THEME

GI malignancies

Management of oesophageal carcinoma

Sean Mackay

MD, FRACS, is an upper GIT and hepatobiliary surgeon, Peter MacCallum Cancer Institute, St Vincent's and Box Hill Hospitals, Victoria, and in private practice, Fitzroy, Victoria. smackay@gisurgical.com

Greg Stefanou

MBBS, FRACP, FACh, PM, is a medical oncologist, clinical haematologist, and palliative care physician, John Fawkner and Bethlehem Hospitals, and Peter MacCallum Cancer Institute, Melbourne, Victoria.

BACKGROUND

Treatments for oesophageal cancers have historically been surgical, and surgical treatment remains the mainstay of treatment for localised oesophageal carcinoma (stage I–III). For stage IV disease, systemic chemotherapy is the mainstay of treatment.

OBJECTIVE

This article provides an overview of curative and palliative management options for oesophageal carcinoma. Surgery, endoscopic treatments, and chemotherapy, radiotherapy and combined modality chemoradiation are considered.

DISCUSSION

Several surgical approaches are available and each has its positive and negative aspects. Recent advances in chemotherapy and radiotherapy have aided the surgeon's work either by down staging tumours and rendering inoperable cases amenable to surgery. These adjuvant treatments also benefit the patient by reducing the risk of mediastinal and distant metastases.

There is a range of therapies available for the management of oesophageal carcinoma. This article attempts to familiarise the reader with these therapies, and by placing each in its context, provide an understanding of why a given patient is recommended to follow a certain treatment course. Potentially curative treatments are dealt with first and subsequently, palliative treatments are described.

Curative treatments

Historically, the basis of treatment for localised oesophageal carcinoma (stage I–III) has been, and remains, surgical resection.[1–3] However, the results for stage III disease in particular, are relatively poor and there has been significant interest in the possibility of using chemotherapy, radiotherapy, or the combination as adjuvant therapy. When modern results for these oncological therapies have been analysed, there has been some interest in the potential of chemo-radiation as a curative therapy.

Surgical treatments

There is a range of surgical approaches for resection of the oesophageal tumour. Choice depends on a number of factors including the site of the tumour, general health of the patient, and the experience and preference of the surgical team.

Abdominal approach

The incidence of cancers at the oesophago-gastric junction (OGJ) is increasing, although the reasons for this are presently not known. The standard operation for a proximal gastric cancer is a radical total gastrectomy, although the proximal gastrectomy does have its proponents.[4,5] If the lesion encroaches onto the oesophagus, then the issue arises of getting an adequate oesophageal margin. The higher the point of division, the more technically difficult the anastomosis.

Left thoracoabdominal

This approach typically involves a right subcostal incision

that extends parallel to the costal margin and then across the left costal margin and into the left chest.[4,5] Access to the lower oesophagus is excellent and hence it is particularly suited to tumours at the OGJ, but once the oesophagus passes behind the arch of the aorta, access is very difficult. Therefore, the surgeon must be confident that the resection may be confined to the distal oesophagus. A pyloroplasty and a feeding jejunostomy are easily performed in this procedure. A disadvantage of this approach is that the cartilage of the costal margin heals poorly and the patient is often left with pain and 'clicking' with even moderate exertion.

Left thoracic (Sweet)

This approach also offers good access to the lower oesophagus.[5] However, it is not possible to perform a pyloroplasty or a feeding jejunostomy which are definite disadvantages. As before, access to the more proximal oesophagus is limited. This approach is often advocated in the more frail patient, with the aim of using one rather than two incisions (ie. abdominal and right chest).

Abdominal and right chest (Ivor Lewis)

This is the standard approach for most oesophago-gastric surgeons.[4,5] It is suitable for lesions of the mid and distal oesophagus. The first phase of surgery is the laparotomy, at which the stomach and duodenum are mobilised and a pyloroplasty and (often) a feeding jejunostomy performed. The abdominal wound is then closed and the patient repositioned for a posterolateral thoracotomy. The thoracic oesophagus is then mobilised and the stomach/gastric tube delivered into the chest. The specimen is resected and the anastomosis performed.

Subtotal (three stage, McKeown)

This is essentially the same approach as the abdominal/right chest except the right chest is closed after the entire thoracic oesophagus has been mobilised. The patient is then repositioned supine whereupon the neck is opened (usually the right side) and the specimen delivered through the neck for resection and anastomosis.[4,6] Advantages of this approach are a slightly larger extent of resection, and the fact that the anastomosis is in the neck rather than the chest. The disadvantage is the increased operating time, the incidence of postoperative swallowing difficulties, and the need to heal three incisions.

Trans-hiatal oesophagectomy (Orringer)

This technique was developed to avoid the need for a thoracotomy, especially in patients with marginal respiratory status. It involves synchronous surgery from the abdomen and the neck, with the oesophageal hiatus being widely opened from the abdomen and the superior mediastinum being approached through the neck.[7] A formal nodal dissection is not possible. Even in the routine case, blood loss is heavier, and there is obviously the risk of catastrophic bleeding from the mediastinum. While the procedure does have its proponents, many oesophago-gastric surgeons would argue that radiation or chemo-radiation is most appropriate for otherwise curable patients who will not withstand a thoracotomy.

Adjuvant and neo-adjuvant therapy

With advances in chemotherapeutic and radiation treatments, practitioners have intuitively looked toward these additional therapeutic options as a way to improve upon the disappointing long term outcomes obtained with surgery alone for later stage disease.[8]

Clinical trials have been conducted, assessing chemotherapy and radiation as definitive, adjuvant, and neo-adjuvant therapy – both in isolation and as combined modality approach (chemo-radiation). Given the apparently systemic nature of both adenocarcinoma and squamous carcinoma of the oesophagus (beyond the earliest stage disease), the addition of chemotherapy has been seen as a means to address micrometastases early in the course of the disease and thus minimise the risk of distant relapse. At the same time, radiation has been postulated as a method of minimising local recurrence in the mediastinum; a difficult area within which to perform a wide lymphadenectomy.

Both treatment modalities have the potential to pre-operatively downstage tumours and render inoperable cases amenable to surgery. Chemo-radiation combines the potential benefits of treating micrometastases with improved control of local disease, and also offers the possibility of downstaging inoperable tumours. The two modalities further complement each other in that most chemotherapeutic agents utilised against oesophageal carcinoma potentiate radiation, acting as radio-sensitisers (eg. cisplatin). It is important to note that these potential advantages come at the cost of significant risk of toxicity in a population that has high rates of comorbid disease, and who are already destined for (or having already undergone) major surgery.

Clinical trials have been variable and disparate in their design, dosages, and accrual numbers. They have not consistently discriminated between adenocarcinoma and squamous cell carcinoma. Results and interpretations have at times, conflicted. Therefore, the available data, although plentiful,

are difficult to interpret.

In essence it is true to say that both adjuvant and neo-adjuvant therapies for oesophageal carcinoma remain unproven and controversial.[6,9] The following is a synopsis and interpretation of key data for each approach.

Radiation as primary therapy

Sufficient, adequately powered randomised trials comparing radiation to surgery have not been conducted. Nonrandomised trials were subject to selection bias with poor surgical candidates and patients with high risk of recurrence or nonresectable disease being referred for inclusion. Overall, the outcome of radiation alone has been worse than that of surgery alone.[10]

Radiation as adjuvant therapy

Randomised trials, as well as meta-analyses, have suggested that neither pre- nor post-operative irradiation improve survival or resectability. The role of this approach is generally limited to palliation in recurrent/advanced disease, typically in debilitated patients who cannot tolerate the addition of chemotherapy.

Pre- and/or post-operative chemotherapy

Overall, trials of pre- and/or post-operative chemotherapy have not demonstrated a benefit in terms of resectability or survival.[3,11–13]

Combined chemo-radiation

Chemo-radiation has been demonstrated to be superior to radiation alone as definitive therapy.[14] In one study conducted by the Radiation Therapy Oncology Group making this comparison, patients receiving chemo-radiation had better median and 5 year survival (27 vs. 0%, $p<.0001$). Local failure was also reduced (46 vs. 65%). The differences were such that the trial was terminated early. There was a significantly higher incidence in grade 3 and 4 toxicity in the chemo-irradiation arm (64 vs. 28%). The toxic death rate was 2% (vs. 0%) in the chemo-radiation arm.

Although adequate direct comparisons between chemo-irradiation and surgery as definitive therapies have not been made, the results of chemo-irradiation alone are such that it cannot be embraced as a definitive therapy in patients with resectable disease, except in the case of a patient who is medically unfit for surgery. Nonetheless, it is the best option for those patients unable to undergo surgery. A case in point is the patient with a postcricoid tumour (often squamous cell tumours, which are seen as more sensitive).

Pre-operative chemo-radiation

There have been at least four randomised trials comparing pre-operative chemo-irradiation to surgery alone.[15–18] Walsh et al[15] demonstrated a significantly improved survival for the pre-operative treatment arm (32 vs. 6% at 3 years, $p=0.01$). This trial however, has weaknesses, including inadequate pretreatment staging. Also highly significant are the unacceptable results in the surgical arm (both in terms of complications, mortality, and overall survival).

Urba et al[16] demonstrated a significantly decreased local recurrence rate in the pre-operative chemotherapy arm (19 vs. 42%). The survival advantage did not reach statistical significance.

In a randomised trial of 256 patients conducted by Burmeister et al,[17] no survival advantage was demonstrated for the pre-operative chemo-irradiation arm. Subgroup analysis did demonstrate increased disease free (but not overall) survival in squamous cell carcinoma.

Despite this lack of strong evidence, chemo-irradiation has been adopted as standard therapy in patients with T3 tumours and/or local nodal disease. This is done on the basis that local recurrence may be reduced, that micrometastases may be treated, or that the tumour may be downstaged (hence facilitating surgery).[3] It is problematic that not all patients' tumours respond to chemo-irradiation and hence, in the nonresponding subgroup, persisting with treatment may cause unnecessary delay in surgery with the potential for disease progression. Treatment related toxicity may also conspire against the patient. A tumour marker or predictive test for likelihood of response would be of utility in this circumstance, but remains a challenge. To date, early positron emission tomography (PET) scanning for signs of response remains the most practical approach.[9,19]

Brachytherapy

In brachytherapy – or internal radiotherapy – the radioactive material is placed in an implant in or near the tumour. It has a short effective treatment distance. It is used as a 'boost' to external beam irradiation. It is also effective in palliating symptoms such as dysphagia or bleeding due to a local lesion.[20,21]

Palliative treatment

Chemotherapy and radiotherapy

Systemic therapy

For symptomatic or imminently symptomatic stage IV disease, systemic chemotherapy remains the mainstay of treatment.[3,9,22] The aim of such therapy is to improve

quality of life by relieving symptoms, and to provide a survival advantage. These benefits must be offset against the potential for toxicity with current regimens.

Nonetheless, studies have shown varying tumour response rates up to 50%. Survival advantage has yet to be consistently demonstrated. More recently, quality of life (QOL) questionnaires have been incorporated into studies and shown QOL improvement in chemotherapy responders.

It is beyond the scope of this article to detail specific chemotherapy regimens. It is worth noting however, that 5-fluorouracil and cisplatin have until recently been the basis of most chemotherapy treatments. Cisplatin in particular, has high potential for toxicity, and specifically, is highly emetogenic.[22] Newer agents such as paclitaxel, docetaxel, and irinotecan have shown higher levels of activity against oesophageal cancer with better tolerability.[3,9,23]

Clearly, appropriate patient selection for palliative chemotherapy and utilisation of an appropriate regimen to suit each patient's requirements are paramount. Not only should treatment efficacy be considered, but also patient performance status, potential for toxicity, and the patient's aims and wishes.

Local therapy

As alluded to in previous discussion, radiation plus or minus chemotherapy can be effectively utilised to palliate symptoms such as dysphagia, bleeding, or obstruction. Isolated symptomatic sites such as bone metastases may be effectively addressed utilising radiation therapy.[8,22,23]

Palliation of dysphagia by mechanical means

If a patient is seen before the development of severe dysphagia, it is often possible to control this symptom with radiation, chemotherapy alone (less commonly), or chemo-radiation. However, if the patient presents with severe dysphagia, then a mechanical solution is necessary to overcome the obstruction.

Serial endoscopic dilatation

This is of historical interest only as the reported rates of perforation are very high at 5–10% (remembering that many of those perforations occurred in patients with very advanced lesions that were not being treated in any other way).[24]

Laser ablation

The NdYAG laser is widely used in this setting (in selected lesions). The best lesions are noncircumferential and form a ridge that projects into the oesophagus. Laser is probably preferable to a metal stent in this group.[25] The NdYAG laser delivers maximal energy 2–3 mm deep to the surface and therefore perforation is a risk, especially in stenosing lesions where the direction of the lumen is not obvious.

Barrett's oesophagus with high grade dysplasia[27]

- Dysplasia in Barrett's oesophagus is a risk factor for development of adenocarcinoma.
- It is not possible to comment safely on the presence of dysplastic changes in tissues that are severely inflamed. Patients should have aggressive acid suppressive therapy and early repeat biopsies.
- In patients who undergo oesophagectomy for high grade dysplasia, up to 43% will be found to have invasive carcinoma not identified on endoscopic surveillance biopsies.

Argon plasma coagulation

This is a form of monopolar diathermy that conducts the energy to the tissues in a superheated 'plasma' of argon.[24] Tissue damage is much more superficial than with laser, and the risk of perforation is lower Indications are similar to laser and early results seem comparable.

Self expanding metal stents

These are the mainstay of the management of malignant dysphagia. Early complication rates are low (2% mortality) and 95% of patients have significant improvement in their dysphagia. Stent migration occurs in only 5% and obstructive episodes requiring intervention in 3% of patients.[26] The great advantage over the older plastic stents are the smaller delivery systems which make them safer to deploy, and the greater internal diameter once fully expanded.

Conclusion

Surgical treatment remains the mainstay of treatment for localised oesophageal carcinoma (stage I–III). However, the results for stage III disease, in particular, are relatively poor. Chemotherapy and radiotherapy may play an important role in downstaging tumours, rendering inoperable cases amenable to surgery, and by reducing the risk of mediastinal and distant metastases. For stage IV disease, systemic chemotherapy is the mainstay of treatment. An understanding of the available options will assist the general practitioner in the important role of supporting patients through all stages of decision making in the progression of their disease.

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References

1. Lerut T, De Leyn P, Coosemans W, Van Raemdonck D, Scheys I, LeSaffre E. Surgical strategies in esophageal carcinoma with emphasis on radical lymphadenectomy. Ann Surg 1992;216:583–90.
2. Altorki NK. The rationale for radical resection. Surg Oncol Clin N Am 1999;8:295–305.
3. Enzinger PC, Mayer RJ. Esophageal cancer. N Engl J Med 2003;349:2241–52.
4. Chassin J. Operative strategy in general surgery. 2nd ed. New York: Springer Verlag, 1994.
5. Griffin S. Surgery for cancer of the oesophagus. In: SM Griffin Sr, editor. Upper gastrointestinal surgery. 2nd ed. Edinburgh: W B Saunders, 2001.
6. McKeown KC. The surgical treatment of carcinoma of the oesophagus. A review of the results in 478 cases. J R Coll Surg Edinb 1985;30:1–14.
7. Orringer MB. Transhiatal esophagectomy without thoracotomy for carcinoma of the thoracic esophagus. Ann Surg 1984;200:282–8.
8. Orringer MB, Forastiere AA, Perez-Tamayo C, Urba S, Takasugi BJ, Bromberg J. Chemotherapy and radiation therapy before transhiatal esophagectomy for esophageal carcinoma. Ann Thorac Surg 1990;49:348–54; discussion 354–5.
9. Ilson DH. Oesophageal cancer: new developments in systemic therapy. Cancer Treat Rev 2003;29:525–32.
10. Sun DR. Ten year follow up of esophageal cancer treated by radical radiation therapy: analysis of 869 patients. Int J Radiat Oncol Biol Phys 1989;16:329–34.
11. Nygaard K, Hagen S, Hansen HS, et al. Pre-operative radiotherapy prolongs survival in operable esophageal carcinoma: a randomised, multicenter study of pre-operative radiotherapy and chemotherapy. The second Scandinavian trial in esophageal cancer. World J Surg 1992;16:1104–9; discussion 1110.
12. Kelsen D. Preoperative chemoradiotherapy for esophageal cancer. J Clin Oncol 2001;19:283–5.
13. Kelsen DP, Ginsberg R, Pajak TF, et al. Chemotherapy followed by surgery compared with surgery alone for localised esophageal cancer. N Engl J Med 1998;339:1979–84.
14. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long term follow up of a prospective randomised trial (RTOG 85–01). Radiation Therapy Oncology Group. JAMA 1999;281:1623–7.
15. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 1996;335:462–7.
16. Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M. Randomised trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol 2001;19:305–13.
17. Burmeister BH, Smithers BM, Gebski V, et al. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. Lancet Oncol 2005;6:659–68.
18. Bosset JF, Gignoux M, Triboulet JP, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous cell cancer of the esophagus. N Engl J Med 1997;337:161–7.
19. Downey RJ, Akhurst T, Ilson D, et al. Whole body 18FDG–PET and the response of esophageal cancer to induction therapy: results of a prospective trial. J Clin Oncol 2003;21:428–32.
20. Jager J, Langendijk H, Pannebakker M, Rijken J, de Jong J. A single session of intraluminal brachytherapy in palliation of oesophageal cancer. Radiother Oncol 1995;37:237–40.
21. Calais G, Dorval E, Louisot P, et al. Radiotherapy with high dose rate brachytherapy boost and concomitant chemotherapy for stages IIB and III esophageal carcinoma: results of a pilot study. Int J Radiat Oncol Biol Phys 1997;38:769–75.
22. Leonard GD, Zhuang SH, Grem JL. Epirubicin, cisplatin, and protracted venous-infusion fluorouracil in advanced esophagogastric cancer. J Clin Oncol 2002;20:4124–5; author reply 4125–6.
23. Richel DJ, Vervenne WL. Systemic treatment of oesophageal cancer. Eur J Gastroenterol Hepatol 2004;16:249–54.
24. Blazeby DA. Palliative treatments of carcinoma of the stomach and oesophagus. In: SM Griffin Sr, editor. Upper gastrointestinal surgery. 2nd ed. Edinburgh: W B Saunders, 2001.
25. Adam A, Ellul J, Watkinson AF, et al. Palliation of inoperable esophageal carcinoma: a prospective randomised trial of laser therapy and stent placement. Radiology 1997;202:344–8.
26. O'Sullivan GJ, Grundy A. Palliation of malignant dysphagia with expanding metallic stents. J Vasc Interv Radiol 1999;10:346–51.
27. Thomson BN, Cade RJ. Oesophagectomy for early adenocarcinoma and dysplasia arising in Barrett's oesophagus. A N Z J Surg 2003;73:121–4.

afp **CORRESPONDENCE** email: afp@racgp.org.au