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Marital status and survival after oesophageal cancer surgery: A population-based nationwide cohort study in Sweden

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Marital status and survival after oesophageal cancer surgery:

A population-based nationwide cohort study in Sweden

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Abstract (word count: 250)

Objectives: A beneficial effect of being married on survival has been shown for several cancer types, but is unclear for oesophageal cancer. The objective of this study was to clarify the potential influence of marital status on the overall and disease-specific survival after curatively intended treatment of oesophageal cancer using a nationwide population-based design, taking into account the known major prognostic variables.

Design: Prospective, population-based cohort

Setting: All Swedish hospitals performing surgery for oesophageal cancer during 2001-2005

Participants: This study included 90% of all oesophageal or junctional cancer patients who underwent surgical resection in Sweden in 2001-2005, with follow-up until death or end of study period (2012).

Primary and secondary outcome measures: Cox regression was used to estimate associations between marital status and 5-year overall and disease-specific mortality, expressed as hazard ratios (HRs) with 95% confidence intervals (CIs), with adjustment for sex, age, tumour stage, histological type, complications, comorbidities and annual surgeon volume.

Results: Of all 606 included patients (80.4% male), 55.1% were married, 9.2% remarried, 22.6% previously married, and 13.0% never married. Compared to married patients, never married (HR 1.02, 95% CI 0.77-1.35), previously married (HR 0.90, 95% CI 0.71-1.15) and remarried patients (HR 0.79, 95% CI 0.55-1.13) had no increased overall 5-year mortality. The corresponding HRs for disease-specific survival, and after excluding the initial 90 days of surgery were similar to the HRs of overall survival.

Conclusions: This study showed no evidence of a better 5-year survival in married compared to non-married patients undergoing surgery for oesophageal cancer.

Keywords: Socioeconomic factors; civil status; health status disparities; prognosis; outcome; oesophagectomy.

Strengths and limitations of this study

Patients with oesophageal cancer have a poor prognosis, even those patients eligible for curative surgery (oesophagectomy).

Being married has been shown to be a marker of better survival after cancer in general and of specific cancer types, but this has not been studied yet for oesophageal cancer.

This nationwide population-based study did not find any evidence that marital status influences long-term survival after oesophagectomy for oesophageal cancer, even after taking into account the known major prognostic variables.

The absence of a clear association between marital status and long-term survival, might be a false negative result related to the relatively small sample size. Yet, it is also possible that the beneficial effect of being married is non-existent for oesophageal cancer.

The main strength of this study is the population-based design with almost complete coverage, and complete follow-up of all patients operated in Sweden for oesophageal cancer in 2001-2005. Moreover, complete data on a large variety of variables enabled adjustment for known prognostic factors. Yet, among limitations are that influence of other confounders or residual confounding by the variables adjusted for, can never be ruled out. The statistical power was however limited to detect weak associations.

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Competing interests: The authors declare that they have no conflict of interest. The Swedish Research Council (SIMSAM) and the Swedish Cancer Society, the funding sources had no role in the design and conduct of the study, collection, management, analysis and interpretation of the data, or preparation review or approval of the manuscript.

Data sharing statement: There is no additional data available

Introduction

The potential influence of marital status on health and life expectancy has since long been a matter of discussion.[1 2] Being married has been shown to be a marker of better survival after cancer in general and of specific cancer types,[3] and the survival discrepancy between married and non-married cancer patients has been claimed to be increasing over time.[4] Having a partner is believed to lead to a healthier lifestyle, e.g. regarding tobacco and alcohol use, physical activity, and social support, and can also influence the choice and adherence to treatment, as well as the time elapsing between early symptoms and a confirmed cancer diagnosis.[2] However, little is known about such influence on oesophageal cancer. Only a few studies have investigated the potential role of socio-economic factors in the prognosis of oesophageal cancer.[5 6] A previous study from our group showed limited evidence of an association between lower education and worse long-term survival in operated patients with oesophageal cancer (only significant increase in patients with tumour stage IV).[7] A recent American study showed that married patients were more likely to be diagnosed with localised disease, and received treatment with curative intent more frequently than non-married patients, also showing a better overall survival.[8] However, patients with oesophageal cancer have an overall very poor prognosis, mainly due to advanced tumour at the time of diagnosis, and only a minority is eligible for curatively intended treatment.[9] Surgery (oesophagectomy) is the cornerstone in radical therapy, and is often combined with oncological therapy.[9] The objective of this study was to clarify the potential influence of marital status on the overall and disease-specific survival after curatively intended treatment of oesophageal cancer using a nationwide population-based design, taking into account the known major prognostic variables.

Methods

Participants

This was a population-based prospective cohort study, which included 90% of all patients with oesophageal or gastroesophageal junctional cancer treated with surgery in Sweden during the period April 2, 2001 and December 31, 2005. Follow-up for survival ended in August 31, 2012. From the full study cohort of 616 patients, 10 patients were excluded because of missing values for marital status, leaving 606 patients for final analysis.

The study was approved by the Regional Ethical Review Board in Stockholm, Sweden. Informed consent was obtained from each patient before inclusion in the study.

Data sources

The organization of the comprehensive nationwide network of clinicians that participated in the data collection has been described elsewhere, and most parts of the design of this clinical cohort study has been presented in detail.[10 11] In brief, information about tumour stage, histology and localization, surgical procedures and complications were prospectively collected for all patients through scrutiny of relevant medical records from 174 hospital departments in Sweden.[11] In September 2012, the cohort was linked to the Patient Register, the Causes of Death Register, and the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA). The Patient Register includes all in-hospital care and outpatient specialist care in Sweden, including codes for diagnoses, surgical procedures and comorbidity with a high level of validity.[12] The Causes of Death Register contains information on date and cause of death for all deceased Swedish residents since 1952.[13] The LISA came into use in 1990 and includes a large variety of variables, including socio-economic status, marital status and work history.[14]

Study exposure and outcome

Four mutually exclusive categories for marital status during the calendar year before surgery were: married (never divorced or widowed), remarried (after widowhood or divorce), previously married (widowed or divorced), and never married. The main outcome measure was overall mortality (including all causes of death) up to 5 years after oesophagectomy for oesophageal cancer. Other outcomes were mortality within 5 years after surgery: 1) after exclusion of deaths within first 90 days of surgery (defined as conditional mortality), 2) with oesophageal cancer as an underlying or contributing cause of death (disease-specific mortality, or death related to oesophageal cancer), and 3) the combination of conditional and disease-specific mortality.

Statistical analyses

The association between marital status and mortality was analysed by means of multivariable Cox regression and expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). The married group was used as reference category. Three regression models were employed: 1) without any adjustments (crude model), 2) adjusted for sex, age and tumour stage (basic model), and 3) further adjusted for histological tumour type, major complications, comorbidities and annual surgeon volume of oesophagectomy for cancer (fully adjusted model)[15]. Due to the limited effect on survival, as shown in a previous study,[7] educational level was not included in the analyses. Age was categorised as <60, 60-74, or ≥75 years, and tumour stage as 0-I, II, III, or IV [16]. Histological type was subdivided in adenocarcinoma and squamous cell carcinoma. Number of major complications (within 30 days of surgery) and comorbidities were both categorised as none, one or more than one, as described previously.[11 17] Surgeon volume was categorised into two equally sized groups based on the median annual number of oesophagectomies per surgeon (<8 or ≥8).[15] To assess effect modification, stratified survival analyses were performed for

tumour stage and histological type using the same regression models, without adjustment for the stratifying variable.

Results

Patients

Characteristics of the 606 study patients are described in Table 1. At the time of surgery, 334 patients were married (55.1%), 56 were remarried (9.2%), 137 were married previously (22.6%), and 79 patients were never married (13.0%). Compared to the married group, the re-married and never married groups were younger (Table 1). The largest proportion of male patients was found in the never married group (87.3%) and the smallest in the previously married group (75.2%). Tumours were as likely to be of an advanced stage (stage IV) in all four groups (range 10.2-12.0%), but fewer early tumours (stage I) were found in the never married group (12.7%) compared to the married group (20.7%). Squamous cell carcinoma was found more frequently in the previously married (29.9%) and never married groups (30.4%), compared to the married (21.3%) and remarried group (23.2%). Of all patients, 53.6-62.8% had co-morbidity at time of surgery, which was least in the remarried group. Married patients were least likely to have been operated on by surgeons with a low annual volume, compared to previously married patients (49.4% versus 58.4%). There were post-operative complications in 35.6-41.8% of the patients. In total, 455 (75.1%) patients died within 5 years of surgery, of whom 429 (94.3%) had oesophageal cancer as an underlying or contributing cause of death.

Marital status and mortality

The proportions of overall and conditional 5-year mortality were highest in the never married group (Table 1). The absolute 5-year survival rates for married, remarried, previously married, and never married patients were 25.7%, 37.5%, 22.6%, and 16.5% respectively. Short-term mortality was slightly lower in the never married group (6.3% versus 8.1-8.9% in the other groups) (Table 1). The HRs for mortality after oesophagectomy according to marital status are presented in Table 2. Compared with the married group, no increased HRs of mortality were found in the other marital status groups. The fully adjusted HR of overall 5-year mortality was similar in never married patients compared to married patients (HR 1.02, 95% CI 0.77-1.35), and the corresponding HRs were very similar for disease-specific survival and survival after excluding the initial 90 days after surgery (Table 2). The fully adjusted HR for the various definitions of 5-year mortality was lower in the remarried group (HR ranging from 0.74 to 0.80) and in the previously married group (HR ranging from 0.90 to 0.94), but no statistically significant associations were identified (Table 2). The results for disease-specific survival, and for overall or disease-specific survival after excluding the initial 90 days of surgery, were all similar to the HRs of overall survival (Table 2).

The fully adjusted subgroup analyses for all-cause and disease-specific mortality by tumour stage and histological type showed similar results as the main analyses, and no statistically significant associations were identified (data not shown).

Discussion

This study did not show any improved survival among married oesophageal cancer patients undergoing oesophagectomy compared to other marital status groups after adjustment for several prognostic variables.

The main strength of this study is the population-based design with almost complete coverage, and complete follow-up of all patients operated in Sweden for oesophageal cancer in 2001-2005. Moreover, complete data on a large variety of variables enabled adjustment for known prognostic factors. Yet, among limitations are that influence of other confounders or residual confounding by the variables adjusted for, can never be ruled out. The statistical power was limited to detect weak associations. Changes in marital status after surgery were considered of limited impact on the results, since these only occurred in 3.3% of all patients. Moreover, we did not have data on co-habiting without being married, or extent of social networks, which could have led to an underestimation of potential associations. Despite the multi-centre design, differences between hospitals and treatment are unlikely to have influenced any associations between marital status and survival.

The absence of a clear association between marital status and long-term survival, such as found for some other cancer types and oesophageal cancer in the large American study mentioned earlier (including all diagnosed patients),[3 8] might be a false negative result related to the relatively small sample size. Yet, it is also possible that the beneficial effect of being married is non-existent for oesophageal cancer receiving surgery, which has a limited chance of survival despite its curative intent.[9] To conclude, this study showed no evidence of improved survival of married compared to non-married patients after having undergone surgery for oesophageal cancer.

List of abbreviations

CI: confidence interval

HR: hazard ratio

LISA: Longitudinal Integration Database for Health Insurance and Labour Market Studies

Authors' contributions: All authors have made substantial contributions to conception and design of the article, JL and PL have been responsible for the acquisition of the data, the statistical analyses and interpretation of the data were performed by NB, FM and AJ; 2) NB has drafted the manuscript, and all authors revised it critically for important intellectual content; and 3) all authors have given final approval of the version to be published.

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Table 1: Demographic, treatment, and tumour characteristics and mortality after oesophagectomy for cancer, categorised by marital status at the time of diagnosis.

	Marital status				Total
	Married	***Remarried***	***Previously Married****	***Never married***	
	N (%)	*N (%)*	*N (%)*	*N (%)*	N (%)
Total	334 (55.1)	56 (9.2)	137 (22.6)	79 (13.0)	606 (100.0)
Age					
<60 years	63 (18.9)	18 (32.1)	31 (22.6)	33 (41.8)	145 (23.9)
60-74 years	199 (59.6)	34 (60.7)	69 (50.4)	37 (46.8)	339 (55.9)
≥75 years	72 (21.6)	4 (7.1)	37 (27.0)	9 (11.4)	122 (20.1)
Sex					
Male	270 (80.8)	45 (80.4)	103 (75.2)	69 (87.3)	487 (80.4)
Female	64 (19.2)	11 (19.6)	34 (24.8)	10 (12.7)	119 (19.6)
Tumour stage					
0-I	69 (20.7)	12 (21.4)	23 (16.8)	10 (12.7)	114 (18.8)
II	100 (29.9)	12 (21.4)	42 (30.7)	24 (30.4)	178 (29.4)
III	125 (37.4)	26 (46.4)	58 (42.3)	36 (45.6)	245 (40.4)
IV	40 (12.0)	6 (10.7)	14 (10.2)	9 (11.4)	69 (11.4)
Histology					
Adenocarcinoma	263 (78.7)	43 (76.8)	96 (70.1)	55 (69.6)	457 (75.4)
Squamous cell carcinoma	71 (21.3)	13 (23.2)	41 (29.9)	24 (30.4)	149 (24.6)
Co-morbidity					
None	126 (37.7)	26 (46.4)	51 (37.2)	33 (41.8)	236 (38.9)
One	117 (35.0)	21 (37.5)	49 (35.8)	25 (31.7)	212 (35.0)
More than one	91 (27.3)	9 (16.1)	37 (27.0)	21 (26.6)	158 (26.1)
Surgical volume					
Low (<8 operations/year)	165 (49.4)	30 (53.6)	80 (58.4)	43 (54.4)	318 (52.5)
High (≥8 operations/year)	169 (50.6)	26 (46.4)	57 (41.6)	36 (45.6)	288 (47.5)
Post-operative complications					
None	215 (64.4)	35 (62.5)	85 (62.0)	46 (58.2)	381 (62.9)
One	85 (25.5)	14 (25.0)	28 (20.4)	17 (21.5)	144 (23.8)
More than one	34 (10.2)	7 (12.5)	24 (17.5)	16 (20.3)	81 (13.4)
Mortality, 90 days					
Within 90 days	27 (8.1)	5 (8.9)	11 (8.0)	5 (6.3)	48 (7.9)
Overall within 5 years	248 (74.3)	35 (62.5)	106 (77.4)	66 (83.5)	455 (75.1)
Conditional within 5 years**	221 (72.0)	30 (58.8)	95 (75.4)	61 (82.4)	407 (72.9)

**Previously married was defined as patients who have been married before but are living alone (after death of partner or divorce). **Conditional mortality: excluding first 90 days after surgery.*

Table 2: Multi-variable Cox regression models analysing the association between marital status at the time of diagnosis and mortality after oesophagectomy for cancer, expressed as hazard ratios (HR) with 95% confidence intervals (CI).

	Marital status			
	Married (Reference)	***Remarried HR (95% CI)***	***Previously married* HR (95% CI)***	***Never married HR (95% CI)***
Overall 5-year mortality				
Model 1	1	0.77 (0.54-1.10)	1.09 (0.87-1.37)	1.14 (0.87-1.49)
Model 2	1	0.79 (0.55-1.13)	0.95 (0.75-1.20)	1.03 (0.78-1.36)
Model 3	1	0.79 (0.55-1.13)	0.90 (0.71-1.15)	1.02 (0.77-1.35)
Conditional[a] overall 5-year mortality				
Model 1	1	0.73 (0.50-1.07)	1.11 (0.87-1.41)	1.18 (0.89-1.57)
Model 2	1	0.73 (0.50-1.08)	0.96 (0.75-1.23)	1.04 (0.78-1.38)
Model 3	1	0.74 (0.50-1.08)	0.93 (0.72-1.20)	1.05 (0.78-1.41)
Disease-specific[b] 5-year mortality				
Model 1	1	0.79 (0.56-1.13)	1.11 (0.88-1.40)	1.19 (0.89-1.57)
Model 2	1	0.80 (0.56-1.15)	0.96 (0.76-1.22)	1.03 (0.77-1.34)
Model 3	1	0.80 (0.56-1.15)	0.92 (0.72-1.17)	1.04 (0.78-1.39)
Conditional[a] disease- specific[b] 5-year mortality				
Model 1	1	0.75 (0.51-1.10)	1.12 (0.87-1.43)	1.21 (0.90-1.63)
Model 2	1	0.74 (0.50-1.09)	0.97 (0.76-1.25)	1.02 (0.76-1.38)
Model 3	1	0.74 (0.51-1.10)	0.94 (0.73-1.22)	1.05 (0.78-1.42)

*Values are expressed as hazard ratios (HR). *Previously married was defined as patients who have been married before but are living alone (after death of partner of divorce). [a]Conditional mortality: excluding first 90 days after surgery. [b]Disease-specific mortality: oesop*hageal or junctional cancer as underlying or contributing cause. *Model 1: unadjusted. Model 2: adjusted for sex, age, tumour stage. Model 3: adjusted for sex, age, tumour stage, histology, major complications, comorbidity and surgeon volume.*

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6,7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	6,7
Study size	10	Explain how the study size was arrived at	6,7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	7

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6, 8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	9, Table 1
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross-sectional study—Report numbers of outcome events or summary measures	-
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9, Table 2
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3-4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

STUDY PROTOCOL

Project title:

Marital status in relation to 5-year survival after oesophageal cancer surgery (SECC)

Collaborators (in alphabetic order)

Anna, Asif, Fredrik, Jesper (last author), Nele (first author), Pernilla, Rickard.

Objectives

To clarify the potential effects of the socio-economic factor marital status and changes of marital status on the overall survival within 5 years after oesophageal cancer surgery, using the SECC database linked to the LISA-registry.

Background

In some studies, marital status and patient's partner's level of education has influenced choice of, and adherence to, treatment [1-3].
Little is known about the specific impact of marital status on the outcome after oesophageal cancer surgery. Several studies have explored determinants on short-term survival (in-hospital or 30-days), after oesophageal cancer *diagnosis* [4-10]. Other studies have investigated determinants for long-term survival after oesophageal cancer *surgery* [11-15], but most of these prognostic studies focused on clinical and tumor-related characteristics. Only a minority of these studies included determinants used to describe the socio-economic status of the patient (e.g. ethnicity, marital status, education status, smoking, and ´deprived´ socio-economic status) [4, 10, 12, 16-19]. Taken together, surprisingly little is known about the specific impact of marital status on survival after oesophageal cancer surgery.

Methods

Data collection

The following databases are linked and will be used:

- SECC-database (Swedish Esophageal and Cardia Cancer database): an all-encompassing, nationwide research database that includes almost all esophageal and cardia cancer patients in Sweden treated with surgery. SECC contains detailed patient file-based information about tumor pathology and localization, TNM stage, surgical procedures, techniques and complications, and additionally contains repeated health-related quality of life (HRQL) assessments and clinical (prognostic)

factors such as BMI. The SECC register was initiated in April 2001 and since then until December 2005 about 90% of all surgically treated esophageal cancer patients are included. The almost complete national coverage and the detailed prospective data collection and objective manual review of each case ensure a good validity. The patients are followed up at least 5 years for survival (up to 2012).

- LISA-registry: includes data on marital status and changes in such status.
- The Causes of Death Registry: includes dates and underlying causes of all deaths among persons residing in the country, independently of where they died (including abroad). Only a small number of deaths do not have a recorded cause of death, e.g. 0.5% in Sweden. This enables us to study disease-specific mortality.
- Patient Registry: will be used to collect data on comorbidities based on discharge diagnoses, surgical procedures, and hospitalisation dates. The Swedish Patient Registry was 85% complete in 1983 and 100% in 1987 and onwards. The Patient Registry provides us with possibilities to better adjust the results for comorbidities.

Study design

This prospective population-based cohort study will be based on the SECC registry (N=616), of patients who underwent oesophageal resection in April 2001 to December 2005, and followed up for 5 years. The specific impact of marital status on long-term survival after surgery will be evaluated.

The data from the available registries will be used for each cohort member, including co-morbidities, operations, cancer, date of death, cause of death, etc.

Study exposures

- Marital status one calendar year before surgery: based on registered marriages; divided in 4 groups (based on data since 1968 and onwards):
  i. “Never married”,
  ii. “Married” (= no divorces/never widow),
  iii. “Remarried” (thus previously divorced or widowed),
  iv. “Living as single but married before” (thus previously divorced or widowed).
- Dynamic changes after operation: possible second time-point to measure exposure - If important changes between operation and death/end of 5y follow-up: re-evaluate time-point of exposure.

Study outcome

1) Overall mortality up to 5 years after oesophagectomy for oesophageal or cardia cancer.
2) Overall mortality up to 5 years after oesophagectomy for oesophageal or cardia cancer, after exclusion of the first 90 days after surgery.

3) Disease-specific mortality up to 5 years after oesophagectomy for oesophageal or cardia cancer.
4) Disease-specific mortality up to 5 years after oesophagectomy for oesophageal or cardia cancer, after exclusion of the first 90 days after surgery.
5) Potential outcome: 90-days overall mortality after oesophagectomy for oesophageal or cardia cancer (possible power problem)

The last surgical resections were performed in 2005, so all patients have sufficiently long follow-up.

Most important possible confounders

(1) Tumour stage: based on TNM classification (categorised in 4 groups: 0-I; II, and III, IV. Stage III=T3N1 is largest group ±60%),

(2) Comorbidities: combined in 3 groups: none – one –more than one; or 2 groups if insufficient statistical power; 6 possible comorbidities: diabetes, cardiovascular disease, pulmonary disease, liver disease, renal failure, other cancer. Data should be complete (not reported = none), but patients can have more than 1 co-morbidity. In former SECC studies hypertension and "other" were also reported, but will not be included in this binary variable.

(3) Age (at surgery): 3 groups: <60y, 60-74y, +75y or continuous.

(4) Sex (adjustment might lead to power problem; only 20% female)

(5) Histological type (adenocarcinoma - 76% or squamous cell carcinoma – 24%),

(6) Complications (surgical or medical; combined in 3 groups: none – one –more than one; or 2 groups if insufficient statistical power. In SECC database: 9 types of surgical complications and 10 medical) (Not in 90 days survival)

(7) Education (depending on SECC study Education)

(8) Surgery volume: 2 equal sized groups

Statistical analyses

The adjusted associations between marital status and survival after oesophageal cancer surgery will be analysed by means of multivariable Cox regression analyses (hazard ratio's) with 95% confidence intervals.
Kaplan-Meier method will be used to present mortality, and comparison between survival curves in various exposure groups will be tested with the log-rank test.

Interaction analysis or separate stratified analysis will be conducted for patients with tumour stage III, histological type (possibly not presented in study) and sex.

Three models will be used:

- Model 1: crude model
- Model 2: age, sex, TNM,
- Model 3: all variables (except for complications in short term/90d mortality)

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Marital status and survival after oesophageal cancer surgery: A population-based nationwide cohort study in Sweden

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Marital status and survival after oesophageal cancer surgery: A population-based nationwide cohort study in Sweden

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Objectives: A beneficial effect of being married on survival has been shown for several cancer types, but is unclear for oesophageal cancer. The objective of this study was to clarify the potential influence of marital status on the overall and disease-specific survival after curatively intended treatment of oesophageal cancer using a nationwide population-based design, taking into account the known major prognostic variables.

Design: Prospective, population-based cohort

Setting: All Swedish hospitals performing surgery for oesophageal cancer during 2001-2005

Participants: This study included 90% of all oesophageal or junctional cancer patients who underwent surgical resection in Sweden in 2001-2005, with follow-up until death or end of study period (2012).

Primary and secondary outcome measures: Cox regression was used to estimate associations between marital status and 5-year overall and disease-specific mortality, expressed as hazard ratios (HRs) with 95% confidence intervals (CIs), with adjustment for sex, age, tumour stage, histological type, complications, comorbidities and annual surgeon volume.

Results: Of all 606 included patients (80.4% male), 55.1% were married, 9.2% remarried, 22.6% previously married, and 13.0% never married. Compared to married patients, never married (HR 1.02, 95% CI 0.77-1.35), previously married (HR 0.90, 95% CI 0.71-1.15) and remarried patients (HR 0.79, 95% CI 0.55-1.13) had no increased overall 5-year mortality. The corresponding HRs for disease-specific survival, and after excluding the initial 90 days of surgery were similar to the HRs of overall survival.

Conclusions: This study showed no evidence of a better 5-year survival in married compared to non-married patients undergoing surgery for oesophageal cancer.

Keywords: Socioeconomic factors; civil status; health status disparities; prognosis; outcome; oesophagectomy.

Strengths and limitations of this study

Patients with oesophageal cancer have a poor prognosis, even those patients eligible for curative surgery (oesophagectomy).

Being married has been shown to be a marker of better survival after cancer in general and of specific cancer types, but this has not been studied yet for oesophageal cancer.

This nationwide population-based study did not find any evidence that marital status influences long-term survival after oesophagectomy for oesophageal cancer, even after taking into account the known major prognostic variables.

The absence of a clear association between marital status and long-term survival, might be a false negative result related to the relatively small sample size. Yet, it is also possible that the beneficial effect of being married is non-existent for oesophageal cancer.

The main strength of this study is the population-based design with almost complete coverage, and complete follow-up of all patients operated in Sweden for oesophageal cancer in 2001-2005. Moreover, complete data on a large variety of variables enabled adjustment for known prognostic factors. Yet, among limitations are that influence of other confounders or residual confounding by the variables adjusted for, can never be ruled out. The statistical power was however limited to detect weak associations.

Introduction

The potential influence of marital status on health and life expectancy has since long been a matter of discussion.[1 2] Being married has been shown to be a marker of better survival after cancer in general and of specific cancer types,[3] and the survival discrepancy between married and non-married cancer patients has been claimed to be increasing over time.[4] Having a partner is believed to lead to a healthier lifestyle, e.g. regarding tobacco and alcohol use, physical activity, and social support, and can also influence the choice and adherence to treatment, as well as the time elapsing between early symptoms and a confirmed cancer diagnosis.[2] However, little is known about such influence on oesophageal cancer. Only a few studies have investigated the potential role of socio-economic factors in the prognosis of oesophageal cancer.[5 6] A previous study from our group showed limited evidence of an association between lower education and worse long-term survival in operated patients with oesophageal cancer (only significant difference in patients with tumour stage IV).[7] A recent American study showed that married patients were more likely to be diagnosed with localised disease, and received treatment with curative intent more frequently than non-married patients, also showing a better overall survival.[8] However, patients with oesophageal cancer have an overall very poor prognosis, mainly due to advanced tumour at the time of diagnosis, and only a minority is eligible for curatively intended treatment.[9] Surgery (oesophagectomy) plays a main role in the curatively intended therapy for most oesophageal cancer.[9] The objective of this study was to clarify the potential influence of marital status on the overall and disease-specific survival after curatively intended treatment of oesophageal cancer using a nationwide population-based design, taking into account the known major prognostic variables.

Methods

Participants

This was a population-based prospective cohort study, which included 90% of all patients with oesophageal or gastroesophageal junctional cancer treated with surgery, the treatment of choice for potentially curable patients in Sweden during the study period, April 2, 2001 and December 31, 2005. Follow-up for survival ended in August 31, 2012. The median duration of follow-up was 619 days. From the full study cohort of 616 patients, 10 patients were excluded because of missing values for marital status, leaving 606 patients for final analysis. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden. Informed consent was obtained from each patient before inclusion in the study.

Data sources

The organization of the comprehensive nationwide network of clinicians that participated in the data collection has been described elsewhere, and most parts of the design of this clinical cohort study has been presented in detail.[10 11] In brief, information about tumour stage, histology and localization, surgical procedures and complications were prospectively collected for all patients through scrutiny of relevant medical records from 174 hospital departments in Sweden.[11] In September 2012, the cohort was linked to the Patient Register, the Causes of Death Register, and the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA). The Patient Register includes all in-hospital care and outpatient specialist care in Sweden, including codes for diagnoses, surgical procedures and comorbidity with a high level of validity.[12] The Causes of Death Register contains information on date and cause of death for all deceased Swedish residents since 1952.[13] The LISA came into use in 1990 and includes a large variety of variables, including socio-economic status, marital status and work history.[14]

Study exposure and outcome

Four mutually exclusive categories for marital status during the calendar year before surgery were: married (never divorced or widowed), remarried (after widowhood or divorce), previously married (widowed or divorced), and never married. An additional analysis was performed grouping all patients in 2 groups: the currently married (married and remarried) and the not currently married patients (previously married and never married).

The main outcome measure was overall mortality (including all causes of death) up to 5 years after oesophagectomy for oesophageal cancer. Other outcomes were mortality within 5 years after surgery: 1) after exclusion of deaths within first 90 days of surgery (defined as conditional mortality), 2) with oesophageal cancer as an underlying or contributing cause of death (disease-specific mortality, or death related to oesophageal cancer), and 3) the combination of conditional and disease-specific mortality.

Statistical analyses

The association between marital status and mortality was analysed by means of multivariable Cox regression and expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). The married group was used as reference category. Three regression models were employed: 1) without any adjustments (crude model), 2) adjusted for sex, age and tumour stage (basic model), and 3) further adjusted for histological tumour type, major complications, comorbidities and annual surgeon volume of oesophagectomy for cancer (fully adjusted model)[15]. Due to the limited effect on survival, as shown in a previous study,[7] educational level was not included in the analyses. Age was categorised as <60, 60-74, or ≥75 years, and tumour stage as 0-I, II, III, or IV according to the sixth edition of the UICC (Union Internationale Contre le Cancer)[16]. Histological type was subdivided in adenocarcinoma and squamous cell carcinoma. Number of major

complications (within 30 days of surgery) and comorbidities were both categorised as none, one or more than one, as described previously.[11 17] Surgeon volume was categorised into two equally sized groups based on the median annual number of oesophagectomies per surgeon (<8 or ≥8).[15] To assess effect modification, stratified survival analyses were performed for tumour stage and histological type using the same regression models, without adjustment for the stratifying variable.

Results

Patients

Characteristics of the 606 study patients are described in Table 1. At the time of surgery, 334 patients were married (55.1%), 56 were remarried (9.2%), 137 were married previously (22.6%), and 79 patients were never married (13.0%). Compared to the married group, the re-married and never married groups were younger (Table 1). The largest proportion of male patients was found in the never married group (87.3%) and the smallest in the previously married group (75.2%). Tumours were as likely to be of an advanced stage (stage IV) in all four groups (range 10.2-12.0%), but fewer early tumours (stage I) were found in the never married group (12.7%) compared to the married group (20.7%). Squamous cell carcinoma was found more frequently in the previously married (29.9%) and never married groups (30.4%), compared to the married (21.3%) and remarried group (23.2%). Of all patients, 53.6-62.8% had co-morbidity at time of surgery, which was least in the remarried group. Married patients were least likely to have been operated on by surgeons with a low annual volume, compared to previously married patients (49.4% versus 58.4%). There were post-operative complications in 35.6-41.8% of the patients. In total, 455 (75.1%) patients died within 5 years

of surgery, of whom 429 (94.3%) had oesophageal cancer as an underlying or contributing cause of death.

Marital status and mortality

The proportions of overall and conditional 5-year mortality were highest in the never married group (Table 1). The absolute 5-year survival rates for married, remarried, previously married, and never married patients were 25.7%, 37.5%, 22.6%, and 16.5% respectively. Short-term mortality was slightly lower in the never married group (6.3% versus 8.1-8.9% in the other groups) (Table 1). The HRs for mortality after oesophagectomy according to marital status are presented in Table 2. Compared with the married group, no increased HRs of mortality were found in the other marital status groups. The fully adjusted HR of overall 5-year mortality was similar in never married patients compared to married patients (HR 1.02, 95% CI 0.77-1.35), and the corresponding HRs were very similar for disease-specific survival and survival after excluding the initial 90 days after surgery (Table 2). The fully adjusted HR for the various definitions of 5-year mortality was lower in the remarried group (HR ranging from 0.74 to 0.80) and in the previously married group (HR ranging from 0.90 to 0.94), but no statistically significant associations were identified (Table 2). The results for disease-specific survival, and for overall or disease-specific survival after excluding the initial 90 days of surgery, were all similar to the HRs of overall survival (Table 2). The fully adjusted HR for overall mortality in the not currently married group is 0.98 (95% CI 0.80-1.19) compared to the currently married group.

The fully adjusted subgroup analyses for all-cause and disease-specific mortality by tumour stage and histological type showed similar results as the main analyses, and no statistically significant associations were identified (data not shown).

Discussion

This study did not show any improved survival among married oesophageal cancer patients undergoing oesophagectomy compared to other marital status groups after adjustment for several prognostic variables.

The main strength of this study is the population-based design with almost complete coverage, and complete follow-up of all patients operated in Sweden for oesophageal cancer in 2001-2005. Moreover, complete data on a large variety of variables enabled adjustment for known prognostic factors. Yet, among limitations are that influence of other confounders or residual confounding by the variables adjusted for, can never be ruled out. The statistical power was limited to detect weak associations, but large effects of marital status on survival in this cohort of cancer patients are unlikely. Changes in marital status after surgery were considered of limited impact on the results, since these only occurred in 3.3% of all patients. Moreover, we did not have data on co-habiting without being married, or extent of social networks, which could have led to an underestimation of potential associations. Despite the multi-centre design, differences between hospitals and treatment are unlikely to have influenced any associations between marital status and survival. Socio-economic variables such as ethnicity and income-level may have an impact on survival as well, yet the underlying mechanisms are different. Socio-economic inequality is a measure for life-time differences, whereas marital status reflects social support at the time of the disease.

The absence of a clear association between marital status and long-term survival, such as found for some other cancer types and oesophageal cancer in the large American study mentioned earlier (including all diagnosed patients),[3 8] might be a false negative result related to the relatively small sample size. Yet, it is also possible that the beneficial effect of being

married is non-existent for oesophageal cancer receiving surgery, which has a limited chance of survival despite its curative intent.[9] Although being married might not influence the survival, social support might be beneficial for other reasons, including health-related quality of life in these patients. To conclude, this study showed no evidence of improved survival of married compared to non-married patients after having undergone surgery for oesophageal cancer.

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Data sharing statement: No additional data available

List of abbreviations

CI: confidence interval

HR: hazard ratio

LISA: Longitudinal Integration Database for Health Insurance and Labour Market Studies

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Table 1: Demographic, treatment, and tumour characteristics and mortality after oesophagectomy for cancer, categorised by marital status at the time of diagnosis.

	Marital status				Total
	Married	*Remarried*	*Previously Married**	*Never married*	
	N (%)	*N (%)*	*N (%)*	*N (%)*	N (%)
Total	334 (55.1)	56 (9.2)	137 (22.6)	79 (13.0)	606 (100.0)
Age					
<60 years	63 (18.9)	18 (32.1)	31 (22.6)	33 (41.8)	145 (23.9)
60-74 years	199 (59.6)	34 (60.7)	69 (50.4)	37 (46.8)	339 (55.9)
≥75 years	72 (21.6)	4 (7.1)	37 (27.0)	9 (11.4)	122 (20.1)
Sex					
Male	270 (80.8)	45 (80.4)	103 (75.2)	69 (87.3)	487 (80.4)
Female	64 (19.2)	11 (19.6)	34 (24.8)	10 (12.7)	119 (19.6)
Tumour stage					
0-I	69 (20.7)	12 (21.4)	23 (16.8)	10 (12.7)	114 (18.8)
II	100 (29.9)	12 (21.4)	42 (30.7)	24 (30.4)	178 (29.4)
III	125 (37.4)	26 (46.4)	58 (42.3)	36 (45.6)	245 (40.4)
IV	40 (12.0)	6 (10.7)	14 (10.2)	9 (11.4)	69 (11.4)
Histology					
Adenocarcinoma	263 (78.7)	43 (76.8)	96 (70.1)	55 (69.6)	457 (75.4)
Squamous cell carcinoma	71 (21.3)	13 (23.2)	41 (29.9)	24 (30.4)	149 (24.6)
Co-morbidity					
None	126 (37.7)	26 (46.4)	51 (37.2)	33 (41.8)	236 (38.9)
One	117 (35.0)	21 (37.5)	49 (35.8)	25 (31.7)	212 (35.0)
More than one	91 (27.3)	9 (16.1)	37 (27.0)	21 (26.6)	158 (26.1)
Surgical volume					
Low (<8 operations/year)	165 (49.4)	30 (53.6)	80 (58.4)	43 (54.4)	318 (52.5)
High (≥8 operations/year)	169 (50.6)	26 (46.4)	57 (41.6)	36 (45.6)	288 (47.5)
Post-operative complications					
None	215 (64.4)	35 (62.5)	85 (62.0)	46 (58.2)	381 (62.9)
One	85 (25.5)	14 (25.0)	28 (20.4)	17 (21.5)	144 (23.8)
More than one	34 (10.2)	7 (12.5)	24 (17.5)	16 (20.3)	81 (13.4)
Mortality, 90 days					
Within 90 days	27 (8.1)	5 (8.9)	11 (8.0)	5 (6.3)	48 (7.9)
Overall within 5 years	248 (74.3)	35 (62.5)	106 (77.4)	66 (83.5)	455 (75.1)
Conditional within 5 years**	221 (72.0)	30 (58.8)	95 (75.4)	61 (82.4)	407 (72.9)

**Previously married was defined as patients who have been married before but are living alone (after death of partner or divorce). **Conditional mortality: excluding first 90 days after surgery.*

Table 2: Multi-variable Cox regression models analysing the association between marital status at the time of diagnosis and mortality after oesophagectomy for cancer, expressed as hazard ratios (HR) with 95% confidence intervals (CI).

	Marital status			
	Married (Reference)	***Remarried HR (95% CI)***	***Previously married* HR (95% CI)***	***Never married HR (95% CI)***
Overall 5-year mortality				
Model 1	1	0.77 (0.54-1.10)	1.09 (0.87-1.37)	1.14 (0.87-1.49)
Model 2	1	0.79 (0.55-1.13)	0.95 (0.75-1.20)	1.03 (0.78-1.36)
Model 3	1	0.79 (0.55-1.13)	0.90 (0.71-1.15)	1.02 (0.77-1.35)
Conditional[a] overall 5-year mortality				
Model 1	1	0.73 (0.50-1.07)	1.11 (0.87-1.41)	1.18 (0.89-1.57)
Model 2	1	0.73 (0.50-1.08)	0.96 (0.75-1.23)	1.04 (0.78-1.38)
Model 3	1	0.74 (0.50-1.08)	0.93 (0.72-1.20)	1.05 (0.78-1.41)
Disease-specific[b] 5-year mortality				
Model 1	1	0.79 (0.56-1.13)	1.11 (0.88-1.40)	1.19 (0.89-1.57)
Model 2	1	0.80 (0.56-1.15)	0.96 (0.76-1.22)	1.03 (0.77-1.34)
Model 3	1	0.80 (0.56-1.15)	0.92 (0.72-1.17)	1.04 (0.78-1.39)
Conditional[a] disease- specific[b] 5-year mortality				
Model 1	1	0.75 (0.51-1.10)	1.12 (0.87-1.43)	1.21 (0.90-1.63)
Model 2	1	0.74 (0.50-1.09)	0.97 (0.76-1.25)	1.02 (0.76-1.38)
Model 3	1	0.74 (0.51-1.10)	0.94 (0.73-1.22)	1.05 (0.78-1.42)

*Values are expressed as hazard ratios (HR). *Previously married was defined as patients who have been married before but are living alone (after death of partner of divorce). [a]Conditional mortality: excluding first 90 days after surgery. [b]Disease-specific mortality: oesop*hageal or junctional cancer as underlying or contributing cause. *Model 1: unadjusted. Model 2: adjusted for sex, age, tumour stage. Model 3: adjusted for sex, age, tumour stage, histology, major complications, comorbidity and surgeon volume.*

Marital status and survival after oesophageal cancer surgery:

A population-based nationwide cohort study in Sweden

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Abstract (word count: 250)

Objectives: A beneficial effect of being married on survival has been shown for several cancer types, but is unclear for oesophageal cancer. The objective of this study was to clarify the potential influence of marital status on the overall and disease-specific survival after curatively intended treatment of oesophageal cancer using a nationwide population-based design, taking into account the known major prognostic variables.

Design: Prospective, population-based cohort

Setting: All Swedish hospitals performing surgery for oesophageal cancer during 2001-2005

Participants: This study included 90% of all oesophageal or junctional cancer patients who underwent surgical resection in Sweden in 2001-2005, with follow-up until death or end of study period (2012).

Primary and secondary outcome measures: Cox regression was used to estimate associations between marital status and 5-year overall and disease-specific mortality, expressed as hazard ratios (HRs) with 95% confidence intervals (CIs), with adjustment for sex, age, tumour stage, histological type, complications, comorbidities and annual surgeon volume.

Results: Of all 606 included patients (80.4% male), 55.1% were married, 9.2% remarried, 22.6% previously married, and 13.0% never married. Compared to married patients, never married (HR 1.02, 95% CI 0.77-1.35), previously married (HR 0.90, 95% CI 0.71-1.15) and remarried patients (HR 0.79, 95% CI 0.55-1.13) had no increased overall 5-year mortality. The corresponding HRs for disease-specific survival, and after excluding the initial 90 days of surgery were similar to the HRs of overall survival.

Conclusions: This study showed no evidence of a better 5-year survival in married compared to non-married patients undergoing surgery for oesophageal cancer.

Keywords: Socioeconomic factors; civil status; health status disparities; prognosis; outcome; oesophagectomy.

Strengths and limitations of this study

Patients with oesophageal cancer have a poor prognosis, even those patients eligible for curative surgery (oesophagectomy).

Being married has been shown to be a marker of better survival after cancer in general and of specific cancer types, but this has not been studied yet for oesophageal cancer.

This nationwide population-based study did not find any evidence that marital status influences long-term survival after oesophagectomy for oesophageal cancer, even after taking into account the known major prognostic variables.

The absence of a clear association between marital status and long-term survival, might be a false negative result related to the relatively small sample size. Yet, it is also possible that the beneficial effect of being married is non-existent for oesophageal cancer.

The main strength of this study is the population-based design with almost complete coverage, and complete follow-up of all patients operated in Sweden for oesophageal cancer in 2001-2005. Moreover, complete data on a large variety of variables enabled adjustment for known prognostic factors. Yet, among limitations are that influence of other confounders or residual confounding by the variables adjusted for, can never be ruled out. The statistical power was however limited to detect weak associations.

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Competing interests: The authors declare that they have no conflict of interest. The Swedish Research Council (SIMSAM) and the Swedish Cancer Society, the funding sources had no role in the design and conduct of the study, collection, management, analysis and interpretation of the data, or preparation review or approval of the manuscript.

Data sharing statement: There is no additional data available

Introduction

The potential influence of marital status on health and life expectancy has since long been a matter of discussion.[1 2] Being married has been shown to be a marker of better survival after cancer in general and of specific cancer types,[3] and the survival discrepancy between married and non-married cancer patients has been claimed to be increasing over time.[4] Having a partner is believed to lead to a healthier lifestyle, e.g. regarding tobacco and alcohol use, physical activity, and social support, and can also influence the choice and adherence to treatment, as well as the time elapsing between early symptoms and a confirmed cancer diagnosis.[2] However, little is known about such influence on oesophageal cancer. Only a few studies have investigated the potential role of socio-economic factors in the prognosis of oesophageal cancer.[5 6] A previous study from our group showed limited evidence of an association between lower education and worse long-term survival in operated patients with oesophageal cancer (only significant difference in patients with tumour stage IV).[7] A recent American study showed that married patients were more likely to be diagnosed with localised disease, and received treatment with curative intent more frequently than non-married patients, also showing a better overall survival.[8] However, patients with oesophageal cancer have an overall very poor prognosis, mainly due to advanced tumour at the time of diagnosis, and only a minority is eligible for curatively intended treatment.[9] Surgery (oesophagectomy) plays a main role in the curatively intended therapy for most oesophageal cancer~~is the cornerstone in radical therapy, and is often combined with oncological therapy~~.[9] The objective of this study was to clarify the potential influence of marital status on the overall and disease-specific survival after curatively intended treatment of oesophageal cancer using a nationwide population-based design, taking into account the known major prognostic variables.

Methods

Participants

This was a population-based prospective cohort study, which included 90% of all patients with oesophageal or gastroesophageal junctional cancer treated with surgery, the treatment of choice for potentially curable patients in Sweden during the study period, April 2, 2001 and December 31, 2005. Follow-up for survival ended in August 31, 2012. The median duration of follow-up was 619 days. From the full study cohort of 616 patients, 10 patients were excluded because of missing values for marital status, leaving 606 patients for final analysis. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden. Informed consent was obtained from each patient before inclusion in the study.

Data sources

The organization of the comprehensive nationwide network of clinicians that participated in the data collection has been described elsewhere, and most parts of the design of this clinical cohort study has been presented in detail.[10 11] In brief, information about tumour stage, histology and localization, surgical procedures and complications were prospectively collected for all patients through scrutiny of relevant medical records from 174 hospital departments in Sweden.[11] In September 2012, the cohort was linked to the Patient Register, the Causes of Death Register, and the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA). The Patient Register includes all in-hospital care and outpatient specialist care in Sweden, including codes for diagnoses, surgical procedures and comorbidity with a high level of validity.[12] The Causes of Death Register contains information on date and cause of death for all deceased Swedish residents since 1952.[13] The LISA came into use in 1990 and includes a large variety of variables, including socio-economic status, marital status and work history.[14]

Study exposure and outcome

Four mutually exclusive categories for marital status during the calendar year before surgery were: married (never divorced or widowed), remarried (after widowhood or divorce), previously married (widowed or divorced), and never married. An additional analysis was performed grouping all patients in 2 groups: the currently married (married and remarried) and the not currently married patients (previously married and never married).

The main outcome measure was overall mortality (including all causes of death) up to 5 years after oesophagectomy for oesophageal cancer. Other outcomes were mortality within 5 years after surgery: 1) after exclusion of deaths within first 90 days of surgery (defined as conditional mortality), 2) with oesophageal cancer as an underlying or contributing cause of death (disease-specific mortality, or death related to oesophageal cancer), and 3) the combination of conditional and disease-specific mortality.

Statistical analyses

The association between marital status and mortality was analysed by means of multivariable Cox regression and expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). The married group was used as reference category. Three regression models were employed: 1) without any adjustments (crude model), 2) adjusted for sex, age and tumour stage (basic model), and 3) further adjusted for histological tumour type, major complications, comorbidities and annual surgeon volume of oesophagectomy for cancer (fully adjusted model)[15]. Due to the limited effect on survival, as shown in a previous study,[7] educational level was not included in the analyses. Age was categorised as <60, 60-74, or ≥75 years, and tumour stage as 0-I, II, III, or IV according to the sixth edition of the UICC (Union Internationale Contre le Cancer)[16]. Histological type was subdivided in adenocarcinoma and squamous cell carcinoma. Number of major

complications (within 30 days of surgery) and comorbidities were both categorised as none, one or more than one, as described previously.[11 17] Surgeon volume was categorised into two equally sized groups based on the median annual number of oesophagectomies per surgeon (<8 or ≥8).[15] To assess effect modification, stratified survival analyses were performed for tumour stage and histological type using the same regression models, without adjustment for the stratifying variable.

Results

Patients

Characteristics of the 606 study patients are described in Table 1. At the time of surgery, 334 patients were married (55.1%), 56 were remarried (9.2%), 137 were married previously (22.6%), and 79 patients were never married (13.0%). Compared to the married group, the re-married and never married groups were younger (Table 1). The largest proportion of male patients was found in the never married group (87.3%) and the smallest in the previously married group (75.2%). Tumours were as likely to be of an advanced stage (stage IV) in all four groups (range 10.2-12.0%), but fewer early tumours (stage I) were found in the never married group (12.7%) compared to the married group (20.7%). Squamous cell carcinoma was found more frequently in the previously married (29.9%) and never married groups (30.4%), compared to the married (21.3%) and remarried group (23.2%). Of all patients, 53.6-62.8% had co-morbidity at time of surgery, which was least in the remarried group. Married patients were least likely to have been operated on by surgeons with a low annual volume, compared to previously married patients (49.4% versus 58.4%). There were post-operative complications in 35.6-41.8% of the patients. In total, 455 (75.1%) patients died within 5 years

of surgery, of whom 429 (94.3%) had oesophageal cancer as an underlying or contributing cause of death.

Marital status and mortality

The proportions of overall and conditional 5-year mortality were highest in the never married group (Table 1). The absolute 5-year survival rates for married, remarried, previously married, and never married patients were 25.7%, 37.5%, 22.6%, and 16.5% respectively. Short-term mortality was slightly lower in the never married group (6.3% versus 8.1-8.9% in the other groups) (Table 1). The HRs for mortality after oesophagectomy according to marital status are presented in Table 2. Compared with the married group, no increased HRs of mortality were found in the other marital status groups. The fully adjusted HR of overall 5-year mortality was similar in never married patients compared to married patients (HR 1.02, 95% CI 0.77-1.35), and the corresponding HRs were very similar for disease-specific survival and survival after excluding the initial 90 days after surgery (Table 2). The fully adjusted HR for the various definitions of 5-year mortality was lower in the remarried group (HR ranging from 0.74 to 0.80) and in the previously married group (HR ranging from 0.90 to 0.94), but no statistically significant associations were identified (Table 2). The results for disease-specific survival, and for overall or disease-specific survival after excluding the initial 90 days of surgery, were all similar to the HRs of overall survival (Table 2). The fully adjusted HR for overall mortality in the not currently married group is 0.98 (95% CI 0.80-1.19) compared to the currently married group.

The fully adjusted subgroup analyses for all-cause and disease-specific mortality by tumour stage and histological type showed similar results as the main analyses, and no statistically significant associations were identified (data not shown).

Discussion

This study did not show any improved survival among married oesophageal cancer patients undergoing oesophagectomy compared to other marital status groups after adjustment for several prognostic variables.

The main strength of this study is the population-based design with almost complete coverage, and complete follow-up of all patients operated in Sweden for oesophageal cancer in 2001-2005. Moreover, complete data on a large variety of variables enabled adjustment for known prognostic factors. Yet, among limitations are that influence of other confounders or residual confounding by the variables adjusted for, can never be ruled out. The statistical power was limited to detect weak associations, but large effects of marital status on survival in this cohort of cancer patients are unlikely. Changes in marital status after surgery were considered of limited impact on the results, since these only occurred in 3.3% of all patients. Moreover, we did not have data on co-habiting without being married, or extent of social networks, which could have led to an underestimation of potential associations. Despite the multi-centre design, differences between hospitals and treatment are unlikely to have influenced any associations between marital status and survival. Socio-economic variables such as ethnicity and income-level may have an impact on survival as well, yet the underlying mechanisms are different. Socio-economic inequality is a measure for life-time differences, whereas marital status reflects social support at the time of the disease.

The absence of a clear association between marital status and long-term survival, such as found for some other cancer types and oesophageal cancer in the large American study mentioned earlier (including all diagnosed patients),[3 8] might be a false negative result related to the relatively small sample size. Yet, it is also possible that the beneficial effect of being

married is non-existent for oesophageal cancer receiving surgery, which has a limited chance of survival despite its curative intent.[9] Although being married might not influence the survival, social support might be beneficial for other reasons, including health-related quality of life in these patients. To conclude, this study showed no evidence of improved survival of married compared to non-married patients after having undergone surgery for oesophageal cancer.

List of abbreviations

CI: confidence interval

HR: hazard ratio

LISA: Longitudinal Integration Database for Health Insurance and Labour Market Studies

Authors' contributions: All authors have made substantial contributions to conception and design of the article, JL and PL have been responsible for the acquisition of the data, the statistical analyses and interpretation of the data were performed by NB, FM and AJ; 2) NB has drafted the manuscript, and all authors revised it critically for important intellectual content; and 3) all authors have given final approval of the version to be published.

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Table 1: Demographic, treatment, and tumour characteristics and mortality after oesophagectomy for cancer, categorised by marital status at the time of diagnosis.

	Marital status				Total
	Married	***Remarried***	***Previously Married****	***Never married***	
	N (%)	*N (%)*	*N (%)*	*N (%)*	N (%)
Total	334 (55.1)	56 (9.2)	137 (22.6)	79 (13.0)	606 (100.0)
Age					
<60 years	63 (18.9)	18 (32.1)	31 (22.6)	33 (41.8)	145 (23.9)
60-74 years	199 (59.6)	34 (60.7)	69 (50.4)	37 (46.8)	339 (55.9)
≥75 years	72 (21.6)	4 (7.1)	37 (27.0)	9 (11.4)	122 (20.1)
Sex					
Male	270 (80.8)	45 (80.4)	103 (75.2)	69 (87.3)	487 (80.4)
Female	64 (19.2)	11 (19.6)	34 (24.8)	10 (12.7)	119 (19.6)
Tumour stage					
0-I	69 (20.7)	12 (21.4)	23 (16.8)	10 (12.7)	114 (18.8)
II	100 (29.9)	12 (21.4)	42 (30.7)	24 (30.4)	178 (29.4)
III	125 (37.4)	26 (46.4)	58 (42.3)	36 (45.6)	245 (40.4)
IV	40 (12.0)	6 (10.7)	14 (10.2)	9 (11.4)	69 (11.4)
Histology					
Adenocarcinoma	263 (78.7)	43 (76.8)	96 (70.1)	55 (69.6)	457 (75.4)
Squamous cell carcinoma	71 (21.3)	13 (23.2)	41 (29.9)	24 (30.4)	149 (24.6)
Co-morbidity					
None	126 (37.7)	26 (46.4)	51 (37.2)	33 (41.8)	236 (38.9)
One	117 (35.0)	21 (37.5)	49 (35.8)	25 (31.7)	212 (35.0)
More than one	91 (27.3)	9 (16.1)	37 (27.0)	21 (26.6)	158 (26.1)
Surgical volume					
Low (<8 operations/year)	165 (49.4)	30 (53.6)	80 (58.4)	43 (54.4)	318 (52.5)
High (≥8 operations/year)	169 (50.6)	26 (46.4)	57 (41.6)	36 (45.6)	288 (47.5)
Post-operative complications					
None	215 (64.4)	35 (62.5)	85 (62.0)	46 (58.2)	381 (62.9)
One	85 (25.5)	14 (25.0)	28 (20.4)	17 (21.5)	144 (23.8)
More than one	34 (10.2)	7 (12.5)	24 (17.5)	16 (20.3)	81 (13.4)
Mortality, 90 days					
Within 90 days	27 (8.1)	5 (8.9)	11 (8.0)	5 (6.3)	48 (7.9)
Overall within 5 years	248 (74.3)	35 (62.5)	106 (77.4)	66 (83.5)	455 (75.1)
Conditional within 5 years**	221 (72.0)	30 (58.8)	95 (75.4)	61 (82.4)	407 (72.9)

**Previously married was defined as patients who have been married before but are living alone (after death of partner or divorce). **Conditional mortality: excluding first 90 days after surgery.*

Table 2: Multi-variable Cox regression models analysing the association between marital status at the time of diagnosis and mortality after oesophagectomy for cancer, expressed as hazard ratios (HR) with 95% confidence intervals (CI).

	Marital status			
	Married (Reference)	***Remarried HR (95% CI)***	***Previously married* HR (95% CI)***	***Never married HR (95% CI)***
Overall 5-year mortality				
Model 1	1	0.77 (0.54-1.10)	1.09 (0.87-1.37)	1.14 (0.87-1.49)
Model 2	1	0.79 (0.55-1.13)	0.95 (0.75-1.20)	1.03 (0.78-1.36)
Model 3	1	0.79 (0.55-1.13)	0.90 (0.71-1.15)	1.02 (0.77-1.35)
Conditional[a] overall 5-year mortality				
Model 1	1	0.73 (0.50-1.07)	1.11 (0.87-1.41)	1.18 (0.89-1.57)
Model 2	1	0.73 (0.50-1.08)	0.96 (0.75-1.23)	1.04 (0.78-1.38)
Model 3	1	0.74 (0.50-1.08)	0.93 (0.72-1.20)	1.05 (0.78-1.41)
Disease-specific[b] 5-year mortality				
Model 1	1	0.79 (0.56-1.13)	1.11 (0.88-1.40)	1.19 (0.89-1.57)
Model 2	1	0.80 (0.56-1.15)	0.96 (0.76-1.22)	1.03 (0.77-1.34)
Model 3	1	0.80 (0.56-1.15)	0.92 (0.72-1.17)	1.04 (0.78-1.39)
Conditional[a] disease- specific[b] 5-year mortality				
Model 1	1	0.75 (0.51-1.10)	1.12 (0.87-1.43)	1.21 (0.90-1.63)
Model 2	1	0.74 (0.50-1.09)	0.97 (0.76-1.25)	1.02 (0.76-1.38)
Model 3	1	0.74 (0.51-1.10)	0.94 (0.73-1.22)	1.05 (0.78-1.42)

*Values are expressed as hazard ratios (HR). *Previously married was defined as patients who have been married before but are living alone (after death of partner of divorce). [a]Conditional mortality: excluding first 90 days after surgery. [b]Disease-specific mortality: oesop*hageal or junctional cancer as underlying or contributing cause. *Model 1: unadjusted. Model 2: adjusted for sex, age, tumour stage. Model 3: adjusted for sex, age, tumour stage, histology, major complications, comorbidity and surgeon volume.*

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6,7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	6,7
Study size	10	Explain how the study size was arrived at	6,7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	7

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6, 8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	9, Table 1
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross-sectional study—Report numbers of outcome events or summary measures	-
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9, Table 2
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3-4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.