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# Six-month postoperative quality of life predicts long-term survival after oesophageal cancer surgery

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## ABSTRACT

**Background:** Patients treated with curatively intended surgery for oesophageal cancer have an approximately 30% chance of 5-year survival. Little is known about associations between postoperative health-related quality of life (HRQL) and long-term survival.

**Hypothesis:** Poor postoperative HRQL after curatively intended oesophageal cancer surgery is associated with a reduced long-term survival.

**Methods:** A Swedish nationwide cohort of oesophageal cancer patients, treated surgically between 2001 and 2005, was followed up until death or end of August 2009. Nine HRQL aspects were selected for analyses from EORTC QLQ-C30 and QLQ-OES18 questionnaires answered 6 months postoperatively. The HRQL measures were categorised into two groups: 'good function' versus 'poor function' and 'no or minor symptoms' versus 'symptomatic'. Associations between HRQL and survival were analysed using Cox proportional hazard ratios (HR) and 95% confidence intervals (CIs), adjusted for potential confounding factors.

**Findings:** All 401 oesophageal cancer patients who survived at least 6 months postoperatively and responded to the questionnaires were included. For each of the nine selected outcomes, poor scores were associated with an increased hazard ratio of mortality: global HRQL (HR = 1.55; 95% CI 1.19–2.02), physical function (HR = 1.56; 95% CI 1.23–1.99), social function (HR = 1.52; 95% CI 1.19–1.94), fatigue (HR = 1.65; 95% CI 1.30–2.11), pain (HR = 1.45; 95% CI 1.22–1.87), dyspnoea (HR = 1.54; 95% CI 1.19–2.01), appetite loss (HR = 1.69; 95% CI 1.32–2.14), dysphagia (HR = 1.69; 95% CI 1.13–2.51) and oesophageal pain (HR = 1.29; 95% CI 1.02–1.65).

**Interpretations:** HRQL assessed 6 months after oesophageal cancer surgery can be used as a clinically useful prognostic factor.

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## 1. Background

Much research has been devoted to identify prognostic factors after curatively intended cancer therapy, but most potential markers have not gained any role in health care since they are difficult to analyse, expensive, and of uncertain validity. Thus, few prognostic markers are used in clinical practice. Oesophageal cancer is associated with a poor prognosis, with

an overall population-based 5-year survival of about 10%, and of about 30% among surgically treated patients.<sup>1</sup> It would be of great clinical benefit if the prognosis after the surgical treatment could be predicted. Health-related quality of life (HRQL) measured before treatment has recently been found to be a possible predictor of survival in several types of cancer, including cancer of the oesophagus.<sup>2</sup> Our recent study of a British hospital based cohort showed that changes in HRQL

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between the time before treatment and 6 months postoperatively are associated with survival.<sup>3</sup> In the present study, we wished to clarify whether a single postoperative HRQL assessment can replace an assessment that requires also a baseline HRQL assessment. Previous studies evaluating postoperative HRQL alone in relation to long-term survival are scarce. If postoperative HRQL measurements are associated with prognosis, these can be used as a readily available tool in the future planning of the clinical care. We hypothesised that poor postoperative HRQL scores regarding nine selected aspects (global HRQL, physical function, social function, fatigue, pain, dyspnoea, appetite loss, dysphagia and oesophageal pain) 6 months after curatively intended oesophageal cancer surgery are associated with poor survival. Patients might for example have early symptoms of yet unidentified tumour recurrence.<sup>4</sup> The chosen aspects were selected on the basis of biological plausibility. The assessment at 6 months postoperatively was considered to be well within the time window between recovery and diagnosed recurrence.<sup>5,6</sup>

## 2. Materials and method

### 2.1. Study design

A Swedish nationwide cohort study was conducted during the study period 2 April 2001 through 30 August 2009. Eligible for inclusion were patients diagnosed with cancer of the oesophagus or gastro-oesophageal junction who underwent macroscopically radical surgical resection between the period 2nd April 2001 and 31st December 2005. The surgically treated patients were followed up until death or the end of the study period (31st August 2009) whichever occurred first. Survival data were assessed through linkage to the Swedish Register of the Total Population. Informed consent was obtained from each participating patient and the ethics committee at Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden approved the study.

### 2.2. Data collection

#### 2.2.1. Clinical data

A nationwide network of hospitals, departments and physicians involved in the treatment of patients with oesophageal cancer provided an almost complete national coverage and facilitated the data collection. The organisation of this network has been described in detail elsewhere.<sup>7,8</sup> In brief, based on an extensive study protocol, data regarding the patient, tumour, hospital, surgery, and complications were collected prospectively through continuous manual scrutiny of the medical records of each participating patient. The Siewert classification was used to define the location of tumours near the gastro-oesophageal junction,<sup>9</sup> whereas the tumour stage was classified according to the Union Internationale Contre le Cancer.<sup>10</sup>

#### 2.2.2. Health-related quality of life data

HRQL was assessed 6 months after the operation, using two questionnaires developed and validated by the European Organisation for Research and Treatment of Cancer (EORTC). The core questionnaire (QLQ-C30) was used to assess

symptoms and problems common in cancer patients, and an oesophageal-specific module (QLQ-OES18) was used to evaluate disease specific symptoms. Tests of psychometric properties for the QLQ-C30 have been performed with good results.<sup>11</sup> Validity assessed as correlations between scales and clinical validity assessed as differences between different patient groups, were both satisfactory. Likewise, reliability assessed with Cronbach's alpha showed satisfying results. Responsiveness was addressed as changes over time, which was also found for patients with changed performance status. Psychometric properties for the QLQ-OES18 was performed with a similar approach, and showed overall satisfying results.<sup>12</sup> The questionnaires were mailed to the patient's home address for self-administration, and up to three reminders were sent out.

### 2.3. Statistical analyses

#### 2.3.1. Health-related quality of life

One global quality of life measure, two functions (physical function, social function) and six symptoms, (fatigue, pain, dyspnoea, appetite loss, dysphagia and oesophageal pain) were analysed. These were selected since previous literature had indicated that it was biologically plausible that they could be associated with survival.<sup>13–19</sup> An additional factor, financial impact, for which we had not proposed a hypothesis concerning any association with survival, was added to assess the validity of the study results. All HRQL items had four response categories: (1) 'not at all', (2) 'a little', (3) 'quite a bit', and (4) 'very much', except for the global quality of life scale, which has a seven step scale ranging from 'very poor' to 'excellent'. The responses to the function scales were dichotomised into 'good' versus 'poor' function. Patients who responded 'quite a bit' or 'very much' to any item within a scale were categorised as having poor function, while the others were categorised as having good function. The responses to the questions forming the symptom scales were dichotomised into 'no or minor symptoms' versus 'symptomatic'. Patients who had at least one response of 'quite a bit' or 'very much' for any item within a symptom scale or for a single item (except for the dysphagia scale with an opposite response direction) were categorised as being symptomatic; other patients were categorised as having minor symptoms. On the global quality of life scale, a response of 4 or worse to either of the two questions included in the scale was considered to represent a poor global quality of life, otherwise, the patient was categorised as having a good global quality of life. All HRQL aspects were also categorised into two groups (dichotomised), above or below the mean and the median score of the group. Patients with missing data were excluded from analyses of that individual scale, but were included in other scale and item analyses if the relevant data were available.

#### 2.3.2. Survival

The survival was assessed in a Kaplan–Meier curve. Cox proportional hazard ratios (HR) with 95% confidence intervals (CIs) were calculated to evaluate associations with survival.<sup>20</sup> A multivariable model with adjustments for potential confounding factors was created. In this model, adjustments

were made for sex; age (<60, 60–70, or >70 years); co morbidity (none, 1–2, or >2); tumour stage (in four groups: 0–I, II, III or IV); tumour histology (squamous cell carcinoma or adenocarcinoma); type of operation ((1) oesophageal resection with removal of the main part of the oesophagus, (2) cardia resection with removal of the distal oesophagus and the proximal part of the stomach, (3) extended total gastrectomy with removal of the distal oesophagus and the total stomach, or (4) total gastrectomy and oesophageal resection, where the main part of the oesophagus and the total stomach were resected), and postoperative complications occurring within 30 d of surgery (none, 1–2, or >2). The following conditions were included among co morbidities: hypertension, angina, heart failure, chronic obstructive pulmonary disease, diabetes, smoking, kidney disease, liver disease, or other specified condition. The following occurrences were considered as complications: perioperative bleeding, leakage or perforation of the anastomosis, stricture of the anastomosis, wound infection needing treatment, wound rupture, gastric perforation, intra-abdominal or intrathoracic abscess, sepsis, ileus, thoracic duct injury, renal failure, reintubation or need for prolonged mechanical ventilation, progressive jaundice, paresis of the recurrent laryngeal nerve, pneumonia, pulmonary thrombosis, deep vein thrombosis, myocardial infarction, atrial fibrillation, stroke, or other specified complication.

The statistical package STATA 9.2 for Windows (STATA Corp, College Station, TX) was used for all data analyses.

### 3. Results

#### 3.1. Patients

During the study period 614 patients underwent potentially curative surgery for oesophageal cancer. Of these, 124 (20%) died within 6 months of surgery. Totally, 88 (18%) of the remaining 490 patients had missing HRQL data at 6 months because of administrative errors, such as late awareness of the patient or that the patient's doctor did not participate, and one patient chose not to participate. Thereafter, 401 patients remained in the present study. Some characteristics of the study patients are shown in Table 1. Most patients were men (81%) of ages of at least 60 years (75%), and a majority had at least one co morbidity (68%). Histologically the tumours were predominantly adenocarcinoma (76%) in tumour stage II–III (70%), located in the distal oesophagus (39%) or in the gastro-oesophageal junction (45%). The most common surgical approach was a transthoracic resection (84%). At least one postoperative complication was recorded in 46% of the patients. The survival is presented in Fig. 1. Since a prerequisite for inclusion in the analyses was survival for at least 6 months postoperatively, the mean survival was relatively high. At 3 years after surgery, 140 (35%) of the 401 included patients were alive and 108 (27%) were alive 5 years postoperatively.

#### 3.2. HRQL functions and symptoms in relation to survival

The associations between the nine selected HRQL functions and symptoms in relation to survival are presented in Table 2. Among the patients reporting a poor global quality of life (27%) there was a 55% increased mortality compared to those

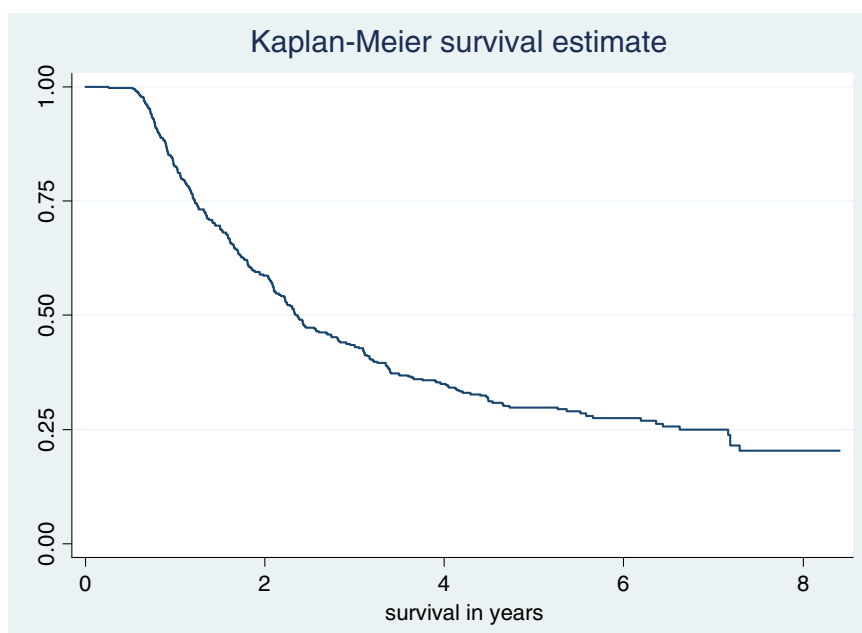
**Table 1 – Patient and tumour characteristics of 401 patients with oesophageal cancer treated with curatively intended surgery surviving at least 6 months postoperatively.**

	Number (%)
<b>Sex</b>	
Male	326 (81)
Female	75 (19)
<b>Age (years)</b>	
<60	101 (25)
60–69	164 (41)
70–84	136 (34)
<b>Co morbidity</b>	
No	127 (32)
Yes	274 (68)
<b>Histological type of tumour</b>	
Adenocarcinoma and dysplasia	303 (76)
Squamous cell carcinoma	98 (24)
<b>Tumour location</b>	
Upper and middle oesophagus	64 (16)
Lower oesophagus	158 (39)
Cardia (Siewert II/III)	179 (45)
<b>Tumour stage</b>	
0–I	84 (21)
II	120 (30)
III	162 (40)
IV	33 (8)
Unknown	2 (1)
<b>Type of operation</b>	
Oesophageal resection	297 (74)
Cardia resection	23 (6)
Extended total gastrectomy	40 (10)
Total gastrectomy and oesophageal resection	41 (10)
<b>Surgical approach</b>	
Transthoracic	337 (84)
Transhiatal (abdominal only)	64 (16)
<b>Complications</b>	
No	218 (54)
Yes	183 (46)

with a good global quality of life (HR = 1.55; 95% CI 1.19–2.02). In patients categorised as having poor physical function (48%) there was a 56% increased mortality (HR = 1.56; 95% CI 1.23–1.99). The patients with poor social function showed a 52% increased mortality within 5 years after surgery (HR = 1.52; 95% CI 1.19–1.94).

Symptomatic fatigue 6 months after surgery was associated with a 65% increased mortality (HR = 1.65; 95% CI 1.30–2.11). For pain and dyspnoea the corresponding figures were 45% and 54%, respectively (HR = 1.45; 95% CI 1.22–1.87 and HR = 1.54; 95% CI 1.19–2.01). The highest HRs for death were found for patients classified as symptomatic from appetite loss (HR = 1.69; 95% CI 1.32–2.14) and dysphagia (HR = 1.69; 95% CI 1.13–2.51). Oesophageal pain was entailed by an increased mortality of 29% compared to that in patients with no or minor symptoms (HR = 1.29; 95% CI 1.02–1.65) (Table 2). The HR for financial issues and survival was 1.08 (95% CI 1.03–1.13).

Analyses using both the mean and the median score of the total group as a cut-off instead of the categorisation



**Fig. 1 – Survival in years presented as a Kaplan–Meier curve for 401 patients operated on oesophageal cancer who survived at least 6 months postoperatively.**

**Table 2 – Hazard ratios (HR) with 95% confidence intervals (CIs) for associations between ‘Poor function’ or ‘Symptomatic’ versus ‘Good function’ or ‘No or minor symptoms’ of health-related quality of life (EORTC QLQ-C30) 6 months postoperatively and survival in 401 patients operated on with a curative intent for oesophageal cancer.**

	Mean score Mean (SD)	Median score Median (IQR)	‘Poor function’ or being ‘Symptomatic’ <sup>c</sup> Number (%)	‘Good function’ or having ‘No or minor symptoms’ <sup>b</sup> Number (%)	Cox proportional ratio <sup>a</sup>		
					HR	95% CI	P-value
Global quality of life	59 (23)	63 (42–75)	110 (27)	291 (73)	1.55	1.19–2.02	<0.01
<i>General functions</i>							
Physical function	76 (22)	80 (60–93)	192 (48)	209 (52)	1.56	1.23–1.99	<0.01
Social function	71 (28)	67 (50–100)	127 (32)	274 (68)	1.52	1.19–1.94	<0.01
<i>General symptoms</i>							
Fatigue	44 (27)	33 (22–67)	194 (48)	207 (52)	1.65	1.30–2.11	<0.01
Pain	28 (29)	17 (0–50)	114 (29)	286 (72)	1.45	1.22–1.87	<0.01
Dyspnoea	34 (32)	33 (0–67)	112 (28)	287 (72)	1.54	1.19–2.01	<0.01
Appetite loss	37 (36)	33 (0–67)	132 (33)	263 (67)	1.69	1.32–2.14	<0.01
<i>Oesophageal specific symptoms</i>							
Dysphagia	24 (27)	22 (0–33)	34 (9)	363 (91)	1.69	1.13–2.51	0.01
Oesophageal pain	27 (24)	22 (11–44)	144 (37)	249 (63)	1.29	1.02–1.65	0.04

SD, standard deviation; IQR, interquartile range.

<sup>a</sup> Adjusting for sex, age, co morbidity, TNM stage, histological type, type of operation and postoperative complications within 30 d.

<sup>b</sup> ‘Good function’/‘No or minor symptoms’ = reporting problems with the function or symptom to the extent ‘1 = not at all’ or ‘2 = a little’ in answer to the included questions.

<sup>c</sup> ‘Poor function’/‘Symptomatic’ = reporting problems with the function or symptom to the extent ‘3 = quite a bit’ or ‘4 = very much’ in answer to at least one of the included questions.

presented above showed results very similar to those presented (data not shown).

#### 4. Discussion

This Swedish nationwide study of patients undergoing surgery for oesophageal cancer identified an increased risk of

mortality of 29–69% among patients with poor HRQL scores 6 months after surgery, in a descending order, regarding appetite loss, dysphagia, fatigue, physical function, global quality of life, dyspnoea, social function, pain, and oesophageal pain.

Strengths of the study include the prospective design, the large and population-based sample, the high participation rate, the use of validated HRQL questionnaires, the high



quality of the clinical data, the complete follow-up, and the adjustment for relevant potential confounding factors. These advantages counteract selection bias, chance errors, misclassification, loss to follow-up, and confounding. Weaknesses include some missing data. Such error was limited, however, and mainly due to administrative errors. The time point of the HRQL assessment might not have been optimal. It was, however, chosen carefully on the basis of when the acute postoperative phase would have subsided and tumour recurrence would rarely have been clinically detected.<sup>5,6</sup> Further, since baseline HRQL data were not available, adjustment for this could not be made. Multiple testing is a source of error, since many hypotheses were addressed. To reduce such chance error, only a selected number of items were evaluated, however, and this selection was based on what was considered clinically relevant according to earlier literature.<sup>13–19</sup> The collapsing of raw answers into two categories deserves attention. The cut-offs were pre-determined and based on where a clinician would be likely to react and try to identify interventions. This method is rather conservative, since one single answer of 'quite a bit' or 'very much' categorises the patient to being 'symptomatic' or having 'poor function'. This method does not differ between those just answering 'quite a bit' to only one question, but 'not at all' to all of the others, and those answering 'very much' to all questions. Any such misclassification should, however, be independent of the longer survival, which would mean that the positive results are rather underestimated. To further attempt to determine whether the cut-off level influenced our results, additional analyses using both the mean score and the median score of the total group as cut-offs were performed. The results remained virtually the same. We also assessed an HRQL aspect which we expected not to be associated with survival, namely financial issues, and found no associations, which strengthens the validity of our positive results.

The results of our previous study in the United Kingdom, including 132 patients who were treated with a curative intent for oesophago-gastric cancer, and comparing baseline HRQL with those at 6 months after therapy, indicated a longer survival to be associated with fewer problems with dyspnoea before treatment and better recovery of physical function, pain, and fatigue after treatment.<sup>3</sup> But, to the best of our knowledge, only one study has addressed the possible relation between postoperative HRQL alone and survival after oesophageal cancer surgery. In that study,<sup>19</sup> social function, pain and activity level at 3 months postoperatively were associated with survival. Longitudinal studies on postoperative HRQL have shown that long-term survivors still have affected HRQL at 3 months and that this usually recovers within 6–12 months of surgery.<sup>6,21</sup>

The findings of the present study might be due partly to yet undetected tumour recurrence, which might be noticed by the patient as symptoms such as pain or fatigue earlier than they can be diagnosed by radiological imaging or clinical examinations. The strong associations found between postoperative HRQL aspects and long-term survival suggest that HRQL measurements could serve as markers of prognosis in patients operated on for oesophageal cancer. Such markers are easily and readily identified and there is no cost attached. Poor HRQL might indicate a need for more intensive follow-

up, while the opposite might be justified in patients with good HRQL.

In conclusion, this large, prospective and population-based study indicates that assessment of specific HRQL items at 6 months after oesophageal cancer surgery can be used as a predictor of survival. Patients reporting poor HRQL might need intensified clinical attention.

## Conflict of interest statement

No conflict of interest.

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