A comparison of staged and concurrent neo-adjuvant chemoradiotherapy in resectable locally advanced oesophageal carcinoma

Abstract

Introduction: Oesophageal cancer is the eighth most common cancer and sixth most common cause of death from cancer worldwide. Current overall five-year survival rates are at best 10%, largely due to the advanced stage of disease at presentation. Systemic disease requires systemic therapy, and thus the standard of care is neo-adjuvant chemoradiotherapy followed by surgery for the vast majority of patients.

Aims: The aim of this retrospective study was to determine overall survival following two neo-adjuvant chemoradiotherapy regimes in patients undergoing multi-modal therapy (including oesophagectomy) for oesophageal carcinoma.

Methods: One hundred and nine consecutive patients treated with neo-adjuvant chemoradiotherapy for oesophageal carcinoma between 2001 and 2011 were divided into two groups: 24/109 (22%) patients who underwent single-cycle induction chemotherapy followed by neo-adjuvant chemoradiotherapy and surgery (‘chemo-first’), and 85/109 (78%) who received concomitant neo-adjuvant chemoradiotherapy, followed by consolidation neo-adjuvant chemotherapy (‘CR-C’ group) prior to surgery. All 109 patients were followed up until the date of death or last clinical interaction. Follow-up and cause of death, if applicable, was determined by review of patient records.

Results: Mean overall survival time for all patients was 50.9 (±7) months; 50.3 (±10) months for ‘chemo-first’ patients versus 43.1 (±7) months for ‘CR-C’ patients (p=0.080). Significantly higher rates of acute treatment-associated toxicity were seen in the ‘chemo-first’ patients (4/24, 16.67%) vs. the ‘CR-C’ patients (2/85, 2.3%) (p=0.001).

Conclusion: There was no statistically significant difference in overall survival between the two groups. The ‘chemo-first’ treatment regime resulted in a greater number of treatment-related toxicities when compared with CR-C.

Introduction

Oesophageal cancer is the tenth most common male and fourteenth most common female cancer (excluding non-melanoma skin cancers) in Ireland. Between 2000 and 2004, there were on average 296 male and 183 female cases of oesophageal cancer diagnosed in Ireland each year. During the same period, there were 296 male and 174 female deaths per year (giving an incidence:mortality ratio of 0.98). In men living in developed countries, only the UK has a higher incidence of oesophageal cancer than Ireland. It is the seventh leading cause of cancer death worldwide, with a 2:1 male to female ratio. Patients will generally present with dysphagia, acid reflux, odynophagia, vomiting, loss of weight and poor appetite. Hiccups have also been shown to be a presenting symptom. Surgery is potentially curative in loco-regionally-advanced (i.e., early stage) oesophageal cancer, but the morbidity and mortality associated with oesophagectomy has restricted its use to a small minority of medically
The majority of patients with oesophageal cancer who are initially staged as surgically curable are shown to have occult progressive systemic disease. Therefore, logically, early systemic therapy is essential. Multi-modal therapy (neo-adjuvant chemoradiotherapy followed by surgery) has been shown to have a 37% three-year survival rate compared with just 7% for those patients who received surgery alone. Chemotherapy, when given with radiation therapy pre-operatively, will produce a complete pathological response (cPR), with tumour eradication, in over one-third of patients. These patients would therefore no longer benefit from resection, but if operated on would be exposed to all the risks of surgery, including a risk of mortality of around 14% overall and 20% in the elderly, as well as a negative impact on their quality of life. Walsh and colleagues have previously shown that a complete clinical response (cCR) is 74% predictive of cPR and that surgery may even be avoided in these patients.

The tumour lethality of external beam radiation therapy is related to its effects on deoxyribonucleic acid (DNA), with the introduction of single-stranded DNA breaks and, to a lesser extent, double-stranded DNA breaks. Absorption of gamma radiation in tissues leads to the immediate production of ionised atoms, which damage DNA. These in turn lead to the formation of unstable, short-lived free radicals, which interact with cellular constituents. The damage induced in a cell by ionising radiation is lethal or potentially lethal; in the latter case, the damage induced may be partially or completely repaired. Chemotherapy exhibits local effects that increase sensitivity of tumour cells to radiotherapy, while it is also used for its systemic killing of micrometastases. The most common chemotherapy protocol administered in oesophageal cancer treatment is ‘CF’, a combination of cisplatin and flurouracil (5-FU).

Combining chemotherapeutic agents with radiotherapy has a multiplicative tumoricidal effect by intensifying the effect on local disease and reducing subsequent metastasis. Neo-adjuvant chemoradiotherapy was reported to enhance survival in a number of randomised trials and in some recent subsequent meta-analyses. The most widely used regime consists of neo-adjuvant chemoradiotherapy given initially, followed by a single one-week course of neo-adjuvant chemotherapy (‘CR-C’). The results of that study have been followed up for 15 years and are well documented. In 2000, due to logistical reasons arising from a surge in demand for radiotherapy facilities at St Luke’s Hospital, Dublin, following the introduction of the Irish BreastCheck programme, the order of the therapy was changed in Ireland. Subsequent patients were given single-cycle induction chemotherapy followed by neo-adjuvant chemoradiotherapy and surgery (‘chemo-first’).

In 2012, the St Luke’s Radiation Oncology Network (SLRON) expanded to include new radiotherapy facilities in Beaumont Hospital, Dublin, and St James’s Hospital, Dublin, and the neo-adjuvant regime is to return to the initial ‘CR-C’ regime. The two regimes have never been compared. At this juncture, it would be worthwhile to evaluate whether both regimes are comparable on a non-inferiority basis, or whether the current ‘chemo-first’ regime is an improvement on the original ‘CR-C’ regime in terms of overall survival. This study reports a retrospective analysis of a prospectively accrued group of patients with oesophageal cancer in order to compare overall survival between two delivery regimes for neo-adjuvant chemotherapy and radiotherapy.
Methods
From 2001 to 2011, 109 consecutive patients with a diagnosis of oesophageal cancer underwent a treatment regime consisting of neo-adjuvant chemotherapy and radiotherapy followed by surgery. A retrospective analysis of overall survival and chemotherapy-related toxicity was made, comparing 24 of these 109 patients, in whom a single course of induction chemotherapy was given prior to chemoradiotherapy and surgery (‘chemo-first’), and 85 of the 109 patients in whom a single dose was given after simultaneous chemoradiotherapy (‘CR-C’). Individual patient data was entered into an oesophageal cancer database containing demographic, clinical, operative, pathological and follow-up data. The database was locked for analysis on May 30, 2011. For the purposes of this study, all patients were followed up until the date of death or last clinical interaction. Follow-up and cause of death, if applicable, were determined by review of patient records. Overall survival was calculated from the date of diagnosis until the date of death or the last recorded clinical interaction.

Inclusion criteria
The following criteria warranted inclusion into the trial:
1. Patient received the appropriate regime of neo-adjuvant chemoradiotherapy (discussed earlier).
2. Biopsy-proven adenocarcinoma or squamous cell carcinoma of the oesophagus (excluding cervical oesophagus) or the oesophageal gastric junction.
3. Leukocyte and platelet counts of greater than 3,500/mm³ and 100,000/mm³, respectively. Patients with levels outside these ranges are not deemed suitable for chemoradiotherapy.
4. Serum creatinine concentration less than 1.4mg/dL. Poor renal function is an absolute contraindication to receiving chemoradiotherapy.

Exclusion criteria
The main criteria for exclusion from this study were patients who did not undergo surgery. These include patients with evidence of distant metastases, an Eastern Cooperative Oncology Group (ECOG) performance status of 3 or 4, or co-morbidities contraindicating surgery. Patients who had previous chemotherapy or radiotherapy, or who had a neo-adjuvant chemoradiotherapy regime other than the one under investigation, were also excluded from this study. There was no restriction on the length of tumour or on the presence or location of lymph node metastases, as these were not considered contraindications to surgery.

Pre-operative tumour staging and classification
Clinical staging of each tumour was elicited through physical examination and a combination of radiologic and endoscopic modalities. Oesophago-gastroscopy (OGD) with measurement of the longitudinal margins of the tumour was performed on all patients. Computerised tomography of the thorax and abdomen was also performed in most cases. Staging of tumours was based on the American Joint Committee on Cancer (AJCC) guidelines for oesophageal cancer. Histopathology established a diagnosis of adenocarcinoma or squamous cell carcinoma in each primary case. Resection specimens were examined for the presence of metastatic lymph node deposits.

Neo-adjuvant chemoradiotherapy
Each patient received one of two chemoradiotherapy regimes; they either received a single dose of neo-adjuvant sensitising chemotherapy followed by neo-adjuvant chemoradiotherapy (‘chemo-first’), or concomitant neo-adjuvant chemoradiotherapy first followed by a single dose of neo-adjuvant chemotherapy (‘CR-C’). As mentioned earlier, division of patients into either group was solely based on the time of their diagnosis with reference to the therapy protocol change in Ireland. All chemotherapy cycles followed the CF protocol – S-FU, dosed at 15 milligrams per kilogram of body weight daily for five days, with cisplatin, 75 milligrams per square metre of body surface area on day seven. External beam photon radiation therapy (typically 40Gy, administered in 15 fractions over a three-week period, Monday to Friday inclusively) was begun concurrently with the final course of chemotherapy. All patients underwent treatment with megavoltage therapy units with 4 or 8MV photons (Cobalt model SEM100, Fairy Engineering, or Phillips model SL75-5 or Dynaray model 10, Radiation Dynamics, respectively). Radial and longitudinal margins of the tumour were defined endoscopically and radiologically, and the treatment fields extended 2-3cm and 5cm beyond the radial and longitudinal margins, respectively.

Statistics
Statistical analyses were performed with Predictive Analytics Software version 18.0 for Windows. Continuous variables were expressed as mean ± standard error of the mean as appropriate, and were compared using analysis of variance (ANOVA) with post-hoc Student-Neuman-Keuls and Dunnett T3 tests for parametric and non-parametric variables, respectively. Categorical variables were compared using a chi-squared test, with Fishers exact test used where appropriate. Survival probabilities for clinical, pathological and treatment variables were estimated by the Kaplan–Meier method and pairwise comparisons were made using a log–rank test. The effect of extent of response to neo-adjuvant chemotherapy and external-beam radiation therapy (either administered sequentially or simultaneously, and then followed by surgical resection), tumour location, age, gender, WHO toxicity grading, TNM stage and time interval between chemotherapy and radiotherapy on survival were examined using logistic regression, and optimal cut-offs were determined using the maximal chi-squared method. Significant univariate factors were included in a Cox proportional hazards regression model to establish independent predictors of survival. P values of less than 0.05 were considered statistically significant.
**Results**

**Patient demographics**

Of the 109 patients studied, 24 (22%) were female and 85 (78%) were male. Twenty-four of the 109 patients (22%) were in the ‘chemo-first’ group (of whom three were female and 21 were male), while 85/109 (78%) were in the ‘CR-C’ group (of whom 64 were male and 21 were female). The mean age upon diagnosis was 66 years (ranging from 39-88 years). Patients were predominantly men in their seventies. Men tended to have received induction chemotherapy versus concomitant chemoradiotherapy, but this result was not statistically significant (p=0.091) (Figure 1). Patient demographic data are summarised in Table 1.

**Toxicity**

In our study, 6/109 (5.5%) patients experienced acute treatment-associated toxicity. Four of the six patients had WHO Grade I toxicity, two in each of the two regimes. In the ‘chemo-first’ group, one patient experienced Grade II toxicity, while another had Grade III toxicity; there were no instances of Grade II or III toxicity in the CR-C group. Thus, significantly higher rates of acute treatment-associated toxicity were seen in the ‘chemo-first’ patients (4/24, 16.7%) vs. the ‘CR-C’ patients (2/85, 2.3%), placing these patients at a relative-risk increase of 3.43 (p=0.001) (Figure 2).

**Overall survival following diagnosis**

The mean (± standard deviation) overall survival time for all 109 included patients was 50.9 (±7) months. There was no detected difference in survival outcomes between the two groups; 50.3 (±10) months in the ‘chemo-first’ group versus 43.1 (±7) months for the ‘CR-C’ group (p=0.95). The results of this are summarised in the Kaplan–Meier survival curve shown, which estimates the survival function from lifetime data (Figure 3).

**Discussion**

The management of oesophageal cancer is in constant evolution. In less than 100 years, the standard of care has evolved from hopelessness, where only palliative measures were possible, through surgery alone – constantly extending resection and refining selection criteria – to surgery following neo-adjuvant therapy, with or without the addition of adjuvant therapy, depending on the findings in the resected specimen. As more effective and targeted therapies are employed, and extended to earlier disease stages, we can anticipate a greater percentage of survivors.

For squamous cell carcinoma (SCC) and adenocarcinoma (AC) of the oesophagus, neo-adjuvant therapy followed by surgery has become the standard of care in North America and parts of Europe. Ideally, complete responders (pCR) to neo-adjuvant therapy should not require surgery. A recent study of 299 patients with a pCR to neo-adjuvant therapy revealed a post-operative mortality rate of 5.7%, despite the cases being drawn from six centres of excellence. Several studies suggest increased morbidity and mortality for patients undergoing preoperative chemoradiation, identifying a further argument against

<table>
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<th>Neo-adjuvant treatment regime</th>
<th>Chemo first</th>
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Table 1: Patient demographics and tumour characteristics.
submitting all these patients to resection, as well as one for ‘fine-tuning’ our neo-adjuvant chemoradiotherapy protocol.

In our study, acute treatment-associated toxicity was seen in a higher percentage of patients treated with chemo-first compared with CR-C, suggesting that combined therapy may be better tolerated if given first and, if optional, may provide a viable treatment strategy in many patients.

Because of time constraints, tumour staging was not assessed in this study; this is a significant limitation as tumour stage and nodal status are known predictors of response to therapy and overall survival outcomes. Furthermore, time constraints on archive retrieval of date of diagnosis, and thus the ability to calculate accurate survival times, limited our Kaplan–Meier analysis of overall survival outcomes. Our interval analysis, presented here, failed to demonstrate a statistically significant difference in overall survival between groups. This apparent oncologic equivalence of both therapies is reassuring and may inform the logistic planning of treatment protocols in the future.

A constraint of this investigation is the study design. As this study took advantage of a change in hospital protocol, it was not a randomised controlled trial. Our original trial employed the CR-C neo-adjuvant treatment regime. This was then changed, for logistical purposes, to chemo-first. With the advent of the newly expanded SLRON radiotherapy capacity, we are now going ‘back to the future’ with a reversion to the originally trialled CR-C. On the basis of our limited study, we anticipate a decrease in treatment-related toxicity, and while we were unable to fully determine if a difference exists in survival between treatment protocols, our provisional data seem to suggest equivalent oncologic outcomes.

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References


