PATIENTS WITH OPERABLE OESOPHAGEAL CARCINOMA WHO HAVE MODERATE - SEVERE DYSPHAGIA AND RECEIVE NEO-ADJUVANT CHEMOTHERAPY (NACT) HAVE POORER OUTCOMES THAN THOSE IN RANDOMIZED CLINICAL TRIALS

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ABSTRACT

Background: Randomised trials have shown that NACT improves outcomes in patients with operable oesophageal carcinoma (OEO2, MAGIC). We asked whether differences between patients enrolled in clinical trials and those seen in routine practice had a prognostic impact.

Methods: A retrospective case series of 41 consecutive patients with operable oesophageal carcinoma receiving NACT at the Mount Vernon Cancer Centre between 2000 and 2008. We collected data on demographic status, symptoms, staging, co-morbidities and outcomes. Dysphagia was scored as the OEO-2 trial, where 4 indicates complete dysphagia. Survival was estimated using the Kaplan-Meier method, and statistical significance was assessed using the chi-squared test and the logrank test as appropriate. All analyses were conducted using 'R'.

Results: Of the 41 patients, 39 were male, 39 had adenocarcinoma and 38 were ECOG performance status 0-1. Median age was 63 years (41-80 years). Clinical stage was: IIa 22 IIb 4 IIIa 15. 28 patients had some degree of co-morbidity, and 32 had a successful resection. Age, stage, performance status and co-morbidity were all similar in our patients as those included in the two randomised trials. 23 of our patients had a score of 2 or more (able to swallow a semi-solid or liquid diet only). The overall survival (OS) of patients who had a dysphagia score of 0 or 1 was better than those with a score of 2 or more (median OS = 36.6 months vs. 9.4 months). All patients who did not progress to surgery had a dysphagia score of 2 or more.

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Conclusions: NACT for operable oesophageal cancer improves survival, margin involvement, lymph node involvement and complete resection. However, patients with a dysphagia score of 2 or more have worse outcomes than those in the randomised trials. This data raises questions about the use of NACT in such patients.

INTRODUCTION

Worldwide, oesophageal cancer affects more than 500,000 people, and is responsible for 400,000 deaths [1]. 7,500 of the cases are in the UK, of who over 4000 die. Well described risk factors include male sex (2:1 compared to women), alcohol consumption, smoking and obesity. Although historically the disease has largely consisted of squamous cell carcinoma, there has been a well described shift in histological type such that adenocarcinoma is now the most prominent [2, 3, 4].

Two major randomised trials have shown that patients with operable oesophageal carcinoma have improved outcomes when given neo-adjuvant chemotherapy (NACT). The OEO-2 trial randomised patients with resectable oesophageal cancer of any cell type to receive two cycles of Cisplatin and 5FU prior to surgery, or surgery alone [5]. Those in the chemotherapy arm were shown to have improved survival with no increase in the occurrence of serious adverse events. The MAGIC trial randomised patients to have three cycles of neo-adjuvant ECF chemotherapy with three cycles of adjuvant ECF chemotherapy, or surgery alone [6]. Again a survival advantage was found in those randomised to the chemotherapy group.

Based on the results of these trials, standard practice for patients diagnosed with a resectable oesophageal cancer is to undergo a course of neo-adjuvant chemotherapy prior to surgical resection. However, there have been concerns about how well the trial population reflects that seen in clinical practice, and whether any difference may have an impact on outcomes of treatment.

The aim of this study is to investigate whether patients seen in routine practice differ from those in trials, and to examine these differences for any prognostic impact.

METHODS

Mount Vernon Cancer Centre (MVCC), UK serves a population of 1.8 million. A database of the Cancer Centre patients was searched for patients with operable oesophageal carcinoma who received NACT between 2000 and 2008. Patient notes were reviewed to collect data on demographic status, symptoms, histology, staging, co-morbidities, surgical procedures, tolerance and adverse effects of chemotherapy, and survival.
Assessment of tumour stage and operability was re-confirmed by a senior clinician, and dysphagia was scored using documented OEO-2 scale [5], ranging from 0-4 where 4 indicates complete dysphagia (see below).

Overall survival was estimated using the Kaplan-Meier method, and statistical significance was assessed using the chi-squared test for proportions and the logrank test for survival data. All analyses were conducted using the statistical software R [7].

**RESULTS**

Of the 41 patients, 39 were male, 39 had adenocarcinoma and 38 were ECOG performance status 0-1. Median age was 63 years (41-80 years). Clinical stage was: Ila 22, IIb 4, IIIa 15. 28 patients had some degree of co-morbidity, and 32 had a successful resection. Age, stage, performance status and co-morbidity were all similar in our patients as those included in the two randomised trials.

<table>
<thead>
<tr>
<th></th>
<th>Median Survival (months)</th>
<th>2 Yr OS (%)</th>
<th>Had Surgery (%)</th>
<th>Perioperative Deaths (%)</th>
<th>Dysphagia Score &gt;2 (%)</th>
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</thead>
<tbody>
<tr>
<td>OEO2</td>
<td>16.8</td>
<td>43</td>
<td>92</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>MAGIC</td>
<td>24</td>
<td>50</td>
<td>97</td>
<td>5.6</td>
<td>35</td>
</tr>
<tr>
<td>MVCC</td>
<td>13.7</td>
<td>38</td>
<td>85</td>
<td>9</td>
<td>56</td>
</tr>
</tbody>
</table>

Median survival from diagnosis was 13.7 months, compared to 16.8 months in the OEO2 trial and 24 months in the MAGIC trial. The 2 year survival was 38%, compared with 43% in OEO2 and 50% in MAGIC.

When comparing survival based on staging of disease, median survival for those with stage 2 disease was 24.9 months compared with 21.7 months for those with stage 3 disease.
23 of our patients had a dysphagia score of 2 or more. The overall survival of patients who had a dysphagia score of 0 or 1 was better at 36.6 months than those with a score of 2 or more, at 9.4 months.
15% of patients did not progress to surgery, compared with 8% in OEO2 and 3% in MAGIC. All patients in our study who did not progress to surgery had a dysphagia score of 2 or more.

DISCUSSION

Data from randomised trials suggests that NACT for operable oesophageal cancer improves survival, margin involvement, lymph node involvement and complete resection. [5, 6]

The median survival in our study population demonstrated a reduced overall survival when compared with trial populations, despite closely correlating demographics. However, further analysis shows that this reduction in survival was due to the poor survival of those with grade 2 or greater dysphagia. This impact was seen irrespective of disease stage and suggests that a dysphagia score may be of some benefit when assessing the suitability of patients for NACT, along with existing prognostic indicators such as staging and performance status.

Our study raises two interesting points: Firstly, populations seen in practice may differ from those recruited to clinical trials. These differences may be subtle yet have significant clinical importance, as a result of which treatments shown to be of benefit in randomized controlled trials may be substantially less effective in routine care. Secondly, it raises questions about the appropriate management of such patients; it seems unclear whether they should be treated more aggressively in order to try and improve outcomes, or treated palliatively to reduce treatment-related side-effects.
REFERENCES