

Long-term outcome in patients operated with hybrid esophagectomy for esophageal cancer – a cohort study

Tobias Hauge^a, Cecilie Delphin Amdal^{b,d}, Ragnhild Sørum Falk^c, Hans-Olaf Johannessen^a, Egil Johnson^{a,e}

^aDepartment of Pediatric and Gastrointestinal Surgery, Oslo University Hospital, Norway

^bDepartment of Oncology, Oslo University Hospital, Norway

^cOslo Centre for Biostatistics and Epidemiology, Oslo University Hospital, Norway

^dDepartment of Research Support Service, Oslo University Hospital, Norway

^eInstitute of Clinical Medicine, University of Oslo, Oslo, Norway;

Corresponding author:

Egil Johnson

Department of Pediatric and Gastrointestinal Surgery, Oslo University Hospital,

Ullevål, Norway, P. O. Box 4956 Nydalen, 0424 Oslo, Norway, Phone:

004747416334, E-mail: egil.johnson@ous-hf.no

Word count: 3321

Abstract

Background: Over the past two decades hybrid or total minimally invasive esophagectomy for esophageal cancer has increasingly been implemented with the aim to improve morbidity, functional result and ultimately the prognosis in these patients. However, more results are warranted and in this single-center study we report long-time outcome in a cohort of cancer patients treated with hybrid esophagectomy (HE).

Material and methods: Hundred and nine patients with esophageal cancer operated with HE from November 2007 to June 2013 were included. Clinical, pathological and survival data were retrieved from the patient administration system and the Norwegian Cause of Death Registry. Patients alive were asked to fill out the Ogilvie dysphagia score, EORTC QLQ-C30 and EORTC QLQ-OG25. Survival was analyzed by Kaplan-Meier method and prognostic factors by uni- and multivariable Cox regression analyses.

Results: Median overall follow-up time was 55 months (range 2 – **135**) after R0-2 resection (n=109) and **76** months (5 – **135**) for R0 resection (n=100). Five-year overall survival rate was 49% and 53%, respectively. Anastomotic leakage rate and 90-days mortality were 5% and 2%, respectively. Chemo(radiotherapy) and R0 resection improved cancer-specific patient survival. Six patients (6%) had later surgery for metastases to mediastinum, hepatoduodenal ligament, brain, lung, liver or bladder median 26 months (4 – 51) after HE. Forty-one out of 51 patients alive (80%) filled out questionnaires after median **65.5** months (**63 – 123**) follow-up. All patients could eat normal food without (n=37) or with (n=4) problems. Nearly half of the patients reported problems with reflux, one third experienced fatigue and anxiety while one out of four had weight loss and episodes of dyspnea.

Conclusion: In this patient series HE offered low postoperative mortality and good overall long-term survival. Most survivors maintained good quality of life more than five years post treatment. There was a low rate of serious postoperative complications.

Key words: hybrid esophagectomy, survival, dysphagia, quality of life

Background

Esophageal cancer (EC) is the seventh most common cause of cancer worldwide. It is the sixth leading cause of cancer-related mortality and is annually responsible for more than 500.000 deaths.

Besides tumors located in the cervical position, surgical resection with two-field lymphadenectomy (thoracic and abdominal) after chemoradiotherapy or chemotherapy, is the mainstay of treatment for stage II-III cancer [1,2]. Five-year overall survival after resection in major studies varies from 39 – 60% [3-9]. The most commonly used method is the Ivor-Lewis esophagectomy initially performed via open surgery by laparotomy and right sided thoracotomy. However, during the past two decades, in order to improve the outcome related to morbidity and length of hospital stay in these patients, hybrid and total minimally invasive access has increasingly been used [10]. With the hybrid approach either the abdominal or thoracic part of the resection is performed minimally invasive. In a multicenter randomized control study [11] of 207 patients with resectable EC in the mid or lower third of the esophagus or at the gastroesophageal junction (Siewert II), 103 patients were randomly assigned to a hybrid esophagectomy (HE) with laparoscopic gastric mobilization and open right-sided thoracotomy versus an open resection with laparotomy and right-sided thoracotomy for the remaining 104 patients. The patients in the HE group had significantly fewer major intraoperative and 30-days postoperative complications compared to the patients who underwent open resection. In particular, a reduction in major pulmonary complications (18% vs 30%) was demonstrated. At 3-year follow-up there was no significant difference in overall survival and disease-free survival between the hybrid and open groups, with 67% versus 55% and 57% versus 48%, respectively. The main aim of this study was to increase the knowledge on long-time outcome regarding survival, health-related quality of life (HRQL) and dysphagia after hybrid resection for esophageal cancer.

Materials and methods

Patients and treatment

From November 2007 to June 2013 HE was the standard resection technique at our hospital. During these years a total of 118 patients with esophageal (C15.3-5) or gastroesophageal cancer (C16.0) underwent esophagectomy. In 109 patients (92%) the access was hybrid. Eight patients (7%) had open surgery and one (1%) had totally minimally invasive resection. Reasons for choosing open access in eight patients were lack of laparoscopic expertise on the part of the surgeon (n=5), previous laparotomies with adhesions (n=2) and one case of gastrectomy and esophageal resection for cancer of the gastroesophageal junction. **The cohort was analyzed by the intention-to-treat approach, meaning that all 109 patients *intended* to undergo hybrid resection were included in the analysis. A total of five operations were converted to open surgery. These five patients were included in the cohort.** Preoperative work-up was as previously reported [12] according to national guidelines for EC [13]. The patients reported whether they were present smokers. Body mass index (BMI) was calculated from in-hospital measurements of height and weight. ASA score was determined by the anesthesiologist (class I-V; I a normal healthy patient, II a patient with mild systemic disease, III a patient with severe systemic disease, IV a patient with severe systemic disease that is a constant threat to life). All patients had gastroscopy, tumor biopsy, and a CT-scan of the chest and abdomen. Selectively MRI of the chest, PET-CT, spirometry and endoscopic ultrasonography (EUS) for tumor staging or cytological examination of lymph nodes were performed. Staging was performed by using the 6th edition of the TNM classification system from 2002. Stages I, IIa, IIb and III corresponded to T1N0M0, T2-3N0M0, T1-2N1M0 and T3N1M0/T4N0-1M0, respectively. In eight patients (7%) there was no residual tumor in the final specimen, and for TNM classification the preoperative cT stage was used based on work-up with a combination of endoscopy (n=8), CT-scans (n=8) and EUS (n=3).

Hybrid surgery with laparoscopy and open right-sided thoracotomy, esophageal resection, partial gastric resection and lymphadenectomy of upper abdomen and mediastinum including the tracheal bifurcation, was performed. Lymphadenectomy included perigastric lymph nodes, perivascular at stations 7 and 9 and periesophageal

lymph nodes, along the main bronchi and the tracheal bifurcation. A tube-shaped substitute for the esophagus was made from the residual stomach with diameter of about 3-5 cm.

Two principal surgeons performed (n=93) or participated in (n=16) all of the HE. Patients with stages IIa, IIb and III and aged 75 or less without severe comorbidity (heart, lung or kidney disease) were assessed for neoadjuvant or perioperative chemo(radio)therapy. Neoadjuvant chemotherapy consisted of 3-weekly cycles of cisplatin and 5-FU with or without radiotherapy of 40 Gy in 20 fractions, applied during chemotherapy cycle 2 and 3[6]. Perioperative chemotherapy consisted of epirubicin, oxaliplatin and xeloda (EOX) or epirubicin, cisplatin and xeloda (ECX), given up to three times before and three times after surgery [14]. Forty-four patients had neoadjuvant treatment with chemotherapy (n=33; CiFU n=19/EOX/ECX n=14), chemoradiotherapy (n=10) or radiotherapy alone (n=1). Another 21 patients received perioperative chemotherapy (EOX/ECX n=19/FLV n=1/FLOX n=1).

Microscopically tumor negative resection margin of more than 1 mm from the tumor was defined as a R0 resection. Microscopically tumor positive resection margins or a free resection margin from the tumor of 1 mm or less was defined as a R1 resection [15]. A R2 resection meant remaining macroscopic residual tumor. Four patients had R2 resections due to intraoperative tumor perforation, metastasis to bone, bone marrow or a remaining metastatic lymph node located proximal to the tumor. Five patients (5%) had R1 resection because of infiltrated resection margins proximally, distally and circumferentially or tumor within 1 mm from the circumferential margin. Five received adjuvant radiation, of which three also had chemotherapy with 5-FU and leucovorin.

Generally, the patients were followed ambulatory each year for five years with clinical examinations, blood samples and a thoracic- and abdominal CT-scan.

Study outcomes

Overall survival for R0-2 resection and R0 resection were calculated from the time of operation to death of any cause or censored at end of follow-up in June 2019 (at least 6 years after initial operation), whichever occurred first. Cancer-specific survival was defined as survival from EC, i.e. time from operation to death of EC. **The cause of death unrelated to esophageal cancer in 11 patients were due to pneumonia (n=5),**

other type of cancers (n=3) (cholangiocarcinoma, lung cancer, B-cell lymphoma), pulmonary edema (n=1), cerebral stroke (n=1) and cardiovascular disease (n=1).

In June 2018, additional operations were recorded, defined as surgery performed more than 4 months after HE for complications, metastasis and de novo cancer. In addition, questionnaires were sent to patients alive for assessment of dysphagia and HRQL. The Ogilvie grading scale [16] was used to determine level of dysphagia. It consists of the following scores: normal diet without problems (score 0), normal diet avoiding certain solid foods (1), semi-solid foods (2), liquids only (3), complete dysphagia, even for liquids (4). Poor dysphagia was defined as score >1. For assessment of HRQL, we used the cancer-specific European Organization for Research and Treatment of Cancer (EORTC) core-questionnaire, QLQ-C30 version 3 [17] together with the disease-specific module QLQ-OG25 [18]. The EORTC QLQ-C30 contains five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain and nausea/vomiting) and six single items (dyspnea, appetite loss, insomnia, constipation, diarrhea and financial difficulties). In addition, there is a global quality of life scale [17]. The EORTC QLQ-OG25 is a gastro-esophageal-specific questionnaire that consists of six symptom scales (dysphagia, eating restrictions, reflux, odynophagia, pain and anxiety) and 10 single items. Both questionnaires are validated for patients with gastro-esophageal cancer [18]. For both the EORTC questionnaires, the patient answer scales with Likert type response categories ranging from 0 (“not at all”) to 4 (“very much”) and from 1 (“very poor”) to 7 (“excellent”) for question 29 and 30 in the EORTC QLQ-30. All scores were linearly transformed to a 0-100 scale where high score represents a high degree of function or a high degree of side effects/problems. For every scale, the mean value was calculated. Further, number of patients with reduced HRQL (function ≤ 50 / symptoms ≥ 50) was also calculated.

Ethics

Demographics, treatment, disease extent, tumor characteristics, complications, delayed operations, survival, dysphagia and HRQL were registered in a database established in 2010 with legal basis in section 26 of the Health Personnel Act, at the Department of Gastrointestinal and Pediatric Surgery at Oslo University Hospital, Ullevål. All data were retrieved from the patient administration system - retrospectively during 2007-

2010 and mainly prospectively from 2010 to 2013. In addition, data on HRQL and dysphagia were reported from the patients in June 2018. In 2018 this database was upon permission by a regional health committee (2018/720/REK NORD) converted from an Excel quality assurance database into an e-Reg research database, in which the information about the patients was stored.

Statistical analyses

Descriptive analyses were used for demographic data, where data were presented as frequencies and proportions for **categorical data and mean, median and range for continuous data. Overall survival probabilities were estimated with the Kaplan-Meier estimator. To take into account the competing risk of death due to other causes than EC, we have calculated the cause-specific mortality by the Aalen-Johansen estimator. For overall survival,** univariable and multivariable cox proportional hazard analysis was performed for the following potential prognostic variables: gender, histology, oncotherapy, BMI, pathological Tumor Node Metastasis (pTNM) stages, ASA score, and smoking. ASA score could not be included in the multivariable model due to high multicollinearity with the other variables, thus omitted from the model. **Further, to reduce the number of variables in the multivariable model (due to the limited number of death), we excluded the two least significant variables.** Results were presented as hazard ratio (HR) with 95% confidence intervals (CI). P-values below 0.05 were considered significant. Graphpad InStat 3, Graphpad prism 6 for windows (Graphpad Software, San Diego, CA, USA) and IBM SPSS version 25 were used for all calculations.

Results

Patient and tumor characteristics of the 109 patients were presented in Table 1. The tumors were located above or at the level of the carina (n=3; 3%), in the distal esophagus (n=41; 38%) and at the gastro-esophageal junction (n=65; 60%). In June 2018, 51 patients were alive, out of which 41 patients (80%) took part in our clinical trial regarding long-time follow-up on HRQL and level of dysphagia. All 41 patients graded the level of dysphagia (Ogilvie score). Out of the in total 54 questions each patient had to answer regarding HRQL, four patients did not answer one question and one patient did not fill out the EORTC QLQ-OG25. The patients who answered the questionnaires were similar to the total group regarding age, gender, histology, ASA score and BMI.

Short-term results

In five out of the 109 patients (5%), laparoscopy was converted into laparotomy because of prolonged procedures (n=2), perforation of the small intestine (n=1), hemorrhaging (n=1) or tight anatomical conditions at the esophageal hiatus (n=1). Hundred patients had a R0 resection (92%), while nine patients (8%) had R1 (n=5) or R2 (n=4) resection. The median number of lymph nodes demonstrated in the specimens were 13 (range 3–38), of whom 60 patients (55%) had metastasis to median 2.5 (1–14) regional lymph nodes. Anastomotic leakage afflicted 5 patients (5%), treated with drain (n=1) or stent (n=4). Five patients (5%) were re-operated for chylothorax (n=2), hemorrhage (n=2) and air leakage from the right lower lobe (lobectomy) (n=1). There was no in-hospital mortality. Thirty- and 90-days mortality was 0% and 2%, respectively. Postoperative stay at primary hospital was median 16 days (range 9 – 88).

Long-term results

In June 2019, median follow-up time of surviving patients was 87 months (range 73–135). The median follow-up time among patients with R0-2 was 55 months (range 2–135), while the subgroup with R0 resection patients had 76 months (range 5–135). **As of June 2019**, forty-eight patients were alive which corresponded to a fraction of 44% in

the R0-2 group and 48% in the R0 group, respectively. The 5-year overall survival rate was 49% (95% CI 39–58) and 53% (95% CI 43–62), respectively (Figure 1). The nine patients with R1-2 resection survived less than 5 years. Among R0 resection patients, the **5-year cumulative mortality for EC cancer was 45% (95% CI 35–54)** (Figure 2). Further, stratified by stage showed **2-year cumulative mortality for EC cancer 8%, 15%, 36% and 45%** for stages I, IIA, IIB and III, respectively. **The overall survival rates did not differ by histology or by use of chemo(radio)therapy (data not show).**

Prognostic factors

Patients with R0 resection who received chemo(radio)therapy had improved **overall survival** compared to those treated with HE alone (**HR 0.4, 95% CI 0.3–0.8**) (Table 2). Patients with TNM stages IIB and III had decreased **survival** compared to stage I patients. Gender, histology, ASA stage, BMI or smoking was not associated with **survival**.

Additional surgical treatment

Five out of the 41 patients (12%) alive who responded to our survey, underwent additional surgery after 4–98 months. One of these patients was operated at a local hospital. In total, 13 of the 109 patients (12%) had registered operations at least 4 months after HE. Six had operations because of locoregional recurrence (hepatoduodenal ligament, mediastinum) or metastases to brain, lung, liver and bladder after 4–51 months, and three had surgery for complications (Table 3). Four were operated for cancer of thyroid, mamma, colon and lung, of which one patient died 5 months after lobectomy.

Patient-reported outcome measures

Forty-one patients (80%) completed the HRQL questionnaires median 65.5 months (range 63–123) after initial surgery. Most of them (83%) reported preserved function and low symptom burden (Table 4). Reflux was the most frequently reported symptom affecting nearly half of the patients. Around one third of the patients had problems with fatigue and anxiety while only a few patients had eating problems. All patients could eat

normal food without (n=37) or with some (n=4) problems. Additional major symptoms in one fourth of the patients were weight loss and episodes of dyspnea.

Discussion

In this single-center study of patients treated with HE resection for esophageal cancer the 5-year overall survival rate of 49% compared well with major prior studies in open surgery [3-6,8-9]. Chemo(radio)therapy seemed to improve the prognosis for patients with HE and R0 resections, as demonstrated by multivariable analysis.

In spite of the obvious pitfalls of a single armed patient series, and the mixture of retrospectively and prospectively registered data, the basic clinical and pTNM data of this study is not deviant from similar long-term follow-up studies. There seems to be only one single sufficiently powered and well performed multi-center RCT of HE versus open esophageal resection (Miro-study) [9]. The complication rate, mortality and long-term survival data of the HE in the current study is similar to the HE arm in the Miro-study.

Totally minimally invasive esophagectomy (MIE) was introduced in 2013 and was soon practiced as standard procedure for esophageal resection in Oslo University Hospital, in order to reduce the surgical trauma of open thoracotomy and hopefully reducing respiratory complications. In addition, MIE allows minutely thoracic lymphadenectomy and mesoesophageal resection which in combination with modern neoadjuvant treatment hopefully may further improve long-term oncological outcome. MIE as well as HE has been shown to reduce postoperative morbidity and length of hospital stay compared to open surgery [7,8,10,11,19,20]. Moreover, in a recent meta-analysis on long-term survival HE or MIE compared well with and may even be better than open esophagectomy [21].

There are obvious and important differences in preoperative investigations and treatment regimens between the HE and MIE eras. PET-CT is now part of standard preoperative investigation, increasing the detection of occult metastases and thereby reducing the number of patients undergoing futile surgery.

Preoperative chemoradiotherapy has become the new standard due to the results of the CROSS trial [5], but there is recently an increasing awareness of potential higher rates of serious complications after chemoradiotherapy [22]. This study is not suited for a

direct comparison, but four out of five with anastomotic leakages occurred in patients receiving chemotherapy (n=4), whilst the fifth patient received radiotherapy.

The most important results from the HE series, on which to perform further comparison with the treatment results of the MIE era, is the low rate of perioperative severe complications, especially anastomotic leakage, the low rate of postoperative deaths and the comparably high rate of 5-year survival. Today's performance in MIE does not regularly challenge an anastomotic leakage rate of less than 5 % [23].

Moreover, we observed a very low level of dysphagia since only one out of four patients with an initial stenotic anastomosis maintained this problem that required repetitive dilations.

The long-term survival data clearly demonstrates the importance of lymph node negative versus positive status in histology of operative specimens. Patients with lymph node negative specimens (pT1-3N0) had > 80% cancer specific 5-year survival compared to < 35% in lymph node positive cases. There was obviously a benefit of neoadjuvant and perioperative platinumbased chemotherapy, but there is a clear demand for a more effective treatment in lymph node positive patients. The FLOT regime has become a new standard, and ongoing RCTs of chemoradiotherapy versus chemotherapy (ESOPEC, Neo-AEGIS) will give important information on this issue [24,25].

The median number of lymph nodes was lower (n=13) than recommended (n=15) by the recent AJCC TNM (8th edition) classification. Reasons for this were probably owing to less focus on extensive lymph node dissection by the surgeon as well as lymph node identification, as confirmed by the pathologist.

The effect of routine controls, with respect to cancer-specific survival after EC surgery, has not been clarified [26]. Routine follow-up after esophagectomy is not recommended in Norwegian or most international guidelines, but in times of significant changes in treatment algorithm it is necessary in order to catch up with adverse/inadvertent reactions and perform long-time follow up survival analysis. The patients treated by HE therefore had yearly follow-up until 5 years after surgery. Six patients in the recent series were operated for recurrent disease. Two patients with asymptomatic/CT verified metastases may have been cured by re-resectional surgery. The survival benefit of re-resections in the other four patients is at best uncertain (Table 3).

The high proportion of patients with reflux problems were as expected due to substitution of the esophagus with a tubularized gastric conduit with loss of native anti-reflux mechanisms. A few patients developed some degree of retention mainly from a redundant conduit, that in one case was repositioned with a satisfactory result 61 months after initial resection (Table 3) [27]. A serious consequence of persistent conduit retention was for a cancer-free patient aged 72, who ultimately died from recurrent aspiration pneumonias after 9.5 years. The clinical challenge and treatment of conduit retention following resection has been extensively described in a US study from University of Pittsburgh Medical Center [28].

In this study global HRQL, physical and social functions were comparable to European and Norwegian reference data [29,30]. However, the low number of respondents (41/51) and the broad standard deviation make it uncertain whether the results are representative for EC survivors in general. Lack of pretreatment HRQL data deprives us of the opportunity to study change in HRQL and symptoms after treatment.

Others have found that patients reported better HRQL 6-24 months after HE or MIE than after open surgery [11,31-33], but after 3 years there was no longer a significant difference between the treatment arms [11]. In a prospective Swedish nationwide population-based cohort of patients there was a general deterioration in 23 out of 25 HRQL aspects at 5 and 10 years after surgery. Reflux, eating difficulties, diarrhea and appetite loss were the main complaints reported [34]. More studies with patient-reported outcomes are warranted in order to obtain more knowledge about the long-term adverse effect and HRQL in these patients.

In conclusion, in this single-center study of EC patients treated with curative intent, HE was safe with low rate of serious postoperative complications and low mortality. Patients had low degree of dysphagia, relatively long-time survival with acceptable impact on HRQL.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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Figure legends

Figure 1. Overall survival (R0-2, R1-2, R0).

Figure 2. Cumulative mortality by cause of death of all patients (R0-2)