controversial topics in surgery

The management of a patient with an operable carcinoma of the oesophagus

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These two papers appear more complementary than meets the eye! The majority of oesophageal cancer is adenocarcinoma in origin; for these, both authors advocate neoadjuvant chemotherapy followed by resection, thus conferring the advantages of treating micrometastases as well as the benefits of resection for local control and additional increase in R0 resection rate. Chemoradiotherapy would seem ideal to treat proximal squamous cancers. Dr Crosby rightly indicates the poor quality of life following

open resection: use of minimally invasive surgery might improve postoperative quality of life. Staging CT PET has reduced our own resection rate by 15%; this should be followed by an improvement in the 1–3-year survival rate following resection. There is no doubt that improvements in the management of oesophageal cancer are around the corner.

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An oncologist's view

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Patients choose between treatments for different reasons. As clinicians we must discuss treatment options available giving unbiased information in a form the patient can understand to help the patient make an informed choice. Given the lack of randomised evidence and our inevitable personal biases, it is perhaps unsurprising that we fall short of this Utopian aspiration.

Oesophageal cancer is a devastating disease. Despite improvements, the majority of patients present with advanced disease and ultimately die of their disease. In the UK, the majority of patients are discussed at multidisciplinary team prior to referral to a designated specialist upper gastrointestinal surgeon. Most patients who have resectable disease and are fit for surgery will be offered neo-adjuvant chemotherapy followed by surgery. Unfortunately, only about 20% of patients with oesophageal cancer are suitable for this approach. Of these, the majority do not survive 2 years after surgery¹ and never regain their former quality of life.² A further 50% of the survivors will die over the following 3 years so that only 20% of this already select group will survive 5 years.³

Chemoradiotherapy (CRT) is an alternative to surgery. It is superior to single-agent radiotherapy in terms of

improved survival, albeit, at the expense of increased toxicity.⁴ Studies of CRT, predominantly in squamous cell carcinoma, have shown a consistent survival rate of 30–40% at 2 years, and 20–30% at 3–5 years. CRT can be given to most 'operable' patients and also to patients unsuitable for surgery due to disease extent or medical co-morbidities.

Attempts to combine CRT and surgery as 'triple modality therapy' have resulted in modest improvements in survival, improvement in the rate of complete (R0) resection and improvement in local disease control, at the expense of increased operative morbidity and possibly mortality over surgery alone.⁵ However, two important trials in Europe failed to show a survival advantage for routinely operating on patients after CRT.^{6,7} We would argue that there are two treatment options for patients with locally advanced, operable oesophageal carcinoma – pre-operative chemotherapy or primary CRT and selective surgery. How do we decide between these two treatment options?

In practical terms, these are very different treatments. CRT is given as an out-patient over 5–6 weeks, delivering 25 fractions (approximately 2 min/day) of radiotherapy, concurrently with chemotherapy. This may be preceded by a 6-week

course of neo-adjuvant chemotherapy. There is a 40–50% rate of World Health Organization Grade 3–4 (serious or life-threatening) acute toxicities, predominantly haematological, as a result of the chemotherapy; this is easily managed, with a mortality of less than 2%. Overall, 90–100% of patients complete the intended treatment. In the longer term, there may be a greater risk of post-therapy stricture requiring dilatation or a stent after CRT.⁶

Surgery is performed over 4–6 h and the patient discharged from hospital after approximately 10–18 days, with a short stay in an intensive or high-dependency care unit. In specialist centres, postoperative morbidity is around 40%, mainly consisting of pulmonary morbidity and anastomotic leaks, and an in-hospital mortality of approximately 5%. About 20% of patients also have problems with anastomotic strictures or a dumping syndrome later after surgery.

There is little data on quality of life between the two treatments. A prospective study evaluated the quality of life of patients surviving at least 3 years after surgery.⁸ Although most aspects of quality of life returned to baseline, patients reported residual problems with reflux, dyspnoea and diarrhoea even 3 years after surgery. There is even less data regarding quality of life after CRT. A non-randomised study comparing CRT with treatment including surgery showed that quality of life was diminished after CRT, but the deterioration was less dramatic than following oesophagectomy.² Similarly, in the French study (FFCD 9102) of CRT, with or without surgery, quality of life was worse after surgery but no different between the treatment arms at 2 years.⁹

Quality of life is determined not only by the effects of treatment but, perhaps more importantly, by the state of disease control. The patterns of disease relapse after surgery and CRT are quite different. CRT is associated with a local failure rate of 40–50%^{6,7} and surgery, with or without CRT, with better local disease control.⁵ However, the majority of patients with locally advanced disease have systemic disease and the majority eventually succumb to metastatic disease.

One may expect patients to be heavily influenced by information regarding survival. Although there is a lack of randomised data, some studies have compared survival outcomes after surgery and CRT. A Chinese study randomised 80 patients with squamous cell oesophageal carcinoma to surgery or CRT and found no difference in early overall and disease-free survival.¹⁰ Two large European studies investigated the role of surgery following CRT versus CRT alone, predominantly in squamous cell carcinoma of the oesophagus.^{6,7} The 2-year survival in the two arms was approximately 35% and 40%, the non-significant difference being reversed in the German and French trials. A Chinese study¹¹ presented in abstract form only compared radiotherapy with surgery alone in 269 patients with squamous cell carcinoma and found a non-significant trend towards improved survival following non-surgical therapy. Finally, a

Swedish study in 91 patients with adenocarcinoma and squamous cell carcinoma, also reported in abstract form only, found no difference between primary CRT and surgery alone.¹² These studies can be criticised for poor trial design, heterogeneity of treatment regimens and being underpowered to show clinically meaningful differences between the treatment arms. However, based on these results, it would seem unlikely that there is a large survival difference between the treatment approaches.

The best published outcomes have been achieved in selected, usually single-centre case series, for both surgery and CRT. However, one must always defer to randomised trial evidence to obtain the best estimate of the true intent-to-treat effect. One should be cautious when interpreting data between surgery-only series and trials of neo-adjuvant therapy, where patients are randomised some months prior to surgery, and included in analyses, irrespective of the outcome of that surgery.

Are there other patient- or disease-related factors that may inform our decision making? Histological tumour type is important. Squamous cell carcinomas occur more commonly in the middle and upper-third of the oesophagus, where surgery is more challenging, particularly for disease above the carina. In addition, these patients may be unfit for surgery due to cardiorespiratory disease as a result of common aetiological factors including cigarette smoking and alcohol. Local disease response may be greater for squamous cell cancers following CRT,⁴ although patients are more likely to suffer secondary malignancies of the upper aerodigestive tract.

There is less data for the use of primary CRT in adenocarcinomas, which predominantly affect the lower third of the oesophagus and gastro-oesophageal junction, more commonly in young, otherwise fit, male Caucasians. Encompassing regional lymph node stations with radiotherapy is certainly technically more challenging in the upper abdomen as opposed to the mediastinum. Despite this, there is insufficient evidence to say that CRT is inferior to surgery in adenocarcinoma oesophagus or that surgery is inferior to CRT in patients with squamous cell carcinoma.

Summary

Patients with operable oesophageal cancer should receive a balanced discussion of the complex issues outlined above, from both the surgical and oncological teams. Patients often develop an unshakeable confidence in the treatment described during their first clinical consultation and specialist upper gastrointestinal nurses are key to maintaining equipoise in the giving of clinical information. Individual patient preferences, based on personality and previous experience, are paramount in making treatment choices.

Where possible, patients should be entered into clinical trials such as the CRUK SCOPE 1 trial of definitive chemoradiotherapy with or without cetuximab and the MRC OE05 trial of chemotherapy before surgery in adenocarcinoma of the oesophagus; the availability of such trials may influence treatment recommendations. A feasibility study is due to open soon to establish whether a full multicentre randomised controlled trial comparing definitive CRT with treatment including surgery is possible in the UK. The study will establish methods for best communicating the treatment options to patients eligible for either treatment approach (Blazeby, personal communication).

Outside of clinical trials, we would currently recommend the following approach: For a patient with an operable squamous cell carcinoma, we would recommend primary CRT, offering primary organ preservation in parallel with squamous cancers of other sites including the head and neck, anus and cervix, with surgery for selected patients who have residual or relapsed disease. For a similar patient with an adenocarcinoma, we would recommend pre-operative chemotherapy followed by an oesophagectomy ... but then again we are biased!

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A surgeon's view

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The incidence of oesophageal cancer is increasing rapidly in the UK, and recent decades have seen a change in the pattern of the disease, with a marked increase in the incidence of adenocarcinoma of the lower third of the oesophagus and a concentration of tumours at the oesophagogastric junction.¹ The majority present with locally advanced disease. We will limit our discussion to the most frequently encountered clinical scenario – the patient with a T3 adenocarcinoma of the lower oesophagus or gastro-oesophageal junction.

The only treatment modality consistently shown to provide a realistic chance of cure is resection. Despite this, there is no doubt that resection alone may fail due to its inability to treat adequately what is usually already a systemic disease. O'Sullivan *et al.*² reported that 88% (44 out of 50) of patients undergoing surgery for potentially curable disease had bone marrow micrometastases at the time of resection and these cells were viable and tumourigenic in mice. This is entirely consistent with long-term outcomes

after oesophagectomy, with 5-year survival still languishing below 30%.³ We believe that treatment aimed at cure requires a multimodal strategy in order to provide the best possibility of long-term success. This necessitates a balancing of the risks of treatment against the realistic prospect of cure, taking into account factors such as patient age, comorbidity and location and stage of the tumour.

Whilst there remains no convincing evidence to support the use of adjuvant chemotherapy after oesophagectomy, there is now clear evidence to support the use of neo-adjuvant chemotherapy prior to resection. The MRC OEO2 trial randomised 802 patients to receive either surgery alone or surgery after two cycles of cisplatin and 5-fluorouracil (5-FU), and demonstrated a 9% survival benefit after 2 years for those patients who received chemotherapy – 2-year survival rates were 34% and 43%, respectively.⁴ In addition, patients who received chemotherapy were more likely to achieve R0 resection (complete microscopic tumour removal) and less likely to have lymph-node positive disease than patients who underwent surgery alone (60% vs 54%, $P < 0.0001$; and 58% vs 68%, $P = 0.009$, respectively). Concerns about the possibility of higher postoperative morbidity and mortality after chemotherapy were largely unfounded with comparable complication and mortality rates in both groups. Long-term results of the MRC OEO2 trial have recently been reported and confirm the survival benefit of neo-adjuvant chemotherapy with 5-year survival rates of 17% for surgery alone and 23% for surgery after chemotherapy. Experience with neo-adjuvant cisplatin and 5-FU in our own centre has confirmed that chemotherapy is generally well tolerated, with 94% of patients completing two cycles, and has a beneficial effect on resection margins, with 79% of patients achieving R0 resection, and 2-year survival of 58%.⁵

It must be appreciated, however, that the results of the MRC OEO2 trial are at odds with the earlier Intergroup trial from the US.⁶ This trial randomised 467 patients to receive either surgery alone or surgery after three cycles of cisplatin and 5-FU (followed by a possible two cycles postoperatively) and failed to demonstrate a survival benefit for neo-adjuvant chemotherapy, although it did show a higher R0 resection rate in patients who received chemotherapy. It has been suggested that the difference in the findings of these two trials may be accounted for by the more extensive chemotherapy regimen in the Intergroup trial – with any potential benefit from the larger chemotherapy dose being offset by an increased risk of toxicity (only 83% received at least two pre-operative cycles and only 52% received any postoperative chemotherapy) – and in the longer time taken to reach surgery (median 93 days compared with 63 days).

Unfortunately, the likelihood of significant tumour regression following neo-adjuvant chemotherapy remains disappointingly small – complete pathological response

(whereby viable tumour cells are completely replaced by fibrosis) is a favourable prognostic indicator but is rarely seen in practice. For this reason, some centres have focused on the use of chemoradiotherapy prior to surgery – there appears to be a synergistic effect when these two modalities are administered concurrently with some trials reporting complete pathological response rates of up to 30%. One randomised controlled trial demonstrated a significantly reduced 3-year mortality rate after neo-adjuvant chemoradiation followed by surgery compared with surgery alone;⁷ several other trials, however, have failed to demonstrate such a benefit.⁸ There are concerns about increased postoperative morbidity and mortality associated with chemoradiation and it is predominantly for this reason that the use of neo-adjuvant chemoradiation has not found wide-spread favour in the UK.

The historically high mortality rates, and poor long-term survival associated with oesophagectomy as the traditional single modality treatment, have led some to advocate a policy of less radical surgery in favour of lower mortality rates. In recent years, however, the lower postoperative mortality rates have justified adopting a more radical approach towards resection. We believe that the primary aim of surgical resection should be to achieve complete macroscopic and microscopic removal of all tumour (R0 resection) as this has been shown to be an independent predictor of long-term survival.⁹ To achieve this, we take a radical approach to the primary tumour, removing all peri-oesophageal tissue as well as pleura and diaphragm if necessary. As a result, we invariably perform a radical lymphadenectomy; we believe that this extensive lymph node dissection is important in allowing adequate staging of lymph node positive disease, another known independent prognostic indicator for survival,⁹ and, whilst we concede that extensive lymphadenectomy has not been shown unequivocally to improve survival,¹⁰ it may improve long-term locoregional disease control.¹¹ It is important to appreciate that the R status (unlike the N status) is the only independent prognostic factor over which the surgeon has any control!

Furthermore, there is now growing evidence that outcomes are significantly better in specialist centres. Birkmeyer *et al.*¹² showed a difference in mortality rate of almost 12% between ‘very high volume’ (20 or more resections per annum) and ‘very low volume’ centres (less than 2 resections per annum), although most UK surgeons would consider a ‘very high volume’ unit to carry out in excess of 50 resections per annum. Many such centres report mortality rates of 5% or less. Improvements in intensive care have effectively nullified the concept of 30-day mortality after oesophageal surgery and we believe that all units should now report in-hospital mortality along with 1-year survival, which may ultimately be a more meaningful marker of suitability and outcome.³

Summary

We would advocate that the management of a patient with an operable T3 carcinoma of the oesophagus should consist of multimodal therapy with neo-adjuvant chemotherapy followed by radical surgery aimed at achieving an R0 resection. In the future, it is likely that neo-adjuvant regimens will improve significantly: the MRC OEO5 trial, comparing OEO2 style chemotherapy with four cycles of epirubicin, cisplatin, and capecitabine, is currently recruiting and there is considerable research aimed at identifying potential markers of response to chemotherapy before treatment in order to allow individual tailored chemotherapy aimed at those likely to derive most benefit.

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