The Implications of the Introduction of Neoadjuvant Chemoradiotherapy for Oesophageal Cancer in a Low Volume Centre

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Introduction

Oesophageal cancer remains the seventh leading cause of cancer related mortality in the world [1], and the majority of patients present at an advanced stage of disease [2,3]. Oesophagectomy was the standard treatment for localised oesophageal cancer, and remains a high risk procedure associated with significant morbidity and mortality [1,4,5]. In order to improve outcomes, the management of this disease has evolved to become tri-modal, combining neoadjuvant chemotherapy and radiotherapy with surgical resection [1,6].

A multimodal treatment approach for oesophageal cancer could involve neoadjuvant chemotherapy, along with radiotherapy [6]. Neoadjuvant chemotherapy may have several advantages, such as the facilitation of complete resection by tumour downstaging [6,7], improved tolerance when compared to postoperative chemotherapy [6] and the early treatment of micrometastases [6,7]. Similarly, neoadjuvant radiotherapy has been shown to...
improve the pathological complete response rate and local tumour downstaging [6,8]. However, the disadvantages of neoadjuvant therapy may include delayed surgery, impaired wound healing, increased risk of respiratory complications as well as increased morbidity and mortality of the oesophagectomy itself [6,8]. The CROSStrial demonstrated improved rates of both overall and disease-free survival among patients who received neoadjuvant therapy followed by surgery [6,8,9]. Moreover, Hagry et al. [10] concluded that neoadjuvant therapy has acceptable complication rates relative to its effectiveness in down-staging of tumours, resulting in an improved chance for complete resection [10]. This study aims to identify the effect of neoadjuvant therapy on perioperative morbidity and mortality, by performing a retrospective review of patients who underwent oesophagectomy for oesophageal cancer at Canberra Hospital.

Methods

The medical records for all patients who underwent an oesophagectomy for oesophageal cancer at the Canberra Hospital, from 1st January 2001 through 31st December 2012, were reviewed. Ninety-eight patients were identified, all of whom had histologically confirmed primary squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma of the oesophagus or gastro-oesophageal junction. Patients with cancer found to be arising from the stomach were excluded from this review. Patients with stage IV cancer did not undergo oesophagectomy, and were excluded from this study.

Patients were placed in one of two groups based on whether they received neoadjuvant therapy or not, as prescribed by medical and radiation oncologists. For each group, mean age, gender, received neoadjuvant therapy or not, as prescribed by medical

Results

Ninety-eight patients (73 men and 25 women, median age 63.4 years) with cancer of the oesophagus or gastro-oesophageal junction were reviewed, all of whom underwent oesophagectomy between January, 2001 and December, 2012. Of these patients, 39 underwent neoadjuvant therapy, while 59 underwent surgery alone. Of the 39 patients that underwent neoadjuvant therapy, 26 (67%) received chemoradiotherapy alone, 3 (8%) received radiotherapy alone, while 10 (26%) received both. The majority of tumours were adenocarcinomas (83%) located in the oesophagus (81%). The majority of patients had stage III oesophageal cancer (51%). The median age of patients receiving neoadjuvant therapy was 61 years, compared to 64 years in the surgery alone group (Table 1). The percentage of patients who underwent neoadjuvant therapy increased markedly for the years 2007-2012 when compared to the years 2001-2006 (Table 2).

Perioperative complications were recorded as grades I to V, most of the patients with grade III and all patients with complications of grade IV occurred in the group that did not receive neoadjuvant therapy (Table 3). The perioperative mortality rate was 3.8% (3 patients), with all deaths (grade V complication) occurring in the surgery alone group.

R0 resection was achieved in 87 patients (88.8%). A higher percentage of patients (100%) who received neoadjuvant therapy had complete resection, compared to those who did not (81.5%), although this difference did not reach statistical significance (Table 4).

Table 1 Demographic and clinical characteristics.

| Neoadjuvant therapy | Yes | No | P-Value |
|---------------------|-----|----|---------|
| Sex (M/F)           | 16/96 | 40/14 | 0.255 |
| Mean age (Years)    | 61.08 | 64.46 | 0.198 |
| Tumour Site         |     |    | 0.611 |
| Oesophagus          | 20   | 43  |       |
| Gastro-oesophageal Junction | 5 | 11  |       |
| Tumour Type         |     |    | 1     |
| Adenocarcinoma      | 20   | 43  |       |
| Adenosquamous Carcinoma | 1 | 1   |       |
| Squamous cell carcinoma | 4 | 10  |       |
| AJCC Stage          |     |    | 0.025 |
| 0                   | 2    | 1   |       |
| I                   | 0    | 14  |       |
| II                  | 8    | 12  |       |
| III                 | 15   | 27  |       |

Table 2 The number and proportion of oesophagectomy patients who underwent neoadjuvant therapy for the years 2001-2006 and 2007-2012.

| Year             | Neoadjuvant Therapy | Total | P-Value |
|------------------|---------------------|-------|---------|
| 2001-2006        | Yes: 6 (14%)        | No: 37 (86%) | 43 (100%) | <0.001 |
| 2007-2012        | Yes: 33 (60%)       | No: 22 (40%) | 55 (100%) |       |

This study was approved by the Human Research Ethics Committee, ACT Government Health Directorate.
Disease free survival, expressed as the proportion of patients without recurrence postoperatively, revealed no significant difference between both patient groups (P-value 0.38) (Figure 1). The median disease free survival for the neoadjuvant therapy group was 58.4 months (CI 15.3, 101.4), compared to 49 months (CI 7.9, 92.0) for the surgery alone group. The overall median disease free survival was 49.2 months (CI 39.1, 68.3).

Discussion

Previously, oesophagectomy or definitive chemoradiotherapy were the only treatment options used in the management of localised oesophageal cancer [11]. In recent years, multimodality treatment strategies involving neoadjuvant chemotherapy and radiotherapy followed by surgery have become more widespread, as these have been shown to improve disease free survival [12]. The impact of neoadjuvant therapy on perioperative morbidity and mortality has been uncertain [12,13]. This study revealed a decrease in adverse events after the introduction of neoadjuvant therapy in a low volume hospital. When considering perioperative mortality, there were three deaths in the surgery alone group, compared to no deaths in the neoadjuvant therapy group. There was no increase in perioperative complications as a consequence of neoadjuvant therapy. A recent meta-analysis found higher rates of complete resection among patients who underwent neoadjuvant therapy [14]. This study had a similar finding, with a higher percentage of complete resection among patients treated with neoadjuvant therapy, although this difference did not reach statistical significance. This finding suggests that neoadjuvant therapy may be beneficial in practice, by the facilitation of tumour downstaging [6]. Alternatively, neoadjuvant therapy may have resulted in a degree of patient selection due to the possible deterioration of the patient’s condition during their preoperative period.

With regard to disease free survival, this study was unable to detect a significant difference in recurrence rates between the two patient groups. The randomised controlled trial performed by the CROSS group revealed improved rates of both overall and disease-free survival among patients who received neoadjuvant chemoradiotherapy followed by surgery [14]. Other studies have suggested that neoadjuvant therapy may play a role in reducing disease recurrence, by facilitating complete resection and targeting micrometastases [6].

This study has various limitations. As a retrospective review, the nonrandomised allocation of patients may have led to selection bias. Further, patients were less likely to undergo neoadjuvant therapy in the first half of the study period (2001-2006) when compared to the second half of the study period (2007-2012). The decrease in morbidity and mortality in the neoadjuvant group may have resulted from improvement in perioperative care in the later years of the study.

Conclusion

Overall, this study revealed that the administration of neoadjuvant therapy to patients with cancer of the oesophagus or gastro-oesophageal junction, at the Canberra Hospital between 2001 and 2012, was associated with a decrease in the rate of perioperative complications. Furthermore, neoadjuvant therapy may be associated with improved rates of complete resection. Unfortunately, in our small group of patients, we were unable to detect an improved disease free survival in the neoadjuvant therapy group.

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