

Neoadjuvant Therapy in Oesophageal Cancer- An International Standard of Care

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Abstract

Despite low postoperative mortality rates, the long-term outcomes from surgical-based treatment for oesophageal cancer remain poor. Neoadjuvant (NA) Chemoradiotherapy (CRT) or chemotherapy has both been used to improve these outcomes. The optimal NA approach is yet to be defined through high quality evidence and remains the preference of individual clinicians. The evidence for neoadjuvant treatment is stronger and based on the current evidence NA CRT can be recommended as a treatment approach in oesophageal cancer for both adenocarcinoma and squamous cell carcinoma, but further work is needed to establish its superiority over NA chemotherapy alone, particularly for adenocarcinoma.

Keywords: Neoadjuvant chemoradiotherapy; Oesophageal cancer

Introduction

Oesophageal cancer remains a highly lethal malignancy. In 2008, an estimated 482,300 new oesophageal cancer cases and 406,800 deaths occurred worldwide [1]. Surgical resection remains the mainstay of treatment but despite low postoperative mortality rates, long term outcomes remain disappointing. This is due in part to both systemic relapse and locally advanced disease at presentation, resulting in R1 resection (positive circumferential margin) in up to 33% of patients [2]. Neoadjuvant (NA) treatment is defined as treatment given prior to definitive treatment, usually in the context locally advanced or tumours with high metastatic potential. Both chemoradiotherapy (CRT), and chemotherapy alone have been investigated as NA treatments to improve outcomes by down staging the tumour and eradicating micro metastatic disease at an early stage. It is clear that some form of NA therapy improves survival in oesophageal cancer, but to date there is a paucity of head to head phase III trials comparing these NA strategies [3] and it is often clinician, institutional or country of practice preferences that dictate the NA approach [4]. NA CRT approaches predominate in North America and Europe but have not been adopted widely in the UK over previous concerns over the risks of post-operative complications and deaths.

Neoadjuvant Chemoradiotherapy

NA CRT has been the subject of several trials and meta-analyses [3]. The rationale for this additional modality stems from the poor outcomes with surgery alone arm and the potential radiosensitising effects of chemotherapy. Its use pre, rather than post-operatively, has several potential advantages. Patients will probably tolerate CRT much better preoperatively than after an oesophagectomy due to the prolonged recovery period needed. The target volume delineation for RT is also easier to define when the tumour is in situ. The most recent systematic review of NA CRT was conducted by Gwynne et al. published in 2014 [3]. This review identified 10 prospective RCTs, and several meta-analyses. Many of the RCTs were started in the 1990s and

do not reflect the progress in diagnostics and treatment approaches to this disease in that time. Three of the later RCTs favoured the use of NA CRT as did the three most recent meta-analyses (Table 1). The latter supported a survival benefit for NA CRT, with conflicting impact on the rate of postoperative complications [5-7]. It is highly relevant that the 3 of the RCTs showing a survival advantage for NA CRT were undertaken in the era of conformal radiotherapy. The largest and perhaps most important of these is the CROSS trial [8]. This study randomised 368 patients with potentially resectable oesophageal and GOJ tumours to either CRT with paclitaxel/carboplatin to surgery alone. Patients followed a rigorous staging protocol using: pulmonary function tests, upper endoscopy, and endoscopic ultrasound (EUS) and neck ultrasound. Radiotherapy was standardised to 41.4Gy in 23#. The CROSS trial reported a significant improvement in overall survival with a median survival of 49 months in the CRT arm versus 24 months in the surgery-only arm. The improvement in survival has been attributed to an increase in R0 resection rather than an absence of distant metastases. This trial showed no increase in post-operative morbidity or mortality and led to the cautious re-introduction of the NA CRT approach in the UK. NeoSCOPE, which has recently closed to recruitment is, a randomised UK phase II study in 85 patients of two NA CRT regimens (two cycles of oxaliplatin and capecitabine followed by RT, 45 Gy in 25 fractions with either concurrent oxaliplatin and capecitabine or paclitaxel and carboplatin), before surgery, for resectable adenocarcinoma of the oesophagus/oesophagogastric junction. It was an opportunity to establish the safety of NA CRT while evaluating a number of components of oesophageal RT planning and the effects of these on treatment outcome, including pathological response. Results are expected in 2016 [9]. While the immediate post-operative complications of NA CRT dominate current thinking, there is increasing data for the long-term cardiac mortality after NA CRT. Frandsen et al. [10] in ASCO 2015 reported a retrospective study of over 40000 patients, RT increased the risk of heart disease related death by 2.8%, 5.3% and 9.4% at 5, 10 + 20 years respectively with a hazard ratio of 1.45 $p < 0.05$ when compared to chemotherapy alone [16]. As more patients are cured of their disease using these approaches, the additional cardiac risks need to be given greater consideration.

Study	Number of studies/patients	Conclusions
Zheng et al 2013	7/523	Survival benefit with CRT High incidence of related complications Lower incidence of loco regional recurrence Similar incidence of distant recurrence No comment on histological subtype
Wang 2012	12/1529	Improved 1.3 and 5 years survival Greater benefit for SCC No increase in post-operative complications
Sjoquist 2011	24/4188	Both NA chemo and NA CRT have survival advantage over surgery alone Benefit of NA CRT over NA chemo not established Survivals similar in AC and SCC

Table 1: Recent meta-analyses in NA CRT for oesophageal cancer.

Neoadjuvant Chemotherapy

For NA chemotherapy, some studies have reported a significant improvement in overall survival with NA chemotherapy, others little or none. In the UK NA chemotherapy remains the standard of care following the data from the OEO2 study [11]. In this trial preoperative chemotherapy with two cycles of cisplatin and 5-fluorouracil (5-FU) and surgery was compared to surgery alone and a survival advantage was confirmed that was maintained in both histological groups. The most recent UK trial looking at NA chemotherapy was the OEO5 trial, presented at ASCO 2015 [11]. The trial randomised 897 patients with GOJ and oesophageal adenocarcinoma to 2 cycles of Cisplatin/5-FU chemotherapy (as OE02) 4 cycles of ECX chemotherapy and reported improved partial response with 4 with ECX(11% vs 3%) but no difference in overall survival at 3 years (CF 39% vs ECX 42%). For a more detailed review of NA chemotherapy see Hingorani et al. [13].

NA Chemotherapy vs. NA Chemoradiotherapy

In order to determine the optimal approach a head to head comparison between NA chemotherapy and NA CRT in adenocarcinomas is needed. Only three studies have been identified [14], reported on the multicentre German POET trial in patients with GOJ adenocarcinomas. Randomisation was between 16 weeks of chemotherapy alone (cisplatin and 5- fluorouracil) or 12 weeks of the same regimen followed by radiotherapy (30 Gy in 15 fractions) with concurrent cisplatin and etoposide. The trial was closed early due to poor accrual, but in the 127 patients randomised a higher pCR rate was seen in the CRT group (16% versus 2%), which did translate into a better median survival (33 versus 21 months) and 3 year overall survival (47% versus 28%). The trial has been criticised for a low dose of radiation and a prolonged non-conventional schedule of induction and concurrent chemotherapy, which would not be considered standard practice [15]. In a phase II study, randomised 78 patients to NA chemotherapy or NA CRT (35Gy in15 fractions). They found similar toxicity and overall survival (P = 0.38) between the two groups, but statistically significant improvement in pCR (P = 0.01) and a reduction in R1 resection rates (P = 0.04) in the CRT arm. The other study by Luu et al. [16] was retrospective and failed to show any survival advantage over NA chemotherapy. The currently recruiting All Ireland Co-Operative Research Group (AICRG) Neo-AEGIS trial [17] is randomising between CROSS type NA CRT and MAGIC type chemotherapy (3 cycles ECX pre and post-surgery). The primary

endpoint of the trial is overall survival with secondary endpoints of pCR rates among others. A trial of this kind, using optimal CRT and chemotherapy schedules will hopefully determine the optimal NA regimen for the future.

Conclusion

In conclusion, NA CRT is a valid approach for the management of operable oesophageal cancer, although its superiority over NA chemotherapy is not yet proven. For adenocarcinomas results from the Neo-AEGIS trial will be eagerly awaited. Further studies are needed to test the optimal NA approach for SCC. Further work is also needed to individualise NA therapy according to tumour patient characteristics.

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