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GUIDELINES FOR CLINICAL PRACTICE

# Systematic review of health-related quality of life after esophagectomy for esophageal cancer

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## Abstract

This study is aimed to assess the long-term health-related quality of life (HRQL) of patients after esophagectomy for esophageal cancer in comparison with established norms, and to evaluate changes in HRQL during the different stages of follow-up after esophageal resection. A systematic review was performed by searching medical databases (Medline, Embase and the Cochrane Library) for potentially relevant studies that appeared between January 1975 and March 2011. Studies were included if they addressed the question of HRQL after esophageal resection for esophageal cancer. Two researchers independently performed the study selection, data extraction and analysis processes. Twenty-one observational studies were included with a total of 1282 (12-355) patients. Five studies were performed with short form-36 (SF-36) and 16 with European Organization for Research and Treatment of Cancer (EORTC) QLQ C30 (14 of them also utilized the disease-specific OES18 or its previous version OES24). The analysis of long-term generic HRQL with SF-36 showed pooled scores for physical, role and social function after esophagectomy similar to United States norms, but lower pooled scores for physical function, vitality and general health perception. The analysis of HRQL conducted using the Global EORTC C30 global scale during a 6-mo follow-up showed that global scale and physical function were better at the baseline. The symptom scales indicated worsened fatigue, dyspnea and diarrhea 6 mo after esophagectomy. In contrast, however, emotional function had significantly improved after 6 mo. In conclusion, short- and long-term HRQL is deeply affected after esophagectomy for cancer. The impairment of physical function may be a long-term consequence of esophagectomy involving either the respiratory system or the alimentary tract. The short- and long-term improvement in the emotional function of patients who have undergone successful operations may be attributed to the impression that they have survived a near-death experience.



**Key words:** Health-related quality of life; Esophageal cancer; Esophagectomy; Short form 36; European Organization for Research and Treatment of Cancer QLQ C30; European Organization for Research and Treatment of Cancer OES18

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## INTRODUCTION

Esophageal cancer is an increasingly common cancer with a poor prognosis. During recent decades, the incidence of esophageal cancer has risen steadily, and it is now the fastest rising solid tumor in most Western countries. Moreover, moderate to high incidence rates have been reported in other areas, including parts of China, Central Asia, South and East Africa, South America, Northern France, and the United States among African-Americans[1]. Despite recent improvements in diagnosis, surgical treatment and (neo)-adjuvant therapy, the prognosis of patients with esophageal cancer remains poor, with overall 5-year survival rates of only 5%-15%[1,2]. Esophagectomy is the standard treatment for those patients who present with resectable esophageal cancer[3-5], but it offers a limited (25%-35%) chance of cure[5,6] and is associated with a considerable risk of serious complications[4,5,7]. Therefore, the use of chemotherapy or radiotherapy in combination with surgery has been tested. Nevertheless, meta-analyses of randomized trials of neoadjuvant chemotherapy and chemoradiation followed by surgery and surgery alone for patients with esophageal carcinoma showed only minor survival advantages[8,9]. Only patients with a complete pathologic response to neoadjuvant therapy enjoy a significantly better chance of survival, whereas non-responders have a worse prognosis than patients undergoing surgery alone[10,11].

For a long time, morbidity and mortality represented the main (and often the only) outcome measure that could be used to evaluate esophagectomy for esophageal cancer. The morbidity and mortality rates associated with the procedure and the poor patient survival rate left almost no space for further consideration. However, in recent years, along with the increase in the success of the therapy, health-related quality of life (HRQL) has generally become accepted as an important outcome parameter, along with long-term survival, mortality, and complication rates. In fact, knowledge of risk factors for poor postoperative HRQL may be relevant to clinical decision making. Moreover, these findings may be used to inform patients of the long-term consequences of surgery. On this basis, the aim of this systematic review was to analyze quality of life after curative surgery for esophageal cancer.

## INCLUSION AND EXCLUSION CRITERIA

Since we expected to find only observational studies, the checklist proposed by Meta-analysis of Observational Studies in Epidemiology group 38 was used as a guideline to perform this systematic review[12]. We defined observational studies as reports that used data from existing databases, cross-sectional studies, case series, case-control studies, or studies with a historical control or a cohort design.

Studies were eligible for inclusion if they reported on a series of patients who underwent esophagectomy because of esophageal cancer and if post-operative quality of life was described and analyzed in the "material and methods" and "results" sections. Studies reporting on a mix of esophageal adenocarcinoma and squamous cell cancer patients were included. In contrast, those reporting on malignancies other than esophageal adenocarcinoma or squamous cell cancer were excluded. All studies eligible for inclusion in this systematic review also had to present detailed information on the methods used to assess quality of life and on when the questionnaire was administered. Studies that analyzed HRQL using questionnaires other than short form-36 (SF-36), European Organization for Research and Treatment of Cancer (EORTC) QLQ C30 and OES18/24 and those that only presented their results graphically were excluded. When studies were discovered to report (partially) similar patient data, only the most recent and complete data sets were considered.

## SEARCH STRATEGY

Four medical databases were used in this research: Medline (January 1978 to March 2011), the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials and Embase. These databases were searched with the help of a clinical librarian. The keywords and medical subject headings used were "esophageal cancer", "esophagectomy" and "quality of life", as indicated in Figure 1. Only clinical studies written in English were selected. A manual cross-reference search of the eligible papers was performed to identify additional relevant articles. Based on the initial search results, two researchers (Scarpa M and Valente S) independently selected the studies that matched the inclusion criteria. Data quoted as unpublished and data from abstracts were not used. Any disagreements between the two researchers regarding which studies should be included were resolved through discussion.

## DATA EXTRACTION

Data were extracted only from original articles using a preformatted sheet with a set of pre-defined parameters: demographic data, histologic type, cancer stage, cancer site, type of surgery (two-way or three-way esophagectomy), type of reconstruction (esophagogastroplasty or esophagocoloplasty), neoadjuvant or adjuvant therapy, timing of follow-up and HRQL data gathering, type of questionnaire used, item and total results.

## OUTCOME MEASURE: QUALITY OF LIFE INSTRUMENTS

Studies were included if at least one of the following validated quality of life instruments was used: the EORTC-QLQ-C30, the EORTC-QLQ-OES18 or 24, or the SF-36. A summary of these questionnaires appears below.

The EORTC-QLQ-C30 questionnaire was developed by the Quality of Life division of EORTC. This 30-item questionnaire explores the generic quality of life of patients affected by oncologic diseases. It is a self-report

**Mesh terms: "esophageal cancer" and "esophagectomy" and "quality of life"**

**Key words:**

"esophageal neoplasm" or "esophageal neoplasms" or "neoplasms, esophageal " or" neoplasm, esophageal" or "esophagus neoplasm" or "esophagus neoplasms" or "neoplasm, esophagus" or "neoplasms, esophagus" or "cancer of esophagus" or "cancer of the esophagus" or "esophagus cancer" or "cancer, esophagus" or "cancers, esophagus" or "esophagus cancers" or "esophageal cancer" or "cancer, esophageal" or "cancers, esophageal" or "esophageal cancers" or "esophageal adenocarcinoma" or "adenocarcinoma of the esophagus" or "esophagus adenocarcinoma" or "adenocarcinoma of esophagus" or "adenocarcinoma, esophagus" or "oesophageal neoplasm" or "oesophageal neoplasms" or "neoplasms, oesophageal "or" neoplasm, oesophageal" or "oesophagus neoplasm" or "oesophagus neoplasms" or "neoplasm, oesophagus" or "neoplasms, oesophagus" or "cancer of oesophagus" or "cancer of the oesophagus" or "oesophagus cancer" or "cancer, oesophagus" or "cancers, oesophagus" or "oesophagus cancers" or "oesophageal cancer" or "cancer, oesophageal" or "cancers, oesophageal" or "oesophageal cancers" or "oesophageal adenocarcinoma" or "adenocarcinoma of the oesophagus" or "oesophagus adenocarcinoma" or "adenocarcinoma of oesophagus" or "adenocarcinoma, oesophagus"

**and**

"esophagectomy" or "esophagectomies" or "esophageal resection" or "esophageal resections" or "resection of the esophagus" or "resections of the esophagus" or "esophagogastroplasty" or "esophagogastrectomy" or "oesophagectomy" or "oesophagectomies" or "oesophageal resection" or "oesophageal resections" or "resection of the oesophagus" or "resections of the oesophagus" or "oesophagogastroplasty" or "oesophagogastrectomy"

**and**

"quality of life" or "life qualities" or "life quality" or "health related quality of life" or "HRQL" or "QoL"

**Figure 1 Key words.** HRQL: Health related quality of life; QoL: Quality of life.

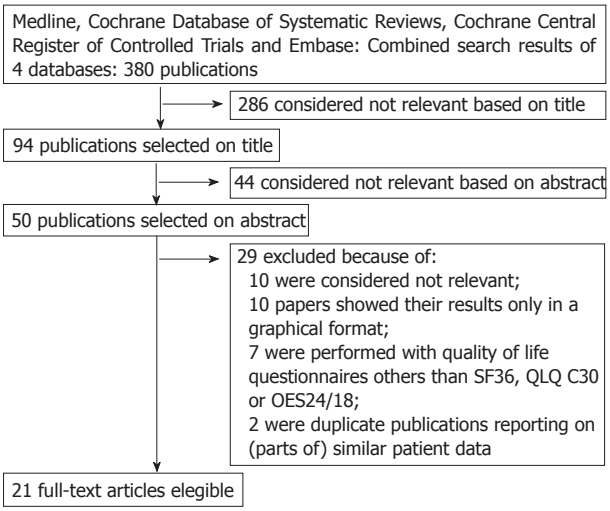



**Figure 2 Study selection.** SF-36: Short form-36.

instrument that includes five functional scales (physical, role, emotional, social and cognitive), three symptom scales (fatigue, nausea and vomiting, and pain), a global health status scale and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties)[13]. The EORTC-QLQ-OES-18 and 24 are two extra modules that are used specifically for esophageal cancer. These questionnaires consist of 18 questions (or 24 in the previous version) assessing dysphagia, deglutition, abdominal/gastrointestinal symptoms, eating difficulties, pain, and emotional problems related to esophageal cancer and to the side effects of chemotherapy/radiotherapy[14]. The SF-36 consists of 36 items within 8 dimensions: psychological functioning, role limitations due to physical problems, pain, general health perceptions, energy/vitality, social functioning, and role limitations due to emotional problems and mental health[15].

## STATISTICS

A clinical statistician was consulted to assess the accuracy of our analysis. The Review Manager 4.2 software (The Cochrane Collaboration, Copenhagen: Nordic Cochrane Centre, 2003) was used to process the data and conduct the analysis. For studies presenting HRQL results obtained from patients who had undergone the same treatment regimen and been presented with the same questionnaire at the same point in time with respect to their surgery, a meta-analysis of the HRQL scores was attempted. The results were presented as weighted mean differences [95% confidence interval (CI)]. Based on previous research, a difference of at least 10 mean score points between time points or comparison groups was considered clinically relevant, whereas a difference of 5-10 was considered weak[16]. $P < 0.05$ was considered to indicate that the results were significant.

## STUDY SELECTION

The studies selected are shown in Figure 2. The initial search yielded 380 articles, of which 349 did not meet the criteria for inclusion. Based on their titles, 286 papers were excluded because they clearly covered a variety of unsuitable topics. Forty-four articles were then excluded on the basis of their abstracts; these were case reports and review articles without original data or articles on forms of neoplasm other than esophageal carcinoma. Of the 50 candidate papers, an additional 29 were then excluded, of which 10 were not focused on quality of life after esophagectomy for esophageal carcinoma[14,17-25], 10 presented their results only in a graphical format[26-35], 7 used quality of life questionnaires other than the SF36, QLQ C30 or OES24/18[36-42] and 2 reported data from the same dataset as other studies[43,44]. Although they reported the same dataset, three studies from the Karolinska Institute of Stockholm were included in the review because they analyzed different aspects of HRQL after esophagectomy[45,46]. However, the patients included in these studies were counted only once in all totals.

The 21 studies included in the analysis were all published between 1995 and 2010 and are listed according

**Table 1 Studies characteristics: Aims of the studies and timing of health-related quality of life recording**

| Sudy | Study aim | Timing post op HRQL measures |
|---|---|---|
| McLarty *et al*[54] | Analysis of HRQL in long term survivors after surgery alone | A single assessment > 60 mo |
| De Boer *et al*[53] | Analysis of HRQL in long term survivors after transhiatal esophagectomy | A single assessment 3.5 (2.1-5.4) yr |
| Headrick *et al*[49] | Analysis of HRQL in long term survivors after esophagectomy for HGD or adenocarcinoma | A single assessment 5.3 (0.5-9) yr |
| Cense *et al*[52] | Analysis of HRQL in long term survivors after esophagocolonplasty | A single assessment 35 (7-97) mo |
| Moraca *et al*[50] | Analysis of HRQL in long term survivors after esophagectomy for HGD or Tis | A single assessment 4.9 (0.5-12) yr |
| Reynolds *et al*[55] | Comparison between HRQL after neoadjuvant CT-RT+ surgery and after surgery alone | Baseline, after CT-RT, 3, 6, 9, 12 mo po |
| Avery *et al*[56] | Comparison between HRQL after neoadjuvant CT-RT+ surgery and after definitive CT-RT | 1, 5, 3, 6, 9 mo |
| van Meerten *et al*[57] | Analysis of HRQL after neoadjuvant CT-RT + surgery | Baseline, after CT-RT, 3, 6, 9, 12 mo po |
| Wang *et al*[59] | Comparison between open surgery and minimally invasive esophagectomy | 2, 4, 12, 24 wk |
| Parameswaran *et al*[58] | Analysis of HRQL after minimally invasive esophagectomy | 6, 12 mo |
| Viklund *et al*[45] | Analysis of HRQL predictors after esophagectomy for cancer (type of recstruction) | A single assessment 6 mo |
| Rutegard *et al*[46] | Analysis of HRQL predictors after esophagectomy for cancer (type of recstruction) | A single assessment 6 mo |
| Rutegard *et al*[47] | Analysis of HRQL predictors after esophagectomy for cancer (type of recstruction) | A single assessment 6 mo |
| Olsen *et al*[60] | Analysis of HRQL in long term survivors (surgery alone or neoadjuvant CT-RT + surgery) | A single assessmentat 24 mo po |
| Lagergren *et al*[61] | Analysis of HRQL in long term survivors (surgery alone or neoadjuvant CT-RT + surgery) | Baseline and 36 mo |
| Djarv *et al*[62] | Analysis of HRQL in long term survivors (surgery alone or neoadjuvant CT-RT + surgery) | 6, 36 mo |
| Courrech Staal *et al*[63] | Analysis of HRQL in long term survivors (surgery alone or neoadjuvant CT-RT + surgery) | A single assessment at 54 (16–162) mo |
| Blazeby *et al*[64] | Comparison between HRQL after surgery alone and after palliative RT | A single assessment 16 (10-24) wk |
| Ariga *et al*[65] | Comparison between surgery alone and definitive CT-RT + salvage surgery | A single assessment 24 mo |
| Schneider *et al*[48] | Comparison between HRQL after emergency and elective esophagectomy | 1 wk and 9 mo |
| Rosmolen *et al*[51] | Comparison between HRQL after endoscopical ablation and esophagectomy for early Barrett's neoplasms | A single assessment at 24 (17–35) mo |

The 21 studies included in the analysis are listed according their aim and then chronologically. HRQL: Health-related quality of life; HGD: High grade dysplasia; CT-RT: Chemotherapy-radiotherapy; op: Operative; po: Post-operative.

their aim and then chronologically in Tables 1 and 2. Five studies were performed using SF36 and 16 using EORTC QLQ C30 (14 of them also utilized the disease-specific OES18 or the previous version, the OES24). Nine studies were observational cross-sectional studies and twelve were prospective ones. Patients were enrolled consecutively in 17 of them. Generic and disease-specific questionnaires were both used in 18 studies, and the HRQL was the primary focus for 15 of them. Five were population-based studies.

### Study characteristics

There were 21 observational studies analyzed, and these studies included data for a total of 1282 patients. The number of patients ranged from 12 to 355 per study. The follow-up duration after esophagectomy, as reported in the articles, was between 4 and 63 mo. The range of mean ages reported by the different papers was 59 to 69 years. The indication for surgery was esophageal adenocarcinoma in 835 patients and squamous cell carcinoma in 395. However, in the series by Schneider *et al*[48], 5 out of 17 patients were operated on for esophageal perforation. Hendrick *et al*[49], Moraca *et al*[50] and Rosmolen *et al*[51] included 35, 24 and 7 patients, respectively, who underwent esophagectomy because of high-grade dysplasia. The characteristics of the patients included in each study are described in Table 3.

### Long term generic HRQL after esophagectomy vs healthy subjects

Five studies analyzed the long-term generic HRQL of 246 patients using the SF-36 questionnaire (median follow-up range: 36-64 mo)[49,50,52-54]. The studies by Moraca *et al*[50] and Cense *et al*[52] were not used for the meta-analysis because the SF-36 scores in the first were not reported in a standard, comparable manner and because all patients reported on in the second underwent esophagocoloplasty. The studies by Hendrick *et al*[49], De Boer *et al*[53] and McLarty *et al*[54] were sufficiently homogenous, and thus, a meta-analysis of their results was attempted. The pooled scores for physical function, physical role, and social function after esophagectomy were similar to sex- and age-matched United States norms, whereas the pooled scores for physical function, vitality and general health perception were lower than the relevant norms ($P = 0.005$, $P < 0.001$ and $P = 0.006$, respectively). In contrast, scores for bodily pain and mental health in long-term survivors after esophagectomy were higher than the relevant norms ($P = 0.08$ and $P = 0.02$, respectively). The significant weighted mean differences that emerged based on the comparison between the long-term generic HRQL of patients who had undergone esophagectomy and that of healthy subjects are shown in Figure 3.

### Generic and disease specific HRQL after neoadjuvant therapy and esophagectomy

Three studies analyzed generic and disease-specific HRQL for 255 patients using the QLC-30 and OES-18 questionnaires at different stages in the follow-up timeline (baseline, 3, 6, 9 and 12 mo) after neoadjuvant therapy and esophagectomy[55-57]. Reynolds *et al*[55] and Avery *et al*[56] compared the HRQL of patients who had undergone neoadjuvant therapy with that of patients who had un-

**Table 2 Studies characteristics: Studies setting and feature**

| Study | Year | Country | Center | Prospective | Consecutive | HRQL as primary endpoint | Preoperative HRQL assessment | SF36 | OES18 /OES24 | QLQ C30 | Population based study |
|---|---|---|---|---|---|---|---|---|---|---|---|
| McLarty *et al*[54] | 1997 | United States | Mayo Clinic, Rochester MI | No | Yes | No | No | Yes | No | No | No |
| De Boer *et al*[53] | 2000 | Netherlands | Academic Medical Centre, Amsterdam | No | No | Yes | No | Yes | No | No | No |
| Headrick *et al*[49] | 2002 | United States | Mayo Clinic, Rochester MI | No | Yes | No | No | Yes | No | No | No |
| Cense *et al*[52] | 2004 | Netherlands | Academic Medical Centre, Amsterdam | No | No | Yes | No | Yes | No | No | No |
| Moraca *et al*[50] | 2006 | United States | Virginia Mason Medical Centre, Seattle | No | Yes | No | No | Yes | No | No | No |
| Reynolds *et al*[55] | 2006 | Ireland | St James's Hospital, Dublin | Yes | Yes | Yes | Yes | No | No | Yes | No |
| Avery *et al*[56] | 2007 | United Kingdom | University of Bristol, Bristol | Yes | Yes | Yes | Yes | No | Yes | Yes | No |
| van Meerten *et al*[57] | 2008 | Netherlands | Erasmus University, Rotterdam | Yes | Yes | Yes | Yes | No | Yes | Yes | No |
| Wang *et al*[59] | 2009 | China | Fudan University, Shanghai | Yes | Yes | Yes | Yes | No | Yes | Yes | No |
| Parameswaran *et al*[58] | 2010 | United Kingdom | Royal Devon and Exeter NHS Trust, Exeter | Yes | Yes | Yes | Yes | No | Yes | Yes | No |
| Viklund *et al*[45] | 2005 | Sweden | Karolinska Institute, Stockholm | Yes | Yes | Yes | No | No | Yes | Yes | Yes |
| Rutegard *et al*[46] | 2008 | Sweden | Karolinska Institute, Stockholm | Yes | No | Yes | No | No | Yes | Yes | Yes |
| Rutegard *et al*[47] | 2008 | Sweden | Karolinska Institute, Stockholm | Yes | No | Yes | No | No | Yes | Yes | Yes |
| Olsen *et al*[60] | 2005 | Sweden | Sahlgrenska University Hospital, Goteborg | No | Yes | No | No | No | Yes | Yes | No |
| Lagergren *et al*[61] | 2007 | United Kingdom | University of Bristol, Bristol | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes |
| Djarv *et al*[62] | 2008 | Sweden | Karolinska Institute, Stockholm | Yes | Yes | Yes | No | No | Yes | Yes | Yes |
| Courrech Staal *et al*[63] | 2010 | Netherlands | Netherlands Cancer Institute, Amsterdam | Yes | Yes | Yes | No | No | Yes | Yes | No |
| Blazeby *et al*[64] | 1995 | United Kingdom | University of Bristol, Bristol | No | Yes | Yes | No | No | No | Yes | No |
| Ariga *et al*[65] | 2009 | Japan | University of Yamaga, Yamaga | Yes | Yes | No | No | No | Yes | Yes | No |
| Schneider *et al*[48] | 2010 | Germany | University of Heidelberg, Heidelberg | Yes | Yes | Yes | Yes | No | Yes | Yes | No |
| Rosmolen *et al*[51] | 2010 | Netherlands | Academic Medical Center, Amsterdam | No | Yes | Yes | No | Yes | Yes | Yes | No |

The 21 studies included in the analysis are listed according their aim and then chronologically. HRQL: Health-related quality of life; SF36: Short form-36.

dergone esophagectomy alone. Based on these studies, data for the patients who had undergone neoadjuvant therapy and esophagectomy were identified. Data from the study by Reynolds *et al*[55] were uploaded for meta-analysis, but could not be used because the standard deviation values were missing. The baseline scores were compared to scores obtained after a 6-mo follow-up. The EORTC- QLQ-C30 global scale results tended to be better at the baseline than at the 6-mo follow-up ($P = 0.08$), and physical function was also better at the baseline ($P < 0.001$). Likewise, the symptom scales showed worsened fatigue, dyspnea and diarrhea 6 mo after the procedure ($P < 0.001$, $P < 0.001$ and $P < 0.001$, respectively). In contrast, emotional function had significantly improved after 6 mo ($P < 0.001$). The significant weighted mean difference results associated with the comparison between the baseline HRQL figures and the figures achieved 6 mo after neoadjuvant therapy and esophagectomy are shown in Figure 4.

### *Generic and disease specific HRQL after minimally invasive esophagectomy*

Two studies prospectively analyzed the generic and disease-specific HRQL of 255 patients using the EORTC-QLQ-C-30 and OES-18 questionnaires at different points on the follow-up timeline (baseline, 3, 6, 9 and 12 mo) after minimally invasive esophagectomy[58,59]. The surgical techniques used in the two studies were similar and included thoracoscopic esophageal mobilization and mediastinal lymphadenectomy, followed by laparoscopic gastric mobilization and resection, and abdominal lymph-

**Table 3 Patient characteristics**

| Study | Patients | Median/[1]mean age (range) | Recruitment period | Adenocarcinoma | Squamous cell carcinoma | Tis/ HGD/ pCR | Stage I | Stage II | Stage III | Stage IV | Lower esophagus or cardias | Medium or upper esophagus | Mean/[1]median follow up (mo) | Esophago-gastroplasty | Esophago-colonplasty | Esophago-jejeunoplasty | Neoadjuvant treatment | Adjuvant RT/CT/ CT+RT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| McLarty *et al*[54] | 107 | 62 (30-81) | 1972-1990 | 72 | 28 | 0 | 34 | 73 | 0 | | 62 | 45 | > 60 | 99 | 3 | 4 | 0 | 9 |
| De Boer *et al*[53] | 35 | 66.4[1] (42-87) | 1993-1996 | 27 | 6 | 2 | 14 | 1 | 18 | | 32 | 3 | > 24 | 35 | 0 | | 0 | |
| Headrick *et al*[49] | 54 | 64 (36-83) | 1991-1997 | 53 | 1 | 5/35 | 7 | 2 | 5 | | 54 | 0 | 63.6[1] (6-108) | | | | | |
| Cense *et al*[52] | 14 | 69.9 (51-81) ECP, 66.4 (42-87) EGP | 1993-2002 | 6 | 7 | 1 | 8 | 3 | 2 | | 10 | 3 | 35 (7-97) | 0 | 14 | | | |
| Moraca *et al*[50] | 36 | 66[1] (43-88) | 1991-2003 | 35 | 0 | 12/24 | 12 | | | | | | 58.8 (6-144) | 36 | 0 | 0 | 0 | 0 |
| Subtotal | 246 (14-107) | | | 193 | 42 | 3 | 75 | 79 | 25 | 0 | 158 | 51 | 0 | 170 | 17 | 4 | 0 | 9 |
| Reynolds *et al*[55] | 107 | 61 (29-79) | 1999-2004 | 34 | 68 | | 25 | 63 | 83 | 3 | | | 3 | | | | 87 | 87 |
| Avery *et al*[56] | 94 | 62.4[1] | 2000-2004 | 64 | 17 | | | 14 | 67 | | | | 1.5 | | | | 69 | 69 |
| van Meerten *et al*[57] | 54 | 59 (40-75) | 2001-2004 | 41 | 12 | 13 | 12 | 6 | 16 | 5 | 49 | 5 | 3 | | | | 54 | 54 |
| Subtotal | 255 (54-107) | | | 239 | 97 | 13 | 37 | 83 | 166 | 8 | 49 | 5 | 7.5 | 0 | 0 | 0 | 210 | 210 |
| Wang *et al*[59] | 56 | 60.7 ± 9.3 VATS 58.2 ± 11.5 open | 2007-2008 | 3 | 52 | | 11 | 37 | 8 | | 10 | 46 | 6 | 56 | | | 0 | |
| Parameswaran *et al*[58] | 62 | 67 (49-80) | 2005-2007 | 57 | 5 | 3 | 7 | 21 | 27 | 4 | | | 12 ± 0.5 | 62 | | | 48 | |
| Subtotal | 118 (56-62) | | | 60 | 57 | 3 | 18 | 58 | 35 | 4 | 10 | 46 | 6 | 118 | 0 | 0 | 48 | 0 |
| Viklund *et al*[45] | | 64 (34-84)[1] | 2001-2003 | | | | | | | | | | 6 | | | | | 16 |
| Rutegard *et al*[46] | | 91 pts < 60, 127 pts 60-70, 137 pts >70 | 2001-2005 | | | | | | | | | | 6 | | | | 37 | |
| Rutegard *et al*[47] | 355 | 91 pts < 60, 127 pts 60-70, 137 pts > 70 | 2001-2005 | 271 | 84 | | 81 | 120 | 133 | 18 | 302 | 53 | 6 | | | | 37 | |
| Subtotal | 355 | | | | | | | | | | | | | | | | | |
| Olsen *et al*[60] | 18 | 62.5 (20-76) | 1997-2001 | | | 3 | 5 | 1 | 9 | | | | 24 | 13 | 4 | 1 | 8 | 8 |
| Lagergren *et al*[61] | 47 | 63 (44-79) | 2000-2003 | 35 | 9 | 8 | 10 | 23 | 6 | | 23 | 24 | > 36 | | | | 29 | |
| Djarv *et al*[62] | 87 | 27 pts < 60, 28 pts 60-70, 32 pts > 70 | 2001-2007 | 68 | 19 | | 34 | 36 | 13 | 3 | 75 | 12 | > 36 | 69 | 2 | 16 | | |
| Courrech Staal *et al*[63] | 36 | | 2009 | 22 | 14 | 0 | 4 | 12 | 12 | 8 | 28 | 8 | 54 (range, 16–162) | | | | 21 | |
| Subtotal | 188 (18-87) | | | 125 | 42 | 8 | 53 | 72 | 40 | 11 | 126 | 44 | | 82 | 6 | 17 | 58 | 8 |
| Blazeby *et al*[64] | 33 | 64 (62-76) | 1993-1994 | 19 | 14 | | | | | | | | 4 (2.5-6) | | | | 0 | |
| Ariga *et al*[65] | 48 | 65.5 (46-78) | 2001-2004 | 0 | 48 | | 10 | 15 | 23 | | 20 | 28 | 41.2 (95% CI: 35.1-47.2) | | | | | |
| Schneider *et al*[48] | 12 | 59 | 2001-2005 | 1 | 11 | | | | | | | | > 9 | 10 | 2 | | | |
| Rosmolen *et al*[51] | 27 | 63.0 (9.5) | 2001-2005 | 27 | 0 | 2 | 19 | 6 | | | | | 24 (IQR 17 – 35) | 23 | 4 | | 0 | 0 |
| Subtotal | 120 (12-48) | | | 47 | 73 | 2 | 29 | 21 | 23 | 0 | 20 | 28 | | 33 | 6 | 0 | 0 | 0 |

The 21 studies included in the analysis are listed according their aim and then chronologically. pts: Patients; ECP: Esophagocolonplasty; EGP: Esophagogastroplasty; VATS: Video assisted thoracoscopy; CI: Confidence interval; HGD: High grade dysplasia; pCR: Pathological complete response; RT: Radiotherapy; CT: Chemotherapy; IQR: Interquartile range.

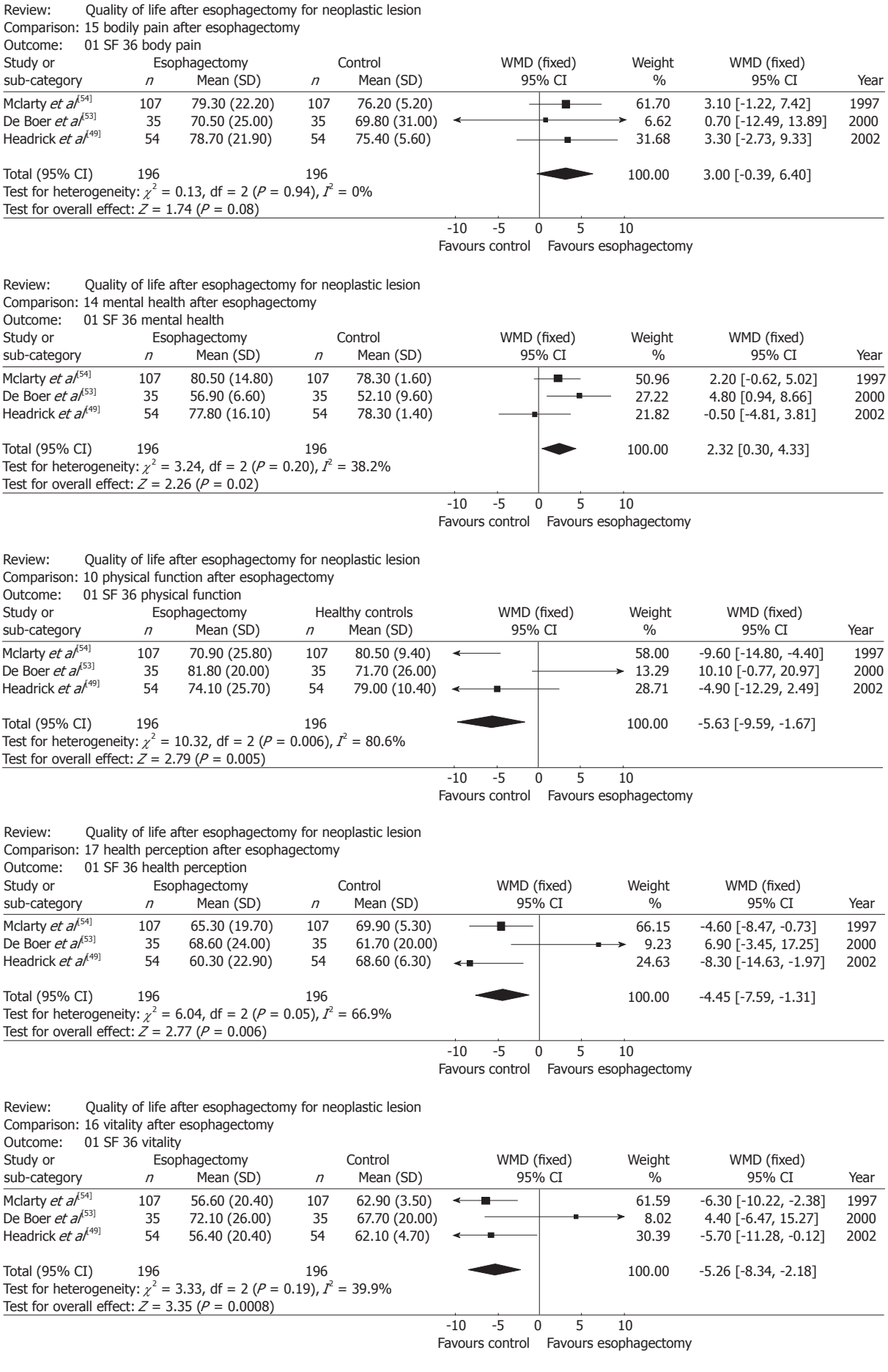



**Figure 3 Long term generic health-related quality of life in patients after esophagectomy for esophageal cancer.** WMD: Weighted mean difference; SF: Short form.

Review: Quality of life after esophagectomy for neoplastic lesion
Comparison: 18 global EORTC C30 scale in patients after neoadjuvant CT-RT and esophagectomy
Outcome: 01 EORTC C30 global scale

| Study or sub-category | Baseline *n* | Baseline Mean (SD) | 6 mo po *n* | 6 mo po Mean (SD) | WMD (fixed) 95% CI | Weight % | WMD (fixed) 95% CI | Year |
|---|---|---|---|---|---|---|---|---|
| Reynolds *et al*[55] | 41 | 82.00 (0.00) | 41 | 74.00 (0.00) | | | Not estimable | 2006 |
| Avery *et al*[56] | 69 | 70.00 (21.00) | 69 | 64.00 (23.00) | | 43.85 | 6.00 [-1.35, 13.35] | 2007 |
| van Meerten *et al*[57] | 50 | 78.00 (15.00) | 50 | 75.00 (18.00) | | 56.15 | 3.00 [-3.49, 9.49] | 2008 |
| Total (95% CI) | 160 | | 160 | | | 100.00 | 4.32 [-0.55, 9.18] | |

Test for heterogeneity: $\chi^2$ = 0.36, df = 1 ($P$ = 0.55), $I^2$ = 0%
Test for overall effect: $Z$ = 1.74 ($P$ = 0.08)

-10 -5 0 5 10
Favours post op Favours baseline

Review: Quality of life after esophagectomy for neoplastic lesion
Comparison: 19 physical function in patients after neoadjuvant CT-RT and esophagectomy
Outcome: 01 EORTC C30 physical function

| Study or sub-category | Baseline *n* | Baseline Mean (SD) | 6 mo post op *n* | 6 mo post op Mean (SD) | WMD (fixed) 95% CI | Weight % | WMD (fixed) 95% CI | Year |
|---|---|---|---|---|---|---|---|---|
| Reynolds *et al*[55] | 41 | 79.00 (0.00) | 41 | 78.00 (0.00) | | | Not estimable | 2006 |
| Avery *et al*[56] | 69 | 89.00 (20.00) | 69 | 76.00 (18.00) | | 44.75 | 13.00 [6.65, 19.35] | 2007 |
| van Meerten *et al*[57] | 50 | 95.00 (8.00) | 50 | 83.00 (19.00) | | 55.25 | 12.00 [6.29, 17.71] | 2008 |
| Total (95% CI) | 160 | | 160 | | | 100.00 | 12.45 [8.20, 16.69] | |

Test for heterogeneity: $\chi^2$ = 0.05, df = 1 ($P$ = 0.82), $I^2$ = 0%
Test for overall effect: $Z$ = 5.74 ($P$ < 0.00001)

-100 -50 0 50 100
Favours post op Favours baseline

Review: Quality of life after esophagectomy for neoplastic lesion
Comparison: 20 emotional function in patients after neoadjuvant CT-RT and esophagectomy
Outcome: 01 EORTC C30 emotional function

| Study or sub-category | Baseline *n* | Baseline Mean (SD) | 6 mo po *n* | 6 mo po Mean (SD) | WMD (fixed) 95% CI | Weight % | WMD (fixed) 95% CI | Year |
|---|---|---|---|---|---|---|---|---|
| Reynolds *et al*[55] | 41 | 76.00 (0.00) | 41 | 75.00 (0.00) | | | Not estimable | 2006 |
| Avery *et al*[56] | 69 | 71.00 (25.00) | 69 | 78.00 (25.00) | | 43.06 | -7.00 [-15.34, 1.34] | 2007 |
| van Meerten *et al*[57] | 50 | 74.00 (19.00) | 50 | 85.00 (18.00) | | 56.94 | -11.00 [-18.25, -3.75] | 2008 |
| Total (95% CI) | 160 | | 160 | | | 100.00 | -9.28 [-14.75, -3.80] | |

Test for heterogeneity: $\chi^2$ = 0.50, df = 1 ($P$ = 0.48), $I^2$ = 0%
Test for overall effect: $Z$ = 3.32 ($P$ = 0.0009)

-100 -50 0 50 100
Favours 6 mo po Favours baseline

Review: Quality of life after esophagectomy for neoplastic lesion
Comparison: 21 fatigue in patients after neoadjuvant CT-RT and esophagectomy
Outcome: 01 EORTC C30 fatigue

| Study or sub-category | Baseline *n* | Baseline Mean (SD) | 6 mo post op *n* | 6 mo post op Mean (SD) | WMD (fixed) 95% CI | Weight % | WMD (fixed) 95% CI | Year |
|---|---|---|---|---|---|---|---|---|
| Reynolds *et al*[55] | 41 | 36.00 (0.00) | 41 | 36.00 (0.00) | | | Not estimable | 2006 |
| Avery *et al*[56] | 69 | 27.00 (25.00) | 69 | 39.00 (26.00) | | 38.33 | -12.00 [-20.51, -3.49] | 2007 |
| van Meerten *et al*[57] | 50 | 14.00 (15.00) | 50 | 28.00 (19.00) | | 61.67 | -14.00 [-20.71, -7.29] | 2008 |
| Total (95% CI) | 160 | | 160 | | | 100.00 | -13.23 [-18.50, -7.96] | |

Test for heterogeneity: $\chi^2$ = 0.13, df = 1 ($P$ = 0.72), $I^2$ = 0%
Test for overall effect: $Z$ = 4.92 ($P$ < 0.00001)

-100 -50 0 50 100
Favours baseline Favours post op

Review: Quality of life after esophagectomy for neoplastic lesion
Comparison: 22 dyspnea in patients after neoadjuvant CT-RT and esophagectomy
Outcome: 01 EORTC C30 dyspnea

| Study or sub-category | Baseline *n* | Baseline Mean (SD) | 6 mo post op *n* | 6 mo post op Mean (SD) | WMD (fixed) 95% CI | Weight % | WMD (fixed) 95% CI | Year |
|---|---|---|---|---|---|---|---|---|
| Reynolds *et al*[55] | 41 | 11.00 (0.00) | 41 | 27.00 (0.00) | | | Not estimable | 2006 |
| Avery *et al*[56] | 69 | 6.00 (17.00) | 69 | 28.00 (30.00) | | 48.18 | -22.00 [-30.14, -13.86] | 2007 |
| van Meerten *et al*[57] | 50 | 7.00 (15.00) | 50 | 20.00 (24.00) | | 51.82 | -13.00 [-20.84, -5.16] | 2008 |
| Total (95% CI) | 160 | | 160 | | | 100.00 | -17.34 [-22.98, -11.69] | |

Test for heterogeneity: $\chi^2$ = 2.44, df = 1 ($P$ = 0.12), $I^2$ = 58.9%
Test for overall effect: $Z$ = 6.02 ($P$ < 0.00001)

-100 -50 0 50 100
Favours baseline Favours post op

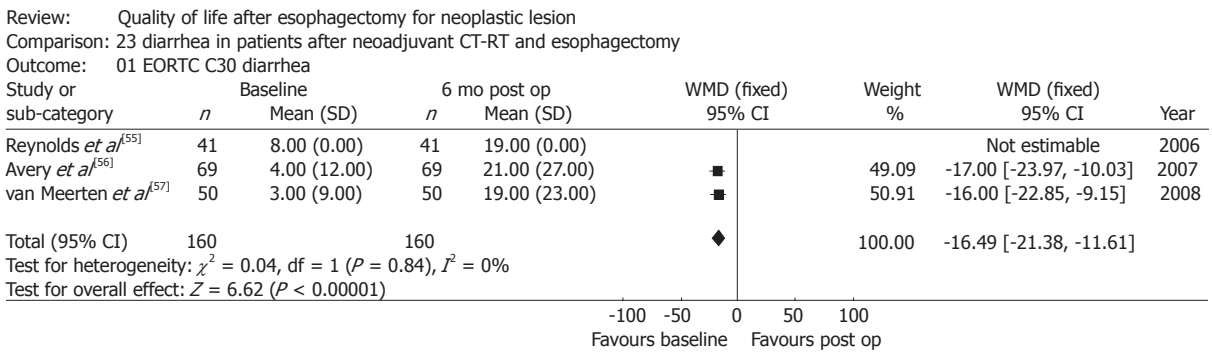



**Figure 4 Generic and disease specific health-related quality of life in patients after neoadjuvant chemotherapy-radiotherapy and esophagectomy for esophageal cancer.** WMD: Weighted mean difference; CT-RT: Chemotherapy-radiotherapy; EORTC: European Organization for Research and Treatment of Cancer; op: Operative; po: Post-operative.

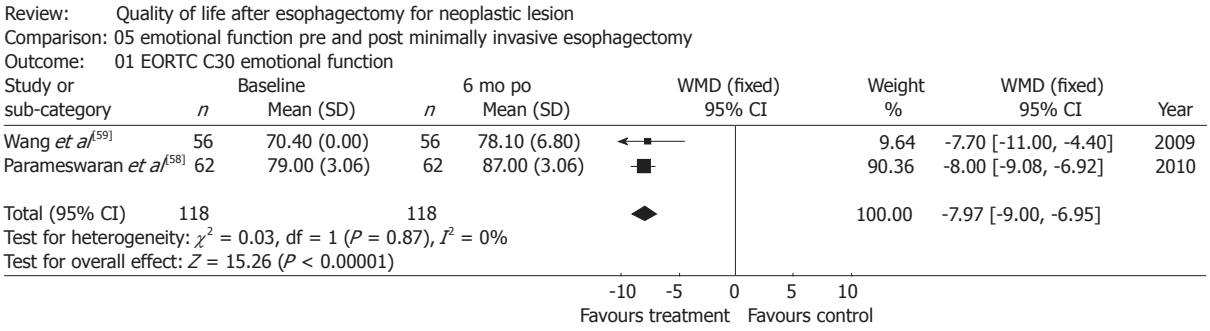
adenectomy. Wang *et al*[59] compared the HRQL results achieved after minimally invasive esophagectomy with those achieved after open esophagectomy, and the study by Parameswaran *et al*[58] was an uncontrolled prospective study. Therefore, the baseline scores were compared to scores obtained during a 6-mo follow-up. Social function, cognitive function, emotional function and dysphagia proved to be significantly improved during the 6-mo follow-up ($P < 0.001$, $P < 0.001$, $P < 0.001$ and $P < 0.001$, respectively). In contrast, physical function was better at the baseline ($P < 0.001$), and role function tended to appear worse at the 6-mo follow-up point. The significant weighted mean difference results associated with the comparison between the baseline HRQL figures and the figures from 6 mo after neoadjuvant therapy and esophagectomy are shown in Figure 5.

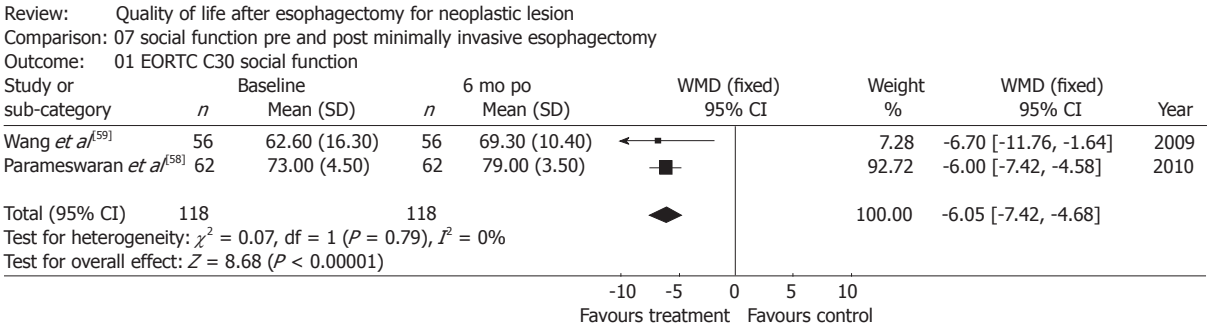
### *Predictors of generic and disease specific HRQL after esophagectomy*

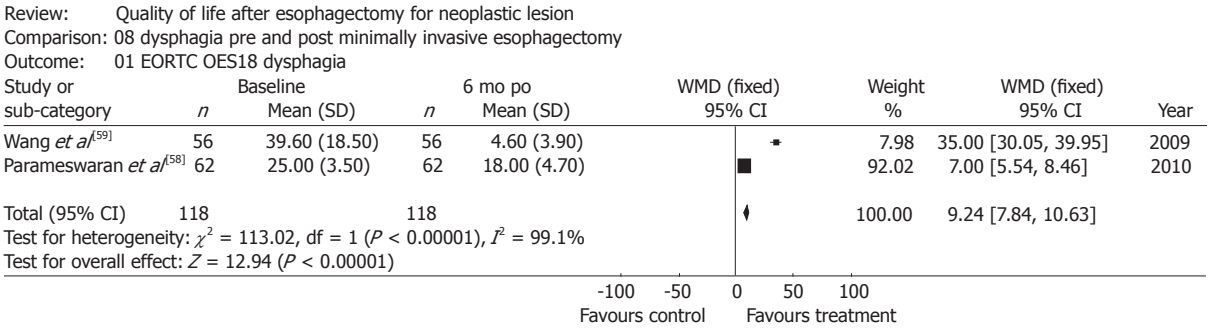
Three articles from the Karolinska Institute, Stockholm specifically investigated predictors of generic and disease-specific HRQL after esophagectomy for cancer by analyzing the data from the Swedish Esophageal and Cardia Cancer register, which had conducted a nationwide, prospective, population-based study of how esophageal surgery-related factors had influenced quality of life 6 mo after surgery[45-47]. Although they reported information from the same dataset, these studies were all included in the review because they analyzed different aspects of HRQL after esophagectomy. The first study, by Viklund *et al*[45], included 100 patients and indicated that surgery-related complications were the main predictor of reduced global quality of life 6 mo after surgery. Except for anastomotic strictures, each of the predefined complications (e.g., anastomotic leakage, infections, cardiopulmonary complications, and operative technical complications) contributed to a decrease in quality-of-life scores. Rutegard *et al*[46], using a larger study population, showed that extensive surgery (characterized as using the transthoracic approach, extensive lymphadenectomy, and wider resection margins and as being of a longer duration) was not associated with worse HRQL measures than less extensive operations. Moreover, they observed that the severity of dysphagia was similar in patients who had handsewn and stapled anastomoses. Technical surgical complications were confirmed to have a deleterious effect on several aspects of HRQL. Finally, the same group concluded that no clinically relevant differences in terms of generic and disease-specific HRQL were found to be correlated with differences in the volume of surgeries conducted at hospitals (low volume: 0-9 operations/year; high volume: > 9 operations/year) or by particular surgeons (low volume: 0-6 operations/year; high-volume: > 6 operations/year)[47].

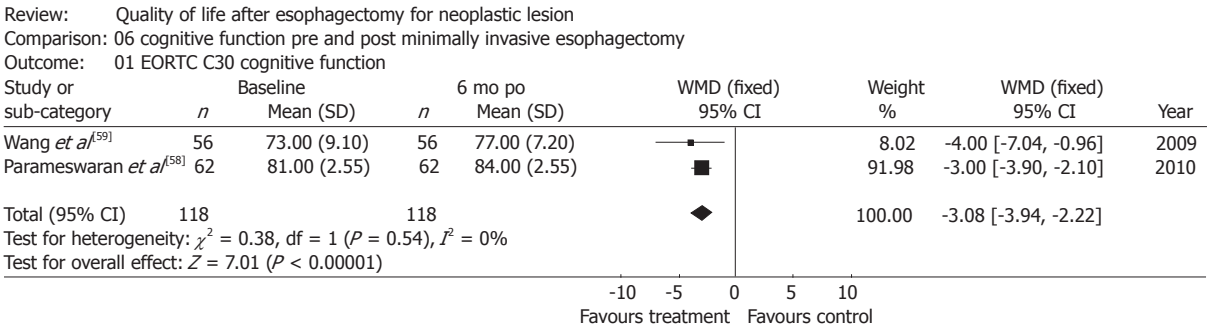
### *Long-term generic and disease-specific HRQL after esophagectomy*

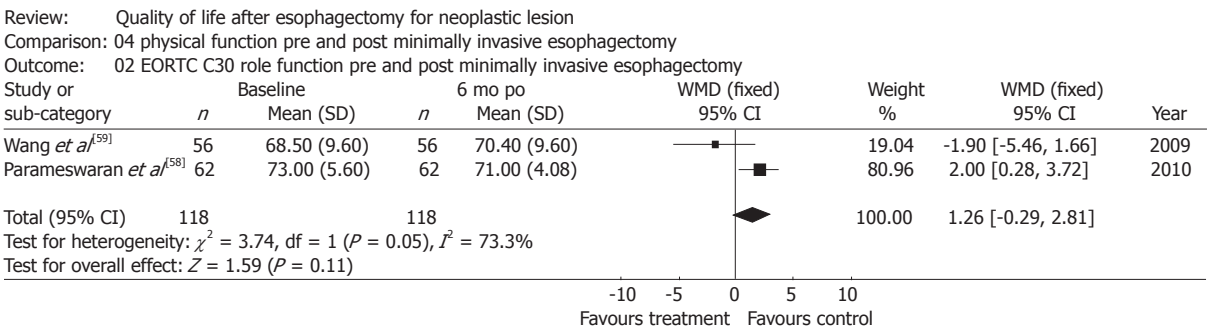
Data from the articles that analyzed long-term generic and disease-specific HRQL after esophagectomy were collected, but their clinical heterogeneity was so high that it was impossible to pool them. Four studies analyzed the generic HRQL of 152 (18-87) patients using the QLC-30 questionnaire and evaluated disease-specific HRQL using the OES-18 questionnaire in conducting long-term follow-up[60-63]. Fagevik *et al*[60] evaluated 18 patients 2 years after thoraco-abdominal esophageal resection and observed that, 2 years after surgery, respiratory function was significantly lower than it was prior to surgery, as was physical performance. In contrast, HQRL was comparable to age- and sex-matched population norms for most other functions. After 2 years, diarrhea, dyspnea, appetite loss and fatigue were still clinically significant. Similarly, Lagergren *et al*[61] analyzed 47 patients who had survived for at least 3 years after esophagectomy for a malignant disease. In these long-term survivors, most HRQL items had returned to preoperative levels by the 3-year assessment; however, their scores for physical function, breathlessness, diarrhea, and reflux remained significantly worse than at the baseline. Nevertheless, patients reported significantly better emotional function 3 years after surgery than before treatment. Djärv *et al*[62] reported the results for a cohort of 87 patients who had survived for at least 3 years after esophagectomy for cancer, using data from the prospective Swedish nationwide population study. As in other studies, these patients reported significantly more problems with fatigue, diarrhea, appetite loss, nausea and


Review: Quality of life after esophagectomy for neoplastic lesion
Comparison: 05 emotional function pre and post minimally invasive esophagectomy
Outcome: 01 EORTC C30 emotional function
Study or sub-category | n | Baseline Mean (SD) | n | 6 mo po Mean (SD) | WMD (fixed) 95% CI | Weight % | WMD (fixed) 95% CI | Year
Wang et al[59] 56 70.40 (0.00) 56 78.10 (6.80) 9.64 -7.70 [-11.00, -4.40] 2009
Parameswaran et al[58] 62 79.00 (3.06) 62 87.00 (3.06) 90.36 -8.00 [-9.08, -6.92] 2010
Total (95% CI) 118 118 100.00 -7.97 [-9.00, -6.95]
Test for heterogeneity: $\chi^2$ = 0.03, df = 1 ($P$ = 0.87), $I^2$ = 0%
Test for overall effect: $Z$ = 15.26 ($P$ < 0.00001)
-10 -5 0 5 10
Favours treatment Favours control


Review: Quality of life after esophagectomy for neoplastic lesion
Comparison: 07 social function pre and post minimally invasive esophagectomy
Outcome: 01 EORTC C30 social function
Study or sub-category | n | Baseline Mean (SD) | n | 6 mo po Mean (SD) | WMD (fixed) 95% CI | Weight % | WMD (fixed) 95% CI | Year
Wang et al[59] 56 62.60 (16.30) 56 69.30 (10.40) 7.28 -6.70 [-11.76, -1.64] 2009
Parameswaran et al[58] 62 73.00 (4.50) 62 79.00 (3.50) 92.72 -6.00 [-7.42, -4.58] 2010
Total (95% CI) 118 118 100.00 -6.05 [-7.42, -4.68]
Test for heterogeneity: $\chi^2$ = 0.07, df = 1 ($P$ = 0.79), $I^2$ = 0%
Test for overall effect: $Z$ = 8.68 ($P$ < 0.00001)
-10 -5 0 5 10
Favours treatment Favours control


Review: Quality of life after esophagectomy for neoplastic lesion
Comparison: 08 dysphagia pre and post minimally invasive esophagectomy
Outcome: 01 EORTC OES18 dysphagia
Study or sub-category | n | Baseline Mean (SD) | n | 6 mo po Mean (SD) | WMD (fixed) 95% CI | Weight % | WMD (fixed) 95% CI | Year
Wang et al[59] 56 39.60 (18.50) 56 4.60 (3.90) 7.98 35.00 [30.05, 39.95] 2009
Parameswaran et al[58] 62 25.00 (3.50) 62 18.00 (4.70) 92.02 7.00 [5.54, 8.46] 2010
Total (95% CI) 118 118 100.00 9.24 [7.84, 10.63]
Test for heterogeneity: $\chi^2$ = 113.02, df = 1 ($P$ < 0.00001), $I^2$ = 99.1%
Test for overall effect: $Z$ = 12.94 ($P$ < 0.00001)
-100 -50 0 50 100
Favours control Favours treatment


Review: Quality of life after esophagectomy for neoplastic lesion
Comparison: 06 cognitive function pre and post minimally invasive esophagectomy
Outcome: 01 EORTC C30 cognitive function
Study or sub-category | n | Baseline Mean (SD) | n | 6 mo po Mean (SD) | WMD (fixed) 95% CI | Weight % | WMD (fixed) 95% CI | Year
Wang et al[59] 56 73.00 (9.10) 56 77.00 (7.20) 8.02 -4.00 [-7.04, -0.96] 2009
Parameswaran et al[58] 62 81.00 (2.55) 62 84.00 (2.55) 91.98 -3.00 [-3.90, -2.10] 2010
Total (95% CI) 118 118 100.00 -3.08 [-3.94, -2.22]
Test for heterogeneity: $\chi^2$ = 0.38, df = 1 ($P$ = 0.54), $I^2$ = 0%
Test for overall effect: $Z$ = 7.01 ($P$ < 0.00001)
-10 -5 0 5 10
Favours treatment Favours control


Review: Quality of life after esophagectomy for neoplastic lesion
Comparison: 04 physical function pre and post minimally invasive esophagectomy
Outcome: 02 EORTC C30 role function pre and post minimally invasive esophagectomy
Study or sub-category | n | Baseline Mean (SD) | n | 6 mo po Mean (SD) | WMD (fixed) 95% CI | Weight % | WMD (fixed) 95% CI | Year
Wang et al[59] 56 68.50 (9.60) 56 70.40 (9.60) 19.04 -1.90 [-5.46, 1.66] 2009
Parameswaran et al[58] 62 73.00 (5.60) 62 71.00 (4.08) 80.96 2.00 [0.28, 3.72] 2010
Total (95% CI) 118 118 100.00 1.26 [-0.29, 2.81]
Test for heterogeneity: $\chi^2$ = 3.74, df = 1 ($P$ = 0.05), $I^2$ = 73.3%
Test for overall effect: $Z$ = 1.59 ($P$ = 0.11)
-10 -5 0 5 10
Favours treatment Favours control

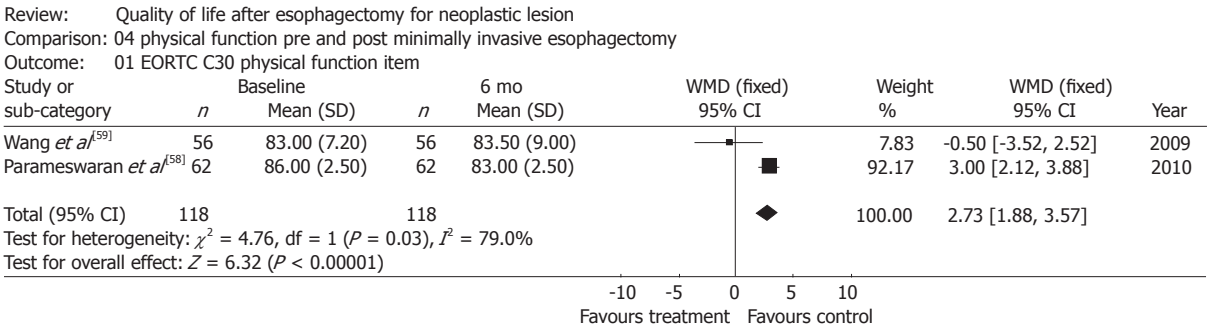



**Figure 5 Generic and disease specific health-related quality of life after minimally invasive surgery for esophageal cancer.** WMD: Weighted mean difference; EORTC: European Organization for Research and Treatment of Cancer; po: Post-operative.

vomiting than did those in the reference population, and they also reported significantly poorer role and social function. Finally, Courrech Staal *et al*[63] compared the generic and disease-specific HRQL of 36 patients with esophagectomy (who had or had not received neoadjuvant therapy) after a median follow-up of 54 mo with the data for a reference sample of patients with esophageal cancer (1031 patients) and with that of the general population (7802 subjects). These long-term survivors reported better health-related quality of life than the reference sample of patients with esophageal cancer, even if their HRQL appeared lower than that of the reference sample of individuals from the general population[63].

## PECULIAR ASPECTS OF HRQL AFTER ESOPHAGECTOMY

Data from the four articles that analyzed peculiar aspects of HRQL after esophagectomy were collected, but although the EORTC questionnaires were used, the level of clinical heterogeneity was so high that it was impossible to pool them[48,51,64,65]. In 1995, in one of the first studies focused on HRQL, Blazeby *et al*[64] observed that patients treated using esophagectomy reported significantly better physical, emotional, cognitive, and global health scores than did those who had received palliative treatment. These patients also had significantly worse pain, fatigue, appetite loss, constipation, and dysphagia. Ariga *et al*[65] performed a prospective direct comparison of outcomes after treatment in patients with resectable esophageal cancer who had received definitive chemoradiation and those who had undergone surgery alone. They surveyed HRQL in patients who had survived more than 2 years using a cross-sectional approach, and concluded that the HRQL of patients who had definitive chemoradiation and that of patients who had undergone surgery alone were similar. Diarrhea, appetite loss and eating problem scores were worse in patients who had undergone surgery alone than in those who had undergone chemoradiation[65]. Moreover, Schneider *et al*[48] compared the HRQL of those patients who had undergone elective and emergency esophagectomy with those who had undergone collar reconstruction. They observed a temporary decrease in postoperative HRQL in both groups and a return to preoperative values during the follow-up except for physical functioning, which remained decreased in patients who had undergone elective esophagectomy for cancer. Finally, Rosmolen *et al*[51] compared HRQL and fear of cancer among 81 patients who had undergone endoscopic treatment and 27 patients who had undergone surgery for early Barrett's neoplasia. They observed that patients in the surgery group reported significantly more eating problems and reflux symptoms on the EORTC-OES18 questionnaire, whereas endoscopy patients reported more fear of recurrence than surgery patients. They concluded that preserving the esophagus after endoscopy, which is preferable from a clinical perspective, may induce fear of cancer recurrence[51].

## CONCLUSION

Esophageal cancer is an increasingly common cancer with a poor prognosis. Esophagectomy is the standard treatment for those patients who present with resectable esophageal cancer[3-5], but it still offers a limited (25%-35%) chance of cure[5,6] and is associated with considerable risk of serious complications[4,5,7]. For a long time, morbidity and mortality represented the main, and often the only, outcome measures that could be used to evaluate esophagectomy for esophageal cancer. The morbidity and mortality rates associated with the procedure and the patients' poor survival rates due to the aggressive nature of the disease left almost no space for further analysis. However, in recent decades, along with the increased success of the therapy, HRQL has become an important outcome parameter in addition to survival, mortality, and complication rates[67]. In fact, postoperative HRQL can yield information that is relevant for clinical decision-making and help to inform patients about the long-term consequences of surgery. With that in mind, this systematic review was designed to collect and analyze data reflecting patterns in HRQL after curative surgery for esophageal cancer.

Twenty-one studies published between 1995 and 2011 were included in this analysis. One limitation of this review is the clinical heterogeneity of the studies included. To increase homogeneity, only studies performed using SF36 or with EORTC-QLQ-C30 and OES18 (or the pre-

vious version, OES24) were included. Nevertheless, virtually every study used a different surgical approach and a different means of comparison, and they also did not present exact data. Furthermore, data for the recruited patients were collected during a range of intervals after surgery. Therefore, it was very difficult and sometimes impossible to obtain sufficiently homogeneous data to recalculate the statistical analyses or perform a meaningful meta-analysis. For example, 5 studies analyzed long-term generic HRQL after esophagectomy in comparison with that of healthy subjects using SF-36 questionnaires distributed at roughly comparable intervals after esophagectomy[49,50,52-54] but two studies could not be used for the meta-analysis, one because the SF-36 scores were not reported in a standard or comparable way and the other because all patients underwent esophagocoloplasty[50,52].

On the other hand, the remaining three studies were sufficiently homogenous, and thus, a meta-analysis of their results was attempted[49,53,54]. In these three studies, the pooled scores for physical, role, and social function after esophagectomy were similar to sex- and age-matched United States norms. In contrast, in a group of patients with similar follow-up, Djärv *et al*[62] and Courrech *et al*[63] observed significantly poorer role and social function. Differences between the HRQL measurement tools (SF36 and QLQ C30) may have created this difference in the results, and cross-cultural differences among the different groups of patients may also have been a factor. Health-related quality of life may vary from one population to another according to differences in cultural heritage, value systems, family structure, medical systems, values and norms related to illness-related communication, and other factors[67].

In the three studies that analyzed long-term generic HRQL after esophagectomy *vs* in healthy subjects, the pooled physical function, vitality and general health perception scores were lower than the sex- and age-matched norms[49,53,54]. Similarly, in patients alive at 3 years analyzed using the EORTC-QLQ-C30 and OES18, Djärv *et al*[62] and Courrech *et al*[63] reported encountering significantly more problems with fatigue, diarrhea, appetite loss, nausea and vomiting than in the reference population. Moreover, Lagergren *et al*[61] and Fagevik *et al*[60] observed that scores for physical function, breathlessness, diarrhea, and reflux were significantly worse than at the baseline. Finally, also in the three studies that prospectively analyzed generic and disease-specific HRQL using QLC-30 and OES-18 questionnaires after neoadjuvant therapy and esophagectomy, the EORTC C30 global scale results tended to be worse 6 mo after esophagectomy, as were physical function, fatigue, dyspnea and diarrhea[55-57]. Physical function impairment is a long-term consequence of esophagectomy that can involve either the respiratory system (which can be impaired by the thoracotomy sequelae) or the alimentary tract (which can be affected by accelerated transit and functional sequelae).

In contrast, in the three studies that compared HRQL after esophagectomy to that of healthy subjects using SF-36, bodily pain and mental health in long-term survivors after esophagectomy was higher than normal[49,53,54]. Similarly, in the three studies that prospectively analyzed generic and disease-specific HRQL using QLC-30 and OES-18 questionnaires after neoadjuvant therapy and esophagectomy, emotional function was significantly better at the time of the 6-mo follow up[55-57]. Moreover, Lagergren *et al*[61] observed that long-term survivors reported significantly better emotional function even 3 years after surgery. The short- and long-term improvement in emotional function in patients successfully operated on for esophageal cancer may be attributed to their sensation of having been quite close to death and having survived. In our opinion, this experience is different to that of having survived a car accident because of the duration, which can give patients sufficient time to experience the challenge in a positive way. On the other hand, it should be noted that this improved emotional function was observed in survivors.

Several studies analyzed a specific aspect of HRQL after esophagectomy. Two studies prospectively analyzed generic and disease-specific HRQL after minimally invasive esophagectomy[58,59]. The surgical techniques reported on in both studies were similar, and thus, it was possible to compare the results. The results were similar to those report by larger studies performed with group of patients who had undergone open esophagectomy, in that these patients experienced significantly improved social function, cognitive function, emotional function and dysphagia. However, physical function worsened 6 mo after esophagectomy[58,59]. In their direct comparison, Wang *et al*[59] concluded that global quality of life and physical functioning were better in the minimally invasive group than in the open surgery group. Additional larger studies should explore the exact benefit of minimally invasive esophagectomy in terms of HRQL.

Data from a Swedish nationwide, prospective, population-based study were used in three studies by the Karolinska Institute, Stockholm that investigated the most important predictors of HRQL after surgery for esophageal cancer using data from 6 mo after surgery[45-47]. Unexpectedly, extensive surgery, as used in the transthoracic approach, was not associated with lower HRQL than less invasive operations[46]. No clinically relevant differences in generic or disease-specific HRQL were observed based on the volume of procedures done at hospitals[47]. Age, sex, and body mass index showed no association with HRQL 6 mo after surgery, but patients with comorbidity, tumors in a more advanced stage (Ⅲ to Ⅳ), or tumors located in the middle or upper esophagus exhibited an increased risk of poor HRQL. Moreover, the occurrence of surgery-related complications was the main predictor of reduced postoperative HRQL[45,47]. Except for anastomotic strictures, each of the predefined complications (e.g., anastomotic leakage, infections, cardiopulmonary complications, and operative technical complications) decreased the patients' HRQL scores. In patients with non-neoplastic diseases such as Crohn's disease or ulcerative

colitis, postoperative complications did not seem to have a long-term effect on HRQL[68,69], so the reasons why patients submitted to esophagectomy can experience postoperative complications that can heavily affect HRQL must be different. Firstly, a 6-mo follow-up period may be not sufficiently long enough, as the problems caused by the complications may be still ongoing. Secondly, the different type of surgery that implies usually has thoracotomy play a direct role. In fact, the complications of a thoracotomy may have direct implications for dyspnea, fatigue and pain.

Some articles analyzed more peculiar aspects of HRQL after esophagectomy[48,64,65]. The observation that patients who received palliative treatment had significantly worse pain, fatigue, appetite loss, constipation, and dysphagia might be expected[64]. In contrast, the results presented by Ariga *et al*[65] are much less expected. They observed that patients with squamous cell carcinoma who underwent definitive chemoradiation had similar general HRQL scores and lower diarrhea, appetite loss and eating problem scores than those who had undergone surgery alone[65]. These results could be mainly attributed to the effect of the loss of function of the stomach transposed in the thorax. Schneider *et al*[48] observed the persistence of decreased physical functioning in patients who had undergone elective esophagectomy for cancer, as compared to patients who had undergone emergency esophagectomy for benign conditions. The conclusions of this study may suggest that the long-term impairment of physical functioning could be due more to the cancer itself or to radiation/chemotherapy than to esophagectomy. Finally, the analysis of the HRQL after endoscopic treatment and surgery for early Barrett's neoplasia showed that conservative, non-definitive treatments such as endoscopic ablation may cause more fear of recurrence than more invasive but definitive treatments, such as esophagectomy[51]. Fear of cancer recurrence may negatively impact HRQL, and proper counseling may be advisable when patients elect such options[51].

In conclusion, short- and long-term generic and disease-specific HRQL is deeply affected by esophagectomy for cancer. The impairment of physical function may be a long-term consequence of esophagectomy and can involve either the respiratory system (which can be impaired by the thoracotomy sequelae) or the alimentary tract (which can be affected by accelerated transit and functional sequelae). The short- and long-term improvement in the emotional function of patients who have been successfully operated on may be attributed to their impression of having survived a near-death experience.

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