PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Marital status and survival after oesophageal cancer surgery: A population-based nationwide cohort study in Sweden
AUTHORS	Brusselaers, Nele; Mattsson, Fredrik; Johar, Asif; Wikman, Anna; Lagergren, Pernilla; Lagargren, Jesper; Ljung, Rickard

VERSION 1 - REVIEW

REVIEWER	RJLF Loffeld MD PhD Department of Internal Medicine Zaans Medisch Centrum Zaandam The Netherlands
REVIEW RETURNED	28-Apr-2014

GENERAL COMMENTS	Although this is a well designed study with clear resluts I have some concerns. The majority of patients with these cancer never undergo surgery because they already have metastases at time of first presentation. these patients are not included.This group will be much larger. In addition, because they receive palliative therapy they need more care. The data of this study would be much more interesting of these patients also were included

REVIEWER	Ayal Aizer Brigham and Women's Hospital, Boston, MA
REVIEW RETURNED	05-May-2014

GENERAL COMMENTS	In this study, the authors examine the association between marital status and outcome in patients with esophageal CA treated with esophagectomy in Sweden, between 2001-2005. The study is well-written and well-presented. It is clear and understandable, and the data source is appropriate. Its limitations are aptly noted by the authors. The inherent issue with this study (as noted by the authors) is that one cannot tell if no association between marriage and outcome exists, or if such an association does exist but the study lacks sufficient power to detect it. More minor considerations are presented here: Introduction: The authors state that surgical resection is a “cornerstone” of therapy for esophageal cancer. However, two European RCTs comparing neoadjuvant therapy +/- surgery did not show an overall survival benefit to surgery (Stahl et al JCO 2005; Bedenne et al JCO 2007). Therefore, such phraseology might not be

	appropriate Methods: Why restrict events to only 5 years of follow up? Consideration should be given to using all available data, including events >5 years after follow up Methods: What staging system was used? Why include stage IV (largely incurable) patients? Methods: Is data relating to use of chemo or RT available? What about the type of esophagectomy? These may be important confounders Methods: The authors could consider adjustment for race in their multivariable models Methods: The authors should consider reporting a median follow up Methods: It might be reasonable to treat married and remarried patients as a single entity. Both groups would be expected to display similar degrees of support, which presumably is one of the sources of benefit from marriage Discussion: What are the implications of the lack of an association between marital status and outcome in this cohort?

VERSION 1 – AUTHOR RESPONSE

Reviewer Name RJLF Loffeld MD PhD
Although this is a well-designed study with clear results I have some concerns. The majority of patients with these cancer never undergo surgery because they already have metastases at time of first presentation. These patients are not included. This group will be much larger. In addition, because they receive palliative therapy they need more care.
The data of this study would be much more interesting of these patients also were included

>> Response: Virtually all patients with oesophageal cancer who were not operated during this study period died within a few months after diagnosis, so studying the long-term effect of social support on survival in the non-operated group is not possible. For potentially curable patients, surgery was the treatment of choice in Sweden during the study period.

We clarified this in the methods section:
“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.”

Reviewer Name Ayal Aizer
In this study, the authors examine the association between marital status and outcome in patients with esophageal CA treated with esophagectomy in Sweden, between 2001-2005. The study is well-written and well-presented. It is clear and understandable, and the data source is appropriate. Its limitations are aptly noted by the authors.

The inherent issue with this study (as noted by the authors) is that one cannot tell if no association between marriage and outcome exists, or if such an association does exist but the study lacks sufficient power to detect it.

>> Response: From these results we could assume that a large effect of marital status is unlikely for this type of cancer.
We added the following sentence in the discussion “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.”

More minor considerations are presented here:

Introduction: The authors state that surgical resection is a “cornerstone” of therapy for esophageal cancer. However, two European RCTs comparing neoadjuvant therapy +/- surgery did not show an overall survival benefit to surgery (Stahl et al JCO 2005; Bedenne et al JCO 2007). Therefore, such phraseology might not be appropriate
>> Response: We rephrased this sentence to “Surgery (oesophagectomy) plays a main role in the curatively intended therapy for most oesophageal cancer.”

Methods: Why restrict events to only 5 years of follow up? Consideration should be given to using all available data, including events >5 years after follow up
>> Response: Patients who survived 5 years of oesophagectomy are typically cured from their cancer and are unlikely to die from oesophageal cancer. Since this study aimed to evaluate social support in relation to cancer-specific death, we decided to use 5 years as the cut-off for follow-up.

Methods: What staging system was used? Why include stage IV (largely incurable) patients?
>> Response: We used the 6th edition of the TNM staging of the UICC (Union Internationale Contre le Cancer)(reference 16). We added the edition in the method section. The patients with tumour stage IV that underwent oesophagectomy typically had a T4 tumour with overgrowth of the crural diaphragm and lymph node metasteses, but no distant metastases or irresectable primary cancer. These patients might still be considered curable.

Methods: Is data relating to use of chemo or RT available? What about the type of esophagectomy? These may be important confounders
>> Response: Chemo and radiotherapy were administered to only 11% of patients of this cohort. The prevailing curatively intended treatment was surgery alone. The type of surgery for oesophageal cancer was mainly Ivor-Lewis resection with a gastric tube pull-up and for cardia cancer the surgical procedure of choice was total gastrectomy with distal oesophageal resection. It is however unlikely that choice of surgical procedure is related somehow to the study exposure (marital status), and thus, the type of surgery would not be a confounder. In other words, we believe being married or not has limited impact on the choice of treatment. Therefore we concluded a-priori during our protocol meeting not to include these factors in our analyses.

Methods: The authors could consider adjustment for race in their multivariable models
>> Response: We discussed proxies for socio-economic status during our protocol meeting and their relationship with marital status. We do not have any reason to believe that race is strongly associated with marital status, and was therefore not included in our models as confounder. “Race” as such is also not included in medical records, yet country of birth of the mother is often used as proxy for ethnicity in Swedish studies.
We added the following sentence to the discussion: “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.”

Methods: The authors should consider reporting a median follow up
>> Response: We added the median follow up in the text: “The median duration of follow-up was 619

days".

Methods: It might be reasonable to treat married and remarried patients as a single entity. Both groups would be expected to display similar degrees of support, which presumably is one of the sources of benefit from marriage
>> Response: We performed an additional analysis with 2 exposure groups instead of 4, using the married + remarried groups as reference group. The hazard ratio for the previously married + never married group combined is 0.98 (95%CI 0.80-1.19) in the fully adjusted model for overall mortality.
Model 1: 1.15 (0.95-1.39) (crude model)
Model 2: 1.01 (0.84-1.23) (adjusted for sex, age, tumour stage)
Model 3: 0.98 (0.80-1.19) (adjusted for sex, age, tumour stage, histology, major complications, comorbidity and surgeon volume).
We added the following sentence in the methods section:
"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)."
And we added this sentence in the result section:
"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".

Discussion: What are the implications of the lack of an association between marital status and outcome in this cohort?
>> Response: These results indicate that social support has limited impact on survival in such an aggressive disease like oesophageal cancer. Therefore, any survival benefit of being married is difficult to detect in a cancer with very poor prognosis from the start.
We added the following sentence at the end of the discussion: "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".

VERSION 2 – REVIEW

REVIEWER	Ayal Aizer Harvard Radiation Oncology Program, Bosto, MA, USA
REVIEW RETURNED	14-May-2014

- The reviewer completed the checklist but made no further comments.