) who underwent curative treatment for oesophago-gastric cancer.

Characteristics	5-ARIs users Number (%)	Non-users Number (%)
Total	64 (100)	1705 (100)
Age (years)		
≤59	0 (0)	357 (21)
60–69	16 (25)	621 (36)
≥70	48 (75)	727 (42)
Mean (standard deviation)	74 (6)	67 (10)
Charlson Comorbidity Index		
0	22 (34)	695 (41)
1	21 (33)	564 (33)
≥2	21 (33)	446 (26)
Education (years)		
<9	25 (39)	625 (37)
9–12	27 (42)	772 (45)
>12	12 (19)	308 (18)
Calendar period		
2006 (July) – 2009	8 (12)	543 (32)
2010–2012	28 (44)	552 (32)
2013–2015	28 (44)	610 (36)
Neoadjuvant chemo(radio)therapy		
No	43 (67)	851 (50)
Yes	21 (33)	854 (50)
Pathological tumour stage		
0-I	26 (41)	532 (31)
II	17 (27)	448 (26)
III-IV	21 (33)	725 (43)
Resection margin status		
Radically resected (R0)	54 (84)	1479 (87)
Not radically resected (R1/R2)	10 (16)	226 (13)
Absolute 5-year all-cause mortality	38 (59)	1056 (62)
Absolute 5-year disease-specific mortality*	31 (48)	906 (53)

*5-year follow-up for all years except those included in 2015 which had a minimum of 4 years.

Risk of mortality

Users of 5-ARIs had an absolute 5-year all-cause mortality rate of 59% compared to 62% among non-users, and the Kaplan–Meier plots showed similar survival trends for these groups (Figure 1). The absolute 5-year disease-specific mortality rate was 48% among 5-ARIs users and 53% among non-users (Table 1).

The multivariable analyses showed that compared with non-users of 5-ARIs, users had no decreased risk of 5-year all-cause mortality (adjusted HR 1.10, 95% CI 0.79–1.52) or 5-year disease-specific mortality (adjusted HR 1.13, 95% CI 0.79–1.63).

Stratified analyses by age, tumour stage, comorbidity and subtype showed no decreased HR of 5-year all-cause mortality in any of the strata, and none of the tests of interaction terms was statistically significant (Table 2). Removing patients with previous cancer did not show any significant changes to the results (adjusted HR 1.09, 95% CI 0.75–1.57). The sensitivity analysis that included patients using 5-ARIs also after surgery did not change the null result (adjusted HR 0.98, 95% CI 0.75–1.30).

Discussion

This study found that 5-ARIs users did not experience any decreased risk of 5-year mortality after curative treatment for

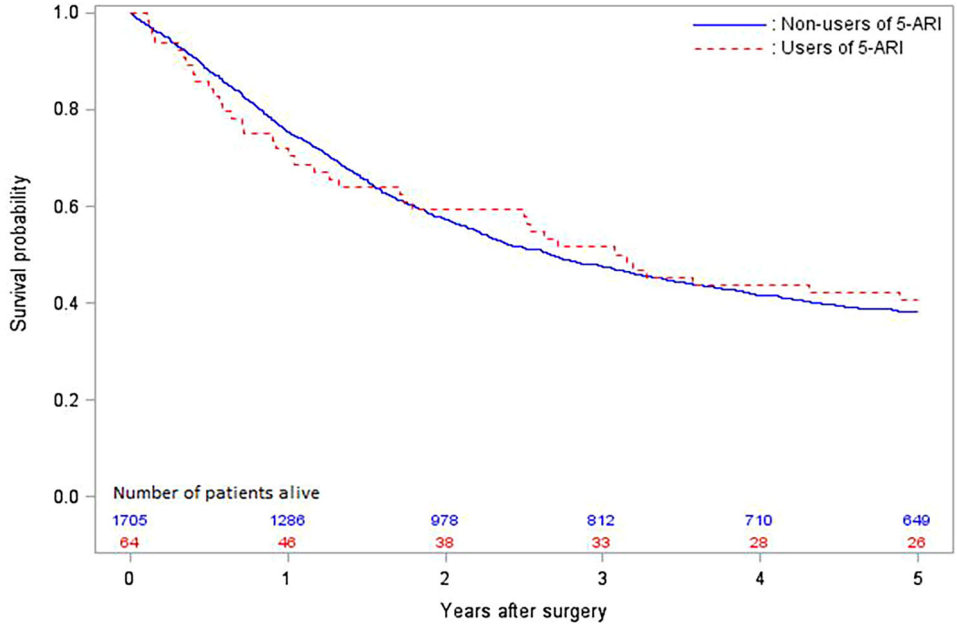

Figure 1. Kaplan–Meier survival curves in patients who underwent curative treatment for oesophago-gastric cancer by use or non-use of 5α-reductase inhibitors (5-ARIs).

Table 2. Associations between the use of 5α-reductase inhibitors (5-ARIs) and 5-year all-cause mortality of patients who underwent curative treatment for oesophago-gastric cancer.

Variables	Number of patients	Crude hazard ratio (95% confidence interval)	Adjusted hazard ratio* (95% confidence interval)	Interaction *p*-value
Total				
Non-users of 5-ARIs	1705	1.00 (Reference)	1.00 (Reference)	
Users of 5-ARIs	64	0.96 (0.70–1.33)	1.10 (0.79–1.52)	
Age (years)				0.690
Below median of 68				
Non-users of 5-ARIs	905	1.00 (Reference)	1.00 (Reference)	
Users of 5-ARIs	11	0.85 (0.38–1.91)	0.95 (0.42–2.14)	
Above median of 68				
Non-users of 5-ARIs	800	1.00 (Reference)	1.00 (Reference)	
Users of 5-ARIs	53	0.89 (0.62–1.26)	1.14 (0.80–1.63)	
Charlson comorbidity index				0.482
0				
Non-users of 5-ARIs	695	1.00 (Reference)	1.00 (Reference)	
Users of 5-ARIs	22	1.07 (0.62–1.86)	1.30 (0.75–2.27)	
≥1				
Non-users of 5-ARIs	1010	1.00 (Reference)	1.00 (Reference)	
Users of 5-ARIs	42	0.89 (0.59–1.32)	1.02 (0.68–1.52)	
Tumour stage				0.116
0-II				
Non-users of 5-ARIs	980	1.00 (Reference)	1.00 (Reference)	
Users of 5-ARIs	43	0.89 (0.55–1.42)	0.82 (0.51–1.31)	
III-IV				
Non-users of 5-ARIs	725	1.00 (Reference)	1.00 (Reference)	
Users of 5-ARIs	21	1.47 (0.94–2.29)	1.38 (0.88–2.16)	
Tumour subtype				
Oesophageal or cardia adenocarcinoma				
Non-users of 5-ARIs	789	1.00 (Reference)	1.00 (Reference)	
Users of 5-ARIs	33	1.22 (0.80–1.85)	1.27 (0.83–1.94)	
Non-cardia gastric adenocarcinoma				0.246
Non-users of 5-ARIs	729	1.00 (Reference)	1.00 (Reference)	
Users of 5-ARIs	29	0.68 (0.39–1.18)	0.84 (0.48–1.47)	
Oesophageal squamous cell carcinoma				0.165
Non-users of 5-ARIs	187	1.00 (Reference)	1.00 (Reference)	
Users of 5-ARIs	2	7.62 (1.88–30.89)	3.59 (0.88–14.68)	

*Adjusted for age, comorbidity, education, calendar year, neoadjuvant chemo(radio)therapy, tumour stage and resection margin status.

oesophago-gastric cancer, independent of tumour subtype and adjustment for the main prognostic factors.

Among the strengths of the study is the population-based design with a high (98%) participation rate, which counteracted selection bias. The detailed and accurate information on the exposure, outcomes and covariates, retrieved from medical records and high-quality Swedish national health registers, reduced information bias and confounding. There are also weaknesses. Residual confounding cannot be excluded in this observational study, and we lacked data on some potential confounders, e.g., smoking, obesity and alcohol overconsumption. However, the adjustment for comorbidity should partly have counteracted confounding from these factors. A limitation was the lack of comparison with a drug targeting a similar disease profile to that of 5-ARIs, but there was no obvious candidate with a reasonable frequency of use. Another weakness was the limited statistical power, particularly in the sub-group analyses, which was mainly due to the low frequency of 5-ARIs users. This study investigated 5-ARIs as a neo-adjuvant therapy, but long-term use of 5-ARIs is common [19,39,40], which could have introduced adjuvant effects. A separate analysis of new-users after surgery was not possible because of insufficient power, but the sensitivity analysis including these patients did not change the results.

No previous study has assessed the use of 5-ARIs in relation to survival in oesophago-gastric cancer, although androgens play an essential role in prostatic tumour progression, and anti-androgenic medications are widely used to improve the survival for some cancer types [41,42]. Experimental research has found that androgen receptors may be involved in tumour progression in several male-predominant tumours, including oesophageal and gastric cancer [26,43–50]. Studies assessing the hypothesis of androgens playing a role in the aetiology, tumour progression, and survival in oesophago-gastric cancer have provided contradictory results [18,19,22,51–53]. Two studies have suggested that 5-ARIs exposure is associated with a decreased risk of oesophageal and gastric cancer [18,19]. Two previous studies from our group found no association between prediagnostic levels of testosterone and the risk or survival of oesophageal cancer [22,54]. The present study found no survival benefits in oesophago-gastric cancer with 5-ARIs medication, contributing to the sparse literature examining whether anti-androgenic medication improves the prognosis for these patients.

Although this study did not find any improved survival in oesophago-gastric cancer associated with the use of 5-ARIs, it cannot exclude the possibility that anti-androgenic therapy may be shown beneficial in the future. The non-significant point estimate in oesophageal squamous cell carcinoma

patients was for example relatively high and the statistical power was limited.

In conclusion, this population-based cohort study using high-quality data on exposures, outcomes and confounders, found that users of the anti-androgenic medications 5-ARIs had no decreased 5-year mortality after having undergone curative treatment for oesophago-gastric cancer.

Author contributions

All authors designed the study. The data was retrieved by F.M. from a previously established cohort (SWEGASS). The data was analysed by S.R. and validated by F.M. S.R. interpreted the results and drafted the paper. All listed authors revised the paper and approved the final version of the article, including the authorship list. S.X. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics approval

This study was approved by the Regional Ethical Review Board in Stockholm (reference number (2017/141-31/2). The study was performed in accordance with the Declaration of Helsinki.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This study was funded partly by Swedish Cancer Society (grant number 19 0043 and 22 2038) and Swedish Research Council (grant number 2019-00209).

Data availability statement

Data supporting the results are available upon request.

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