

# Modern Oncologic and Operative Outcomes for Oesophageal Cancer Treated with Curative Intent

## Abstract:

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## Abstract

The curative approach to oesophageal cancer carries significant risks and a cure is achieved in approximately 20 per cent. There has been a recent trend internationally to observe improved operative and oncological outcomes. This report audits modern outcomes from a high volume centre with a prospective database for the period 2004-08. 603 patients were referred and 310 (52%) were treated with curative intent. Adenocarcinoma represented 68% of the cohort, squamous cell cancer 30%. Of the 310 cases, 227 (73%) underwent surgery, 105 (46%) underwent surgery alone, and 122 (54%) had chemotherapy or combination chemotherapy and radiation therapy. The postoperative mortality rate was 1.7%. The median and 5-year survival of the 310 patients based on intention to treat was 36 months and 36%, respectively, and of the 181 patients undergoing R0 resection, 52 months and 42%, respectively. An in-hospital postoperative mortality rate of less than 2 per cent, and 5-year survival of between 35 and 42% is consistent with benchmarks from international series.

## Introduction

Ireland has one of the highest rates of oesophageal cancer in Europe, with approximately 400 new diagnoses each year. The overall 5-year survival is between 5 and 15%. Where curative therapy can be offered, either surgery alone, surgery combined with chemotherapy and radiation, or occasionally radical chemoradiation alone, the management is fraught, particularly surgery, with a risk of major morbidity and mortality greater than for any other cancer surgical or multimodal treatment.

Encouragingly, the literature suggests improved outcomes compared with a decade ago, particularly for the increasing proportion of patients who can be treated with curative intent. Several advances underpin this improvement, including the advent of CT-PET imaging and endoscopic ultrasound (EUS) to optimise staging, improved physiologic risk assessment for surgery and perioperative care, the increasing trend for oncologic resections to the domain of specialist high-volume surgeons working in multidisciplinary teams in high-volume hospitals, and neoadjuvant therapies. At this time, consequently, reports from specialist centres indicate that oesophageal cancer treated with curative intent can be undertaken with a mortality risk of less than 5% and a predicted 5-year survival of between 30 to 50 per cent. In Ireland, St. James's Hospital is a high-volume oesophageal and gastric centre managing approximately 40% of the national workload, and reporting previous audit up to 2005. The aim of this study was to provide a comprehensive audit of the most recent 5-year period, 2004-2008, with a minimum of one year follow-up, to highlight modern operative and oncological outcomes.

## Methods

Patients attending the Centre at St. James's Hospital, Dublin between 2004 and 2008 with a diagnosis of cancer of the oesophagus or oesophago-gastric junction were included. Adenocarcinoma of the oesophago-gastric (AEG) junction included tumours which had their centre within 5 cm proximal or distal of the anatomical cardia, identified endoscopically, and were classified as per the Siewert criteria. AEG type I involves the distal oesophagus and mostly arises in Barrett's oesophagus, AEG type II arises immediately at the anatomical cardia, and AEG type III is a subcardiac gastric carcinoma infiltrating the oesophagogastric junction from below. All AEG types are considered together as per the latest UICC/AJCC recommendation.

All data are prospectively recorded in a database (Dendrite, London UK). For staging, all patients have CT of the neck, thorax and abdomen and 18-F-deoxyglucose PET scans, with combination CT-PET since 2007. EUS is routine since 2005, and laparoscopy is used for locally advanced tumours below the diaphragm. All patients are discussed at a weekly multidisciplinary conference, and treatment planning is based on predicted tumour stage, and the patient's fitness for treatment. Patients with predicted locally advanced or node-positive disease are considered for neoadjuvant combination chemoradiation therapy, as previously described. Patients with AEG type III tumours have been considered for postoperative chemoradiation or pre and postoperative chemotherapy. Patients, in particular patients with squamous cell cancer, are considered for high-dose radiation therapy with chemotherapy where surgical risks are considered prohibitive, where there is locally advanced features making surgical clearance uncertain, or in some cases due to patient choice.

The surgical principle of wide clearance and a radical lymphadenectomy is the goal in all cases, as previously described. Pathological TNM reporting was based on the UICC/TNM 6th edition (2002). In patients treated with neoadjuvant therapy the extent of residual carcinoma in the oesophagectomy specimen was assigned to one of five categories as per Mandard et al. Patients were followed at 3 monthly intervals for the first year, and at four to six monthly intervals for the subsequent four years. All patients had CT scans in the first and second post-treatment years, or as clinically indicated. Median follow-up for the entire group was 20 months (interquartile range [IQR] 14 to 38). Data were analysed with Stata version 8. Continuous variables were compared with the Mann-Whitney U test and categorical data with the Pearson c-2 test or Fisher exact test. Overall cumulative survival rates were calculated according to the Kaplan-Meier method.

## Results

603 patients were diagnosed or treated with oesophageal cancer. 310 (52%) underwent treatment with curative intent. 293 patients (48%) had treatment with palliative intent due to metastatic disease (62%), locally advanced disease (15%), and lack of fitness for curative therapies (23%). The cohort undergoing curative treatment included 212 males and 98 female patients, with a mean (range) age of 65 (30-86). Of the 310 patients managed at this centre, 209 patients (66%) were tertiary referrals. The majority (67%) of tumours were adenocarcinoma (Table 1). Squamous cell cancers represented 30%, and there were 4 cases of small cell cancer. AEG was the majority, with AEG type I tumours representing 50% of the junctional tumours. Fifteen patients in the adenocarcinoma cohort (7%) presented with intramucosal cancer (Tis). In patients diagnosed with adenocarcinoma, 23 patients (23%) with AEG type I tumours were on Barrett's surveillance programmes, one (0.5%) with a type II tumour and none with type III, representing an overall 11% of patients with adenocarcinoma on Barrett's surveillance.

\*excludes open and close laparotomy

Major surgery was a component of treatment in 227 patients (74%), 7 patients (2%) underwent endoscopic mucosal resection and in 67 (22%) patients no surgery was undertaken. In the surgery group, 105 underwent surgery alone (46%), and 122 (54%) had chemotherapy or a chemotherapy and radiation therapy as part of their treatment. In the non-operative cohort, the majority (79%) were treated with radical radiation therapy in combination with chemotherapy. Twelve patients of 94 (13%) who commenced on neoadjuvant chemoradiation prior to oesophagectomy did not progress to surgery due to worsening performance status or disease progression. The surgical approach was predominantly a 2-stage oesophagectomy (58%), and 3-stage (20%). Transhiatal oesophagectomy (5%) was selectively used for patients with higher operative risks or early tumours. Postoperatively (Table 2) there were four postoperative deaths (1.7%), and 45% of patients had a complication, in particular pneumonia (14%) and atrial fibrillation (13%). Two patients required re-operation, one for gastric conduit ischaemia, and one for small bowel obstruction.

The pathological stages are shown in Table 3 for patients who had surgery initially and those who completed neoadjuvant chemoradiation (n=82) or neoadjuvant chemotherapy (n=17) prior to surgery. The majority of patients in both cohorts were node-positive, 53% in the surgery only group and 54% in the neoadjuvant therapy cohort. In the neoadjuvant group, 20% of patients had a complete pathological response (TRG1), 25% had a major response (TRG2), and 43% had a poor response to neoadjuvant therapy (TRG 3-5). In patients undergoing surgical resection (n=224), 181 (81%) had complete resections with negative margins. The median lymph node harvest was 22 [range (8-62)], with a median of one [IQR (0-4)] involved node.

At a median follow up of 20 months [14-38 (IQR)], the median survival of the 310 patients based on intention to treat was 36 months with a one, three, and five year survival of 76%, 50% and 36% respectively. In the patients treated by surgery or multimodality therapy, the median survival was 42 months, with a one, three and five year survival of 76%, 53% and 38% respectively. 181 patients had surgery with negative margins (R0 resections), with a median survival of 51 months, and a one, three and five year survival of 82%, 60% and 42% respectively (Fig 1). In a

univariate analysis pT stage, pN stage, number of involved nodes, R status, and tumour regression grade were significantly ( $p < 0.05$ ) associated with overall survival. In multivariate analysis, pathological N status and lymph node involvement significantly ( $p < 0.0001$ ) correlated with survival.

Figure 1: Survival of Patients undergoing curative (R0) resections: n = 181  
Median survival = 51 months

### Discussion

This report of modern outcomes from a high-volume centre highlights several points. First, adenocarcinoma is more common than squamous cell cancer, with a ratio of approximately 2:1, consistent with the pattern that has emerged in the West<sup>1,2</sup>. Second, although the authors acknowledge potential for referral bias of more favourable cases, just over half of the referred patients could be treated with curative intent. Third, long-term survival of patients who are treated with curative intent is between 30 and 45%, with the best outcomes observed where a resection with negative margins (R0) can be achieved. Finally, mortality after oesophageal cancer surgery is now rare, in this series less than two per cent. The 5-year survival of curatively treated patients is in keeping with modern benchmarks, and markedly better than the figure of 20% that is commonly quoted<sup>2</sup>. The increasing percentage of adenocarcinoma compared with squamous cell cancer may be a factor, as there is greater potential to diagnose adenocarcinoma at an earlier stage through Barrett's surveillance programmes. In this series, however, only 11% of patients were on surveillance, compared with 54% in a recent series from California<sup>4</sup>. Consequently, improvements in the standards of diagnosis, surveillance, and management of Barrett's oesophagus may be expected to continue to improve outcomes in Ireland.

Other factors are likely to contribute to the improved oncological outcomes reported herein. These include improved staging with CT-PET and EUS, enabling treatment tailored to accurate staging. This particularly applies to the detection of systemic metastatic disease and local extent. The sensitivity however of staging modalities for predicting nodal disease remains low, highlighted by the high nodal positivity in the surgery only group in this study. The most significant impact on improved outcomes may be from the experience of the multidisciplinary team and the hospital with this type of complex treatment. Surgical and hospital experience in complex care results in a virtuous circle of experience that results in continued improvement in outcomes, and this is most strongly evidenced for oesophageal followed by pancreatic cancer. This reflects decision-making and skills of specialist surgeons, oncologists, gastroenterologists, anaesthetists, nurses, and advances in critical care and interventional radiology<sup>1,2,20</sup>.

The operative mortality of less than 2% is also consistent with modern benchmarks from the international literature. Pooled published series between 1990 and 2000 report a 7% mortality rate, and recent multicentre audits in the US and UK show mortality rates of over 10%<sup>21-23</sup>. A previous audit from this centre (1997 and 2003) reported a mortality rate of 5 per cent<sup>14</sup>. The improvement to less than 2 per cent in this Unit may reflect continued surgeon and hospital experience, consistent with reports from high volume academic medical centres<sup>24</sup>. Perioperative clinical pathways, including the use of thoracic epidurals, restricted fluid management, early mobilisation, and enteral nutrition may be important elements in the attainment of optimum outcomes.

In conclusion, in patients treated with curative intent, a 5-year survival rate of 36% for all patients and 42 percent in patients undergoing R0 resection was achieved, outcomes consistent with modern benchmarks. Postoperative deaths are rare. These data may underpin the value of high-volume interdisciplinary experience in the management of cancers that encompass complex surgery.

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