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Neoadjuvant Chemotherapy in Esophageal Cancer: Single Institution Experience

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Abstract

Background: Esophageal cancer is a major clinical problem that has a generally poor prognosis. As a result, there has been interest in combining surgery with neoadjuvant chemotherapy in an attempt to improve clinical outcomes. Evidence for clinical benefit from preoperative chemotherapy exists but it is not clear which patients (stage, tumor location, and histology) will benefit the most from this preoperative treatment.

Methods: This study retrospectively analyzed the outcome of 71 patients with operable esophageal carcinoma treated at Northamptonshire Oncology Centre, UK from January 2001 until July 2008. Patients were treated with two cycles of neoadjuvant chemotherapy followed by surgery. Data were analyzed by Kaplan-Meier plots, Cox regression modeling and chi-squared test.

Results: Median patient's age was 64 years. Male patients represented 83% of the cases. Of patients, 63% had an ECOG performance status of 1. Surgical resection was done for 63 (88.7%) patients. Two year overall survival in this cohort was 5.6%. Univariate analysis identified only surgical resection to be associated with better prognosis ($P<0.0001$). Multivariate analysis identified surgical resection ($P<0.0001$) and pathology type ($P=0.007$) to be the significant independent prognostic factors for survival.

Conclusion: In this retrospective study, survival data for operable esophageal cancer is poor despite the use of neoadjuvant chemotherapy. Lack of a dedicated upper gastrointestinal surgeon and unavailability of PET scan staging during the study period might have attributed to the poor outcome.

Keywords: Neoadjuvant chemotherapy, Esophageal cancer, Surgery

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Introduction

Adenocarcinoma (AC) and squamous cell carcinoma (SCC) are two principle variants of esophageal cancer which account for over 98% of cases.[1] Historically, AC and SCC have been treated as a single disease entity with many older clinical trials not differentiating between the two histologies, even in study populations.[2] Over the years, however, evidence has been compiled to support the idea that AC and SCC represent two separate diseases based on differences in etiology, epidemiology, prognosis, and response to treatment.[3-6] Recent epidemiological data has also shown variations in the incidence of these histological types since AC now accounts for more than 50% of newly diagnosed cases.[7-9]

Debate regarding the current standard of care for the management of esophageal cancer is ongoing.[10-12] Surgical management is the sole curative treatment for tumors confined to the esophagus and resectable peripheral tissues, including the regional lymph nodes. Despite progress in surgical techniques and the extension of surgical resection, survival has not improved, which highlights the need for additional treatment modalities.[13]

From a purely theoretical point of view, preoperative therapy should make it possible to eradicate micro-metastatic disease and shrink the tumor, even to the point of reducing its stage, making surgical resection easier. The objective of neoadjuvant treatment is to increase the chances of R0 (complete surgical resection with no microscopic residual) resectability, to reduce the incidence of local relapse, and enable early treatment of micro-metastases.[12]

Adjuvant chemotherapy with cisplatin-based regimens compared to surgery alone has been examined in three separate phase III trials.[14-16] None have reported a statistically significant difference in overall survival (OS), although Ando and colleagues have reported a five-year disease-free survival advantage (55% vs. 45%, P=0.037).[16] In the neoadjuvant setting there have been multiple randomized trials which compared various chemotherapeutic regimens to surgery alone.[17-25] Clinical complete responses based on direct visualization and an assortment of imaging modalities have ranged from 19% to 58%, but the rate of pathological complete response (PCR) at the time of surgery was a disappointing 2.5%-13%. This is an unsurprising trend considering the relative ineffectiveness of chemotherapy alone in the treatment of esophageal cancer.[17-25]

Neoadjuvant chemoradiation remains a controversial strategy in the treatment of SCC and AC of the esophagus. To date, at least nine randomized phase III clinical trials have compared neoadjuvant chemoradiotherapy with surgery alone.[18,26-34] These trials incorporated multiple chemotherapy regimens, doses of radiotherapy (20-50.4 Gy), and timing of radiotherapy with regard to chemotherapy (sequential vs. concurrent), types of surgical procedures performed, and histological types of esophageal cancer enrolled (AC, SCC, or both). Only two of these trials revealed a significant survival benefit that favored multimodality treatment, and neither was without its imperfections.[29,33]

The current study retrospectively analyzed the outcome of operable esophageal carcinoma in patients who underwent two cycles of neoadjuvant chemotherapy followed by surgery.

Patients and Methods

This study retrospectively analyzed the outcome of 71 patients diagnosed with operable esophageal carcinoma who were treated at Northamptonshire Oncology Centre, UK from January 2001 until July 2008. Histopathologic diagnosis was based on morphology according to WHO criteria.[6] Patients were staged according to the pathological TNM staging system for esophageal cancer with Corresponding American Joint Committee on Cancer stage grouping. Data from the files included information about physical examinations, chest X-rays, computed tomography scans of the chest and abdomen, and upper endoscopy.

Clinical and pathological variables analyzed included patient age, sex, Eastern Cooperative Oncology Group (ECOG) performance status,

Table 1. Clinical and pathological features of the esophageal carcinoma cases with median survival time.

Variable	Cases (%)	Median survival time (months) Estimate	95% CI		x^2	*P*
Age (yrs.)						
≤65	37 (52.1)	6.2	3.2	9.3	0.02	0.88
>65	34 (47.9)	6.3	4.3	8.3		
Sex						
male	59 (83.1)	6.	4.8	7.8	0.9	0.34
female	12 (16.9)	5.2	0	0.5		
ECOG						
0	7 (1.7)	4.4	3.7	5.1		
1	45 (63.4)	7.1	5.9	8.2	1.2	0.731
2	3 (4.2)	5.2	3.4	6.9		
Unknown	16 (22.5)	5.2	2.8	7.5		
Stage						
1	19 (26.7)	5.6	3.6	7.6		
2	17 (23.9)	7.0	2.8	11.2	0.93	0.817
3	23 (32.4)	6.3	3.9	8.7		
Unknown	12 (16.9)	5.2	3.6	7.9		
Pathology type						
AC*	37 (52.1)	5.7	3.3	8.0		
SCC**	19 (26.7)	5.6	2.1	9.1	0.24	0.97
High-grade	9 (12.6)	6.3	6.2	6.4		
Unknown	6 (8.4)	8.1	5.0	11.2		
Surgery						
Yes	63 (88.7)	7.1	6.1	8.1	71.8	<0.0001
No	8 (11.3)	1.7	0.7	2.7		

*AC: Adenocarcinoma
**SCC: Squamous cell carcinoma

tumor stage, pathology type, and treatment modalities. The chemotherapy included: i) cisplatin (80 mg/m^2) on day 1 and infusional 5-fluorouracil (5-FU, 1000 mg/m^2 daily) on days 1-4, or ii) cisplatin (80 mg/m^2) and oral capecitabine (800 mg/m2 BID) on days 1-14. None of our patients received radiotherapy. The primary end point was OS. End points were calculated from the date of diagnosis.

Overall survival was evaluated by Kaplan-Meier and log rank tests. We used the Cox proportional hazards model to estimate the independent factors prognostic for OS. All analyses were performed by using SPSS software (version 17.0, SPSS Inc., Chicago, IL), and a significance level of 0.05 was used.

Results

Clinical features

In this cohort (n=71), the two-year OS was 5.6% (median: 6.3 months, 95% CI: 4.56-8.04; Figure 1). Patients' ages ranged from 50-78 years with a median age of 64 years. Males comprised 83% of the study population. Most patients (63%) had an ECOG performance status of 1 with a median OS of 7.1 months (95% CI: 5.9-8.2). There was no statistically significant difference according to performance status (*P*=0.731). Esophageal AC was diagnosed in 52% of patients, with a median OS of 5.7 months (95% CI: 3.3-8). There was no statistically significant difference between histologic types in terms of OS (*P*=0.79). Pathologic TNM staging in this cohort included the following: 19 (26.8%) patients had stage I disease with a median OS of 5.6 months (95% CI: 3.6-7.6), 17 (23.9%) patients were stage II with a median OS of 7 months (95% CI: 2.8-11.2), and 23 (32.4 %) were diagnosed with stage III disease, with a median OS of 6.3 months (95% CI: 3.9-8.7). The difference in OS between stages was

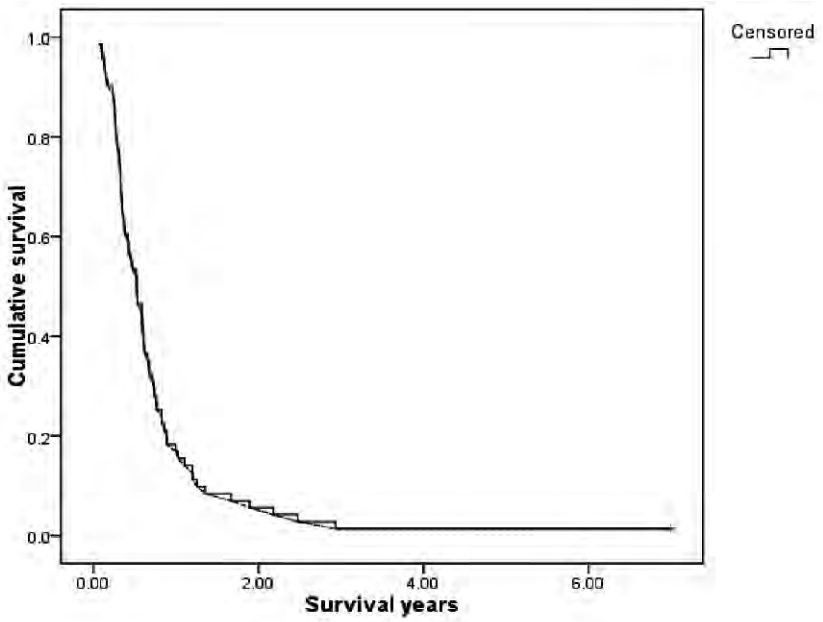

Figure 1. Kaplan-Meier curve for overall survival (OS).

non-significant (*P*=0.817). According to treatment regimen, 59 (83%) patients received cisplatin and 5-FU with a median OS of 5.6 months (95% CI: 3.7-7.4) vs. 8.1 months (95% CI: 5-11.2) for those who received cisplatin and capecitabine (13 patients), which was non-significant (*P*=0.608). Surgical resection was performed in 63 (88.7%) patients who had a median OS of 7.1 months (95% CI: 6.1-8.1) vs. 1.6 months (95% CI: 1.7-2.7) for those who underwent no surgery (Figure 2). This difference was highly significant (*P*<0.0001; Table 1).

Univariate and multivariate analysis

We evaluated various clinicopathologic variables to identify potential prognostic factors for survival. Univariate analysis identified only surgical resection to be associated with patients' prognoses (HR: 26.24, 95% CI: 8.9-77.3, *P*<0.0001). In contrast, as seen in Table 2, patient age, sex, tumor stage 2, ECOG performance status of 1, and SCC pathology were not prognostic for survival.

Cox proportional hazard regression analysis of patient survival based on clinical and pathologic factors was also performed. Multivariate analysis identified surgical resection (HR: 44.03, 95% CI: 13.15-147.3, *P*<0.0001) and high-grade subtype (HR: 7.03, 95% CI: 1.8-26.2, *P*=0.004) as significant independent prognostic factors for survival. In contrast, patient age, sex, stage, and performance status were not significant independent prognostic factors for survival (Table 2).

Discussion

The management of esophageal carcinoma has evolved over the past 30 years, however despite recent improvements in detection and treatment, OS remains poor.

A dramatic shift in the histology of esophageal cancer has been observed in the United States and some parts of Europe,[4] where SCC has become increasingly less common - accounting for less than 30% of all esophageal malignancies. This approximates our finding in this study, where SCC has accounted for about 27% of cases. The risk of SCC has decreased substantially due to smoking cessation, while AC increased due to increases in gastric esophageal reflux disease and Barrett's esophagus, both major risk factors for AC.[35]

Patient outcomes may correlate with the initial stage of cancer at diagnosis, but the best correlation with survival is associated with the surgical pathologic stage. However, in our study the tumor stage did not affect survival which may

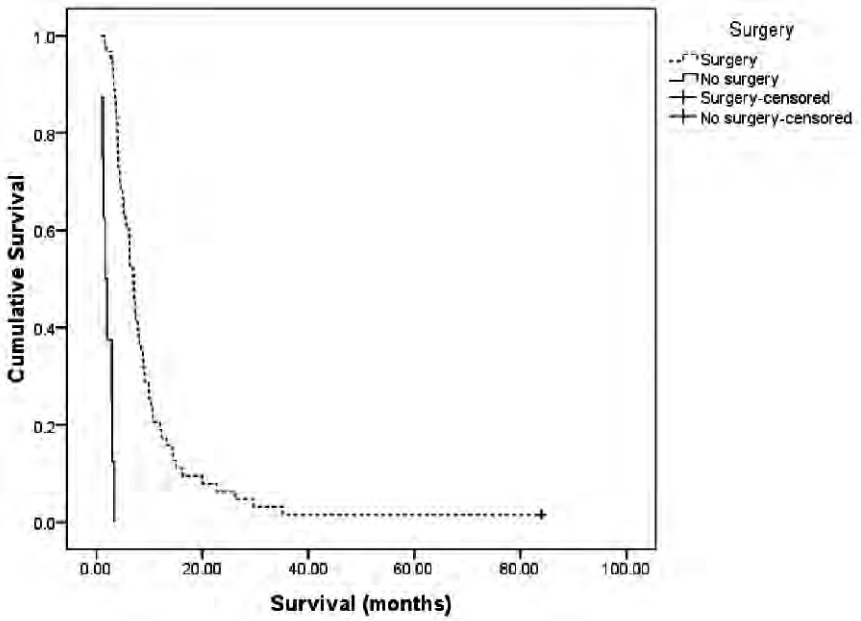

Figure 2. Kaplan-Meier curve for overall survival (OS) in relation to surgery.

be explained by the small number of patients and lack of statistical power, in addition to the inability to accurately stage about 17% of patients due to lack of documentation.

Until recently, therapeutic management of AC and SCC were similar and the results considered together, often without distinction, yet the tumor biology and clinical presentation greatly differ. Nevertheless, a large retrospective surgical series has revealed a prognostic difference between SCC and AC,[36] with poorer survival noted for SCC, which did not correlate with our results, in which survival was the same for both SCC and AC. This could be explained by the small numbers of patients in our study.

Multiple modalities have been employed for the treatment of esophageal carcinoma because of poor survival rates seen in patients only treated with surgical resection. Thus, chemotherapy has been investigated in the preoperative setting.

In our study, the median OS was 6.3 months with a two-year survival of 5.6%, which was similar to that mentioned by Nygaord et al.[18] and Schlag et al.[19] who noted median OS of 7 months., This OS was much lower than reported by Maipang et al.[20] and Law et al.[21] (OS: 17 months), and Ancona et al.[22] (OS: 25 months).

Our OS is also much lower than reported by the UK MRC trial that included 802 patients of all histologies, who were randomized to two cycles of cisplatin and infusional 5-FU vs. surgery alone. A distinction of this trial compared to others was that clinicians were able to give their patients neoadjuvant radiotherapy (25-32.5 Gy) irrespective of randomization; thus, 9% of patients on each arm received radiotherapy. Overall survival improved in the neoadjuvant group (HR: 0.79, 95% CI: 0.67-0.93, *P*=0.004), with a median OS of 16.8 months compared to 13.3 months, respectively. However, several clinical methodological problems were found in this trial, and 10% of the patients received off protocol preoperative radiotherapy. In addition, patients accrued from China were excluded.[23]

The low rate of median OS can be explained by the following: approximately 11% of patients did not undergo surgery, about 32% had stage III disease, accurate staging by PET scan was not available during the study period, and there was no dedicated upper gastrointestinal surgeon available during the study period.

Another large trial by Kelsen et al.[26] evaluated neoadjuvant chemotherapy in the Intergroup (INT) 0113 study with 440 patients; however, no difference in OS was reported. Two large meta-

Table 2. Cox proportional hazard regression analysis of patient survival.

	Cox (OS)			
	Univariate		Multivariate	
Variables	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age (yrs.)			----------	------
≤65	1.04 (0.64-1.6)	0.88		
>65	1.0			
Sex			----------	--------
male	1.36 (0.71-2.07)	0.34		
female	1.0			
ECOG			----------	---------
0	1.0			
1	0.72 (0.32-1.63)	0.43		
2	0.66 (0.17-2.62)	0.56		
Unknown	0.91 (0.39-2.32)	0.91		
Stage			----------	---------
1	1.0	0.69		
2	1.14 (0.58-2.22	0.61		
3	0.84 (0.45-1.58)	0.88		
Unknown	1.05 (0.51-2.2)			
Pathology				
AC	1.0		1.0	
SCC	1.13 (0.65-1.99)	0.65	0.96 (0.11-1.8)	0.89
High-grade	1.10 (0.53-2.31)	0.78	7.03 (1.8-26.2)	0.004
Unknown	1.0 (0.41-2.42)	0.99	15.1 (2.1-107.7)	0.007
Surgery				
Yes	26.24 (8.9-77.3)	<0.00001	44.03 (13.1-147.3)	<0.00001
No	1.0		1.0	

*AC: Adenocarcinoma
**SCC: Squamous cell carcinoma

analyses have failed to demonstrate a survival advantage with neoadjuvant chemotherapy[37,38], although another meta-analysis by Gebski et al.[39] has reported a statistically significant OS benefit with neoadjuvant chemotherapy (HR: 0.90, 95% CI: 0.81-1.00, *P*=0.05), which corresponded to a two-year absolute survival benefit of 7%. In this meta-analysis, no statistically significant benefit was seen in SCC patients treated with neoadjuvant chemotherapy (HR: 0.88, 95% CI: 0.75-1.03, *P*=0.12). Although there was a benefit with AC (HR: 0.78, 95% CI: 0.64-0.95, *P*=0.014), the results were based solely on a single trial whose data was available for review - the MRC trial.[23,39] At least four separate trials compared cisplatin-based perioperative regimens (neoadjuvant and adjuvant chemotherapy) to surgery alone in esophageal cancer.[17,40-42] Those studies which focused solely on esophageal cancer revealed no survival benefits,[17,40] whereas the two trials that included patients with AC of the stomach and gastro-esophageal junction (GEJ) showed benefits.[41,42] The largest trial, published by Cunningham and colleagues, randomized 503 patients with AC to three preoperative and three postoperative courses of epirubicin (50 mg/m^2 day 1) and cisplatin (60 mg/m^2 day 1) with infusional 5-FU (200 mg/m^2 per day for 21 days) vs. surgery alone. Although the majority of patients had gastric AC, approximately 26% of those enrolled had AC of the GEJ or distal esophagus. Despite the fact that 58% of patients were unable to tolerate all six cycles of chemotherapy, the perioperative chemotherapy group had a statistically significant higher likelihood of OS compared to those treated with surgery alone (HR: 0.75, 95% CI: 0.60-0.93, *P*=0.009), with an improved median OS of 24 months vs. 20 months and five-year OS of 36% vs. 23%. Although postoperative complications were not

increased (46% vs. 45%), there was no difference in the rate of R0 resection (69% vs. 66%) or pCR (both 0%). Importantly, there was no evidence of heterogeneity in the treatment effect based on primary tumor location.[41]

In conclusion, in this retrospective study our survival data for operable esophageal cancer was poor despite the use of neoadjuvant chemotherapy. The lack of a dedicated upper gastrointestinal surgeon and unavailability of PET scan staging during the study period possibly attributed to the dismal outcome.

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