



# Management of gastric cancer

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### BACKGROUND

Gastric cancer is a common disease with a high mortality.

### OBJECTIVE

This article aims to outline the management options for patients with gastric cancer.

### DISCUSSION

The mainstay of curative treatment remains surgical resection. The management of early stage gastric cancer is complex with proven benefit of both pre-operative chemotherapy and postoperative chemo-radiotherapy, as well as complex surgical issues and the patient benefits from management by a multidisciplinary team. The most commonly performed operations for gastric cancer are total and subtotal gastrectomy, depending on the location of the tumour and the ability to gain adequate tumour free margins. Common postoperative difficulties include early satiety, postprandial pain and diarrhoea, hypoglycaemic episodes and bile reflux. Adjuvant chemotherapy and radiotherapy has been demonstrated to have a beneficial role in survival. Palliative surgical options are directed at control of symptoms related to bleeding and obstruction. Palliative chemotherapy has been shown to confer a survival benefit, however, with notable toxicity.

**Gastric cancer is a significant cause of morbidity and mortality worldwide. It remains the second most frequently diagnosed cancer in the world accounting for 9.9% of all new cancer diagnoses and 12.1% of all cancer deaths. More than half of cases occur in China and Japan, whereas much lower rates exist in western countries.<sup>1</sup> In Australia, gastric cancer is the tenth most commonly diagnosed cancer accounting for 1902 per 100 000 population in 2001 (2.2% of all new cancer cases). There were 1209 deaths from gastric cancer per 100 000 population (3.3% of all cancer deaths) highlighting this disease's poor prognosis.<sup>2</sup> Geographical differences are not fully understood, but may relate to dietary risk factors (diets high in salted, smoked foods and low in fruit and vegetables). Other risk factors include increasing age, male gender, *Helicobacter pylori* infection, smoking, pernicious anaemia, chronic atrophic gastritis, and family history.<sup>3</sup>**

## Treatment of early stage gastric cancer

Surgical resection remains the primary curative treatment for gastric cancer. Despite this, the overall 5 year survival rate remains poor, ranging between 15–35%.<sup>1</sup> Of patients that relapse after curative surgery, 87% have locoregional recurrence.<sup>4</sup> These figures have prompted many studies addressing surgical issues as well as exploring the role of adjuvant and neo-adjuvant treatment.

The management of early stage gastric cancer is complex, with proven benefit of both pre-operative chemotherapy and postoperative chemo-radiotherapy as well as complex surgical issues. Therefore all patients with a diagnosis of resectable early stage gastric cancer should be referred to an institution with access to a dedicated multidisciplinary team to help guide the patient through what will be a complex management plan.

## Surgical issues

### Extent of resection

A resection margin of at least 5 cm is considered necessary for gastric carcinoma, regardless of the histological subtype. The extent of the resection is determined not only by the adequacy of the resection margin, but also by tumour location, the amount of remaining tissue and the planned method of reconstruction.

### Total gastrectomy

This is the standard surgical treatment for carcinoma of the proximal two-thirds of the stomach. It is also used for some extensive distal cancers, and cancers with associated widespread premalignant field change. The proximal resection margin may be at the oesophago-gastric junction, or in the distal oesophagus depending upon the exact site of the tumour. The distal margin is in the first part of the duodenum, just distal to the pylorus. Although not universal practice in Australia, splenectomy is indicated in lesions of the gastric fundus. Distal pancreatectomy is rarely performed in Australia and generally carries a greater morbidity and mortality. The reconstruction involves anastomosis of a roux-en-Y limb of jejunum to the oesophagus to reduce bile refluxing up the oesophagus.

### Distal gastrectomy

A distal gastrectomy is a reasonable option for an antral or pyloric carcinoma. This operation has two advantages over a total gastrectomy: first, the anastomosis is between stomach and jejunum rather than oesophagus and jejunum, which facilitates better healing (and is usually a technically easier anastomosis); and second, there is still some stomach to act as a reservoir, allowing the patient to eat larger meals.

### Proximal gastrectomy

This procedure has a poor reputation. Although it is possible to obtain an adequate margin for appropriate lesions, the anastomosis of the distal gastric remnant (with pyloromyotomy to open the pylorus after the necessary vagotomy) results in constant alkaline reflux. This complication can occur in an oesophago-gastric resection (eg. Ivor Lewis) but seems to be less common, probably because the anastomosis is much higher.

### Lymphadenectomy and the Japanese approach

Gastric cancer is common in Japan, and various Japanese centres have developed considerable experience in its management. In general, Japanese surgeons tend to favour extensive nodal dissections, with the aim of dealing more thoroughly with the regional as well as local disease.

When adopted in the western setting, the results have generally been disappointing. Two large multicentre, prospective randomised trials comparing limited (D1) with extended (D2) lymphadenectomy demonstrated an overall greater morbidity, mortality, and hospital stay with D2 resection, without improvement in survival. However, the contribution of the 'learning curve' must be considered, as the procedure is not routinely undertaken outside Japan. Further prospective studies and subgroup analyses have shown that pancreas and spleen preserving extended lymphadenectomy, when carried out in specialised centres familiar with the technique, can be achieved with improved long term survival with morbidity and mortality equivalent to a limited lymphadenectomy.<sup>5-7</sup>

### Novel approaches

There is much interest in new endoscopic techniques such as endoscopic mucosal resection. This technique involves local mucosal/submucosal resection via the gastroscope. These techniques will definitely find a role in treating dysplasia (more relevant in the oesophagus with Barrett's mucosa) and perhaps carcinoma in situ, but any role in invasive cancer would currently be considered extremely contentious.

### Postoperative issues

Early satiety is the inevitable result of the reduction/removal of the gastric reservoir. Most patients will find it necessary to have 5-6 small meals per day in order to maintain adequate nutrition. Early dumping presents as postprandial pain and diarrhoea secondary to a hypertonic load being 'dumped' into the jejunum. This results in rapid fluid shifts into the small bowel. It occurs more commonly after subtotal than total gastrectomy. This often improves in the first few weeks with simple dietary modification. Late dumping is a result of reactive hypoglycaemia, with patients complaining of typical hypoglycaemic symptoms. This can be managed by reducing the carbohydrate load in meals, with small amounts of carbohydrate between meals.

Diarrhoea may be secondary to early dumping, or steatorrhoea resulting from bacterial overgrowth in the blind limb of the roux-en-Y reconstruction, loss of gastric acid and poor mixing with duodenal juices.

Bile reflux presents as epigastric pain, heartburn, and/or regurgitation. The roux-en-Y reconstruction is aimed at reducing this problem, however in severe cases, may require a bile diverting reconstruction or revision of the roux limb length.

Nutritional deficiencies include B12 (loss of intrinsic factor made in gastric antrum), iron (often corrects in first 12 months due to jejunal adaptation), and calcium (secondary to vitamin

D malabsorption, a consequence of fat malabsorption). Regular B12 monitoring and 3 monthly intramuscular B12 replacement is required lifelong. Consideration should also be given to oral calcium supplements and monitoring for metabolic bone disease.

### Chemotherapy and radiotherapy

Over the past 2 decades studies have addressed adjuvant and neo-adjuvant treatment options in an attempt to improve survival for early stage gastric cancer, with disappointing results. These include the use of pre- and post-operative radiotherapy<sup>8-10</sup> with the concept of reducing locoregional relapse with little impact on survival. However, two recent studies have changed the landscape of treatment for early stage gastric cancer and have led to a new standard of care.

#### Postoperative chemo-radiotherapy

In 2001 the Southwest Oncology Group/Intergroup 0116 trial was published which prospectively randomised 556 patients between surgery alone and surgery followed by postoperative chemo-radiotherapy.<sup>11</sup> While there was significant acute toxicity with the chemo-radiotherapy arm, median overall survival was improved in figures not previously reported (27 months for surgery alone vs. 36 months for adjuvant therapy  $p < 0.001$ ). Adjuvant therapy is now the standard of care in many centres.

However, this study has been critically debated on many issues. The quality of surgical dissection may be a factor in the overall results. Fifty-four percent of patients only underwent a D0 lymph node dissection which may in itself confer a survival disadvantage. A subgroup analysis revealed a survival benefit of adjuvant therapy only in those undergoing D0 and D1 resections with little impact on those with a D2 resection (only 10% of patients). Therefore adjuvant chemo-radiotherapy may be simply compensatory for patients undergoing less extensive surgery.

#### Pre- and post-operative chemotherapy

A second study, while still in progress, has shown a significant survival benefit for adjuvant treatment in early stage gastric cancer.<sup>12</sup> This study randomised 503 patients with resectable gastric and lower oesophageal tumours to surgery alone or three pre-operative cycles of epirubicin, cisplatin and fluorouracil (ECF) and three postoperative cycles of ECF chemotherapy. Of note there is no radiotherapy component as apposed to previous adjuvant studies. With now longer than 3 year follow up, it has demonstrated a significant 5 year survival benefit of chemotherapy compared to surgery alone (36 vs. 23%  $p = 0.009$ ).

However, a large number of patients were unable to complete the intended course of treatment.

### Palliative treatment

#### Local symptoms

Many patients present with medically or surgically unresectable disease as well as metastatic disease and require palliative management. Local symptoms attributable to the primary lesion include obstruction, bleeding, nausea, and pain from local tumour invasion. In general, palliative resection is not indicated, although surgery may be necessary in the palliative setting for a range of indications (eg. obstruction or bleeding).

#### Management of bleeding complications

In a case of uncontrolled bleeding with severe haemodynamic compromise, the choice of interventions is surgery or endovascular intervention such as angiography and selective arterial embolisation. The exact approach must be tailored to the individual setting, but, in general, resection is preferred to oversewing/under-running a bleeding point (as these techniques essentially rely upon the healing of malignant tissue, which is grossly impaired).

In the less urgent setting, such as where the patient is losing 1–2 units of blood a week without suffering cardiovascular instability, most will respond to a short course of external beam radiotherapy. Regimens vary, but may comprise anything from 5 Gray in a single dose (uncommonly used), through to 10 Gray in five fractions over 5 days (probably the most common). This treatment will usually promptly control blood loss and therefore avoids the potential for surgery.

#### Gastric outlet obstruction

In patients with locally advanced incurable disease presenting with acute or impending obstruction, a palliative bypass in the form of a gastroenterostomy or palliative distal gastrectomy may be undertaken. These procedures carry their associated operative morbidity and mortality. In one study of 75 patients, operative mortality was 25% for gastrojejunostomy and 20% for palliative subtotal gastrectomy. Endoluminal stenting may be an appropriate less invasive approach in selected patients, however this technique is uncommonly used, not available in all centres, and there have been no large series to date to assess its effectiveness.<sup>13,14</sup>

Terminal care in these patients is made difficult by dysphagia and poor oral absorption of medication. Early consideration to parenteral analgesics and antiemetics should be undertaken (eg. subcutaneous infusion methods). Topical analgesia with fentanyl may be more successful than oral

methods. In experienced hands, coeliac nerve blocks may be useful for intractable pain from tumour neural invasion. The complex issues of nutrition in this group of patients is often raised by families and is beyond the scope of this article.

### Systemic disease

Fitter patients with metastatic disease may be considered for palliative chemotherapy. Studies have explored survival advantages of various palliative chemotherapy regimens compared with best supportive care. These studies contain only a small number of patients (20–50 per arm) but consistently demonstrated a significant survival benefit at 1 year of 35–40% versus 10% randomised to best supportive care.<sup>15</sup> Palliative chemotherapy not only carries a survival advantage but can effectively palliate symptoms such as fatigue, appetite, pain, and nausea in those that respond.

Many combination chemotherapy regimens have been explored over the past few decades.<sup>16</sup> The most common are: FAM (fluorouracil, adriamycin and mitomycin), etoposide, leucovorin and fluorouracil (ELF), and ECF. Generally the response rate of these agents is 20–40%.

Epirubicin, cisplatin and fluorouracil has been found to be superior to FAM<sup>17</sup> and is the standard of care in Europe and Australia. However, it is a complicated regimen requiring infusional 5FU and a central access device with its inherent complications of infections and thrombosis as well as the need for line maintenance. Cisplatin is highly emetogenic and may not be tolerated by less fit patients. The high fluid load required to deliver cisplatin as well as the cardiotoxic effects of epirubicin will limit its use to the fittest of patients.

Capecitabine (Xeloda) is an oral agent converted to 5FU by tumour cells with similar efficacy to infusional 5FU. The oral delivery makes it more convenient to patients than infusional delivery. Phase III studies comparing epirubicin, cisplatin and capecitabine (ECX) to ECF are awaited.<sup>18</sup> Single agent infusional 5FU may be an option in less fit but motivated patients but carries a lower response rate of approximately 20%.

The advent of a number of newer chemotherapy agents including taxanes (paclitaxel and docetaxel), oxaliplatin, irinotecan and targeted therapies such as monoclonal antibodies (bevacizumab, cetuximab), and tyrosine kinase inhibitors (erlotinib) are currently being explored to improve the effectiveness and limit the toxicity of palliative treatment for gastric cancer. Early stage trials involving a combination of these agents are eagerly awaited. A greater understanding of the molecular basis of malignancy may allow prediction of the behaviour of gastric cancer and better selection of patients who will benefit from treatment.

Patients should be referred to a medical oncologist for discussion to address the complex decisions of who will

benefit from palliative chemotherapy as well as when to commence therapy and what regimen to use.

### Conclusion

Many treatment options are available to patients with gastric cancer both with curative and palliative benefit. The management of early stage gastric cancer is complex and patients with a diagnosis of resectable early stage gastric cancer should be referred to an institution with access to a dedicated multidisciplinary team to help guide the patient through a complex management plan. Ongoing research will hopefully further improve the outcome for patients diagnosed with this disease that otherwise carries a poor prognosis.

Conflict of interest: none declared.

### References

1. Parkin D, Pisani P, Ferley J, et al. Global cancer statistics. *Ca Cancer J Clin* 1999;49:33–64.
2. Australian Institute of Health and Welfare. *Cancer in Australia, 2001*. Canberra: AIHW & AACR, 2004.
3. Kurtz RC, Sherlock P. The diagnosis of gastric cancer. *Semin Oncol* 1985;12:11–8.
4. Gunderson LL, Sosin H. Adenocarcinoma of the stomach: areas of failure in a re-operation series: clinicopathological correlation and implications for adjuvant therapy. *Int J Radiat Oncol Biol Phys* 1982;8:1–11.
5. Raimes SA. Surgery for cancer of the stomach. In: *A companion to specialist surgical practice: upper gastrointestinal surgery*. 2nd ed. Philadelphia: WB Saunders, 2001.
6. Dicken BJ, Bigam DL, Cass C, et al. Gastric adenocarcinoma: review and considerations for future directions. *Ann Surg* 2005;241:27–39.
7. Allum WH, Griffin SM, Watson A, et al. Guidelines for the management of oesophageal and gastric cancer. *Gut* 2002;50(Suppl V):v1–23.
8. Hallissey MT, Dunn JA, Ward LC, et al. The second British Stomach Cancer Group trial of adjuvant radiotherapy or chemotherapy in respectable gastric cancer: 5 year follow up. *Lancet* 1994;343:1309–12.
9. Bleiberg H, Goffin JC, Dalesio O, et al. Adjuvant radiotherapy and chemotherapy in respectable gastric cancer. A randomised trial of the gastrointestinal tract cancer cooperative group of the EORTC. *Eur J Surg Oncol* 1989;15:535–43.
10. Skoropad VY, Berdov BA, Zagrebina VM. Preoperative radiotherapy in combination with metronidazole for respectable gastric cancer: long term results of a phase II study. *Eur J Surg Oncol* 2002;29:166–70.
11. Macdonald JS, Smalley SR, Bendetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001;345:725–30.
12. Cunningham D, Allum WH, Stenning SP, Weedon S. Perioperative chemotherapy in operable gastric and low oesophageal cancer: final results of a randomised controlled trial (the MAGIC trial, ISRCTN 93793971). *J Clin Oncol* 2005;23(Suppl June).
13. Blazeby JM, Alderson D. Palliative treatments of carcinoma of the oesophagus and stomach. In: *A companion to specialist surgical practice: upper gastrointestinal surgery*. 2nd ed. Philadelphia: WB Saunders, 2001.
14. Parikh AA, Mansfield PF. Gastric adenocarcinoma. In: *Current surgical therapy*. 8th ed. Elsevier Mosby, 2004.
15. Wils J. The treatment of advanced gastric cancer. *Semin Oncol* 1996;23:397–406.
16. DeVita VT. *Cancer principles and practice of oncology*. 6th ed. Lipincott Williams and Wilkins, 2001.
17. Webb A, Cunningham D, Scaffe J, et al. Randomised trial comparing epirubicin, cisplatin and fluorouracil versus fluorouracil, doxorubicin and methotrexate in advanced oesophageal cancer. *J Clin Oncol* 1997;15:261–7.
18. Cho EK, Lee WK, Im SA, et al. Epirubicin, cisplatin and capecitabine in first line chemotherapy for patients with advanced gastric cancer. *J Clin Oncol* 2004;22(July 15 Suppl)14S.