JNDS Journal of the Nuffield Department of Surgical Sciences

Case Study

Management of Resectable Gastric Cancer

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Keywords:
Gastric cancer, total gastrectomy with lower esophagectomy, D2 lymphadenectomy, perioperative FLOT chemotherapy.

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Key Learning Points
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Gastric cancer remains a poor prognosis disease. Endoscopic, histological, cross-sectional imaging and laparoscopy are all typically used to stage cancers as accurately as possible, which is critical for prognosis and treatment planning. Once staged, several clinical trials have shown that perioperative chemotherapy regimens associate with the best survival outcomes for gastric cancer, though disease recurrence remains a significant risk for advanced stage disease. Emerging immunochemotherapy regimens have shown promise for some gastric cancer patients, but how we select patients for these treatments is unclear. The extent of lymph node dissection in gastric cancer surgery has been long contested, but better results from more radical approaches pioneered in East Asia have become evident from trial and registry sources, and D2 lymphadenectomy is now widely accepted as standard of care in the UK. This case report summarises important areas of debate and evidence-based treatment developments in a patient with a stage III gastric cancer, the most common stage at diagnosis.

Abstract

Gastric cancer is one of the commonest malignancies worldwide and is the fourth leading cause of cancer-related death. Commonly presenting at an advanced stage, the prognosis of gastric cancer is dismally poor, with an overall five-year survival of around 15%[1]. Here, I present one typical case, Mr AB, who was diagnosed with stage T3N1M0 gastric adenocarcinoma and underwent total gastrectomy with D2 lymphadenectomy and perioperative chemotherapy. This report will go on to examine the evidence base surrounding the management of non-early resectable gastric cancer relevant to Mr AB's case, in particular D1 versus D2 lymphadenectomy and neoadjuvant chemo-radiotherapy.

Introduction

Gastric cancer is the fifth most common cancer globally, with over 1 million estimated new cases annually[2]. Due to its frequently advanced stage at diagnosis, mortality from gastric cancer is high, with 784,000 deaths globally in 2018[1]. The highest rates of incidence and mortality occur in East Asia, Eastern Europe and South America and risk factors for the disease include a family history, a diet low in fruit and vegetables, smoking, alcohol consumption and Helicobacter pylori infection[2]. Gastric cancer incidence rates have decreased over the last 50 years, mainly attributed to increased standards of hygiene, Helicobacter pylori eradication and improved diet. However, clinicians expect to see an increase in cases in the next century due to ageing populations[1].

The signs and symptoms associated with gastric cancer may include dyspepsia, anorexia or early satiety, weight loss and epigastric pain. If symptoms are present at the time of diagnosis, the disease is often at an advanced stage, with a lower chance of cure[3]. Physical examination is largely unrevealing in early disease, but in late disease, an abdominal mass, and left supraclavicular lymphadenopathy may be present[3].

Gastric cancer is most effectively diagnosed by oesophagogastroduodenoscopy (OGD), during which the tumour localisation within the stomach and its macroscopic type are determined. Histological examination of biopsies then allows for confirmation of the diagnosis, as well as classification of the cancer into histological subgroups, such as intestinal and diffuse, according to the Lauren classification system[4].

Following diagnosis, staging is critical to guide therapy. Staging is based on the tumour (T), nodes (N), metastases (M) classification, proposed by the American Joint Committee on Cancer (AJCC)[5] as summarised in table 1. Endoscopic ultrasound (EUS) is useful in identifying T1 or T2 cancers from advanced cancers, and computerised tomography (CT)/positron emission tomography (PET) provide information regarding locoregional spread of disease and distant metastases[6]. Explorative laparoscopy is also recommended for T1b lesions and above unless palliative gastrectomy is already planned. Performance of laparoscopy allows for visualisation of the peritoneum, biopsy of suspicious lesions, and evaluation of microscopic disease by cytology from peritoneal washings[3].

Tumour (T) Stage	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ: intra-epithelial tumour without invasion of lamina propria
T1	Tumour invades lamina propria or submucosa
T2	Tumour invades muscularis propria or subserosa
T3	Tumour penetrates serosa
T4	Tumour invades adjacent structures
Nodal (N) Stage	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 6 regional lymph nodes
N2	Metastasis in 7 to 15 regional lymph nodes
N3	Metastasis in more than 15 regional lymph nodes
Metastasis (M) Stage	
Mx	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Table 1: Adapted from the AJCC classification of gastric cancer[5].

The main treatment for early gastric cancer is endoscopic resection, whilst for non-early operable gastric cancer (non-metastatic), surgical resection alongside lymphadenectomy and perioperative or adjuvant chemotherapy is standard. The main procedures utilised are distal or total gastrectomy with anastomosis of the oesophagus to the small bowel. For advanced disease, sequential lines of chemotherapy may be used, with median survival less than 1 year. HER-2 positive patients may also benefit from trastuzumab treatment[1].

Clinical Case

Patient Mr AB, a 59-year-old semi-retired business growth consultant, initially presented in April 2020 to his GP with retrosternal chest pain after eating, subsequently diagnosed as acid reflux. He was prescribed omeprazole, which alleviated his symptoms. However, several months later, on examination, his GP noted that Mr AB had lost 5-6kg in weight and a full blood count revealed a normocytic anaemia (Hb 117g/L; MCV 88fL).

Mr AB's past medical history included hypertension, psoriatic arthropathy and mild asthma, which was seasonal due to a tree pollen allergy. He had no known drug allergies and his medications included fusidic acid topical, ramipril, omeprazole, loratadine, beclomethasone and ferrous fumarate. His family history was insignificant. Mr AB drunk 20 units of alcohol per week and quit smoking 25 years ago, having smoked prior to that for 10 years. He lives with his wife and 14-year-old son, and has two daughters, who attend university.

Under the 2-week wait pathway, Mr AB was referred for an OGD. Mr AB expressed frustration that due to the COVID-19 pandemic and lack of face-to-face appointments with his GP, it took several months before he was referred for OGD after his first presentation. The OGD revealed a 3cm ulcerated tumour with rolled edges on the lesser curvature side of the proximal stomach, 1-2cm beyond the gastro-oesophageal junction (GOJ). Pathological examination of biopsy specimens obtained during the procedure showed poorly differentiated adenocarcinoma with features of gastro-intestinal origin. Staging was performed using CT, which revealed no nodal or metastatic disease within the chest, abdomen or pelvis, and PET-CT, which confirmed the local tumour extent and absence of distant disease. Mr AB also underwent a staging laparoscopy, which was entirely clear, with no visible/palpable evidence of the primary gastric tumour and no signs of intra-abdominal disease spread. The tumour was thus staged at T3N1MO.

Mr AB subsequently started a regimen of neoadjuvant FLOT chemotherapy (docetaxel, fluorouracil, folinic acid and oxaliplatin) administered in two weekly cycles, for four cycles. The patient described his experience of chemotherapy as 'debilitating', with decreasing energy levels and worse nausea with each cycle, requiring metoclopramide treatment. Post treatment imaging revealed a reduction in avidity of the known gastric tumour and no evidence of nodal or metastatic disease. Mr AB then underwent a total gastrectomy with lower esophagectomy and D2 lymphadenectomy 6 weeks after the last cycle of chemotherapy.

2 days post-surgery Mr AB required 1-unit red cells after a haemoglobin of 63g/L was recorded. However, the

patient felt well in himself and did not report any dizziness, shortness of breath, haemoptysis, haematemesis, epitaxies or rectal bleeding/dark stool. The next day the patient's haemoglobin level rose to 72g/L and has stayed above 70g/L since, hence he required no further red cell transfusions. Post-operatively he was rehabilitated using enhanced recovery after surgery (ERAS) protocol and discharged 1-week post-gastrectomy. Mr AB is expected to complete a further 4 cycles of adjuvant FLOT chemotherapy.

Discussion of Management

Mr AB received the current gold-standard of care for non-early resectable gastric carcinoma in the UK, of gastrectomy with D2 lymphadenectomy and perioperative FLOT chemotherapy. In recent years, there has been great debate over what constitutes optimum management for gastric cancer, especially between Western and Eastern centres. Many trials have presented conflicting results, and further trials with longer follow-up times are warranted in order provide a satisfactory resolution to these questions.

D1 vs D2 lymphadenectomy

For the purpose of thorough cancer resection and staging of disease, lymphadenectomy is performed in conjunction to gastrectomy. The optimal extent of lymphadenectomy remains a point of contention, however. As shown in figure 1, a D1 dissection must include the nodes with the highest risk of involvement, and thus all perigastric and left gastric artery lymph nodes are removed. Conversely, a D2 dissection entails the removal of the perigastric as well as the coeliac axis lymph node stations[6].

D2 lymphadenectomy is the standard of care for the treatment of gastric adenocarcinoma in high incidence countries such as Japan and South Korea[6]. Large East Asian observational studies, as well as a randomised trial from Taiwan, have shown a better survival with D2 than D1 lymphadenectomy[7,8]. However, similar studies carried out in Western centres, such as The Dutch Gastric Cancer Trial (DGCT)[9] and the UK Medical Research Council (MRC) randomised surgical trial[10], have failed to show a survival benefit after D2 removal, partly explained by high postoperative mortality and morbidity. This has been largely attributed to the performance of pancreaticosplenectomy in conjunction to D2 lymphadenectomy[11]. Pancreas and spleen preserving D2 resection has been shown to reduce morbidity and mortality and is now the procedure of choice for all resectable gastric cancers[12]. Additionally, D2 nodal dissection for T1a disease is not recommended by the Japanese gastric cancer treatment guidelines due to the low chance of nodal metastasis[13]. Yet, on the Dutch D1 versus D2 trial, at least 25% of enrolled patients had T1 disease. The inclusion of these patients may have diluted the true therapeutic effect of D2 lymphadenectomy.

In 2010, the results of the 15-year follow-up of the DGCT were published, showing that D2 lymphadenectomy is associated with a lower recurrence rate (22% for D1 vs 12% for D2) and cancer-related mortality rate (48% for D1 vs 37% for D2)[14]. Subsequently, there is an international consensus supporting that gastrectomy for gastric adenocarcinoma should include a D2 lymphadenectomy in medically fit patients[1]. Patient AB thus underwent a D2 resection, the gold-standard of care according to the UK guidelines.

Neoadjuvant Chemotherapy

Even with negative margins following gastrectomy in early-stage disease, recurrence is common, highlighting the need for effective neoadjuvant/adjuvant therapies. The landmark Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial carried out by the British Medical Research Council in 2006 was instrumental in proving the benefit of peri-operative chemotherapy in the treatment of resectable gastric adenocarcinoma. The trial randomly assigned patients with stage II/III gastric or oesophageal cancer to either perioperative epirubicin, cisplatin, and 5-fluorouracil (ECF) and surgery, or surgery alone. As compared with the surgery group, the perioperative chemotherapy group had a higher likelihood of overall survival (36% vs 23%) and of progression free survival[15].

However, the trial does have several notable flaws; namely the low post-operative chemotherapy completion rate, and the inability to attribute the benefit found to either pre- or postoperative regimens of treatment15. Despite this, following the results of the MAGIC trial, neoadjuvant ECF chemotherapy became the standard of

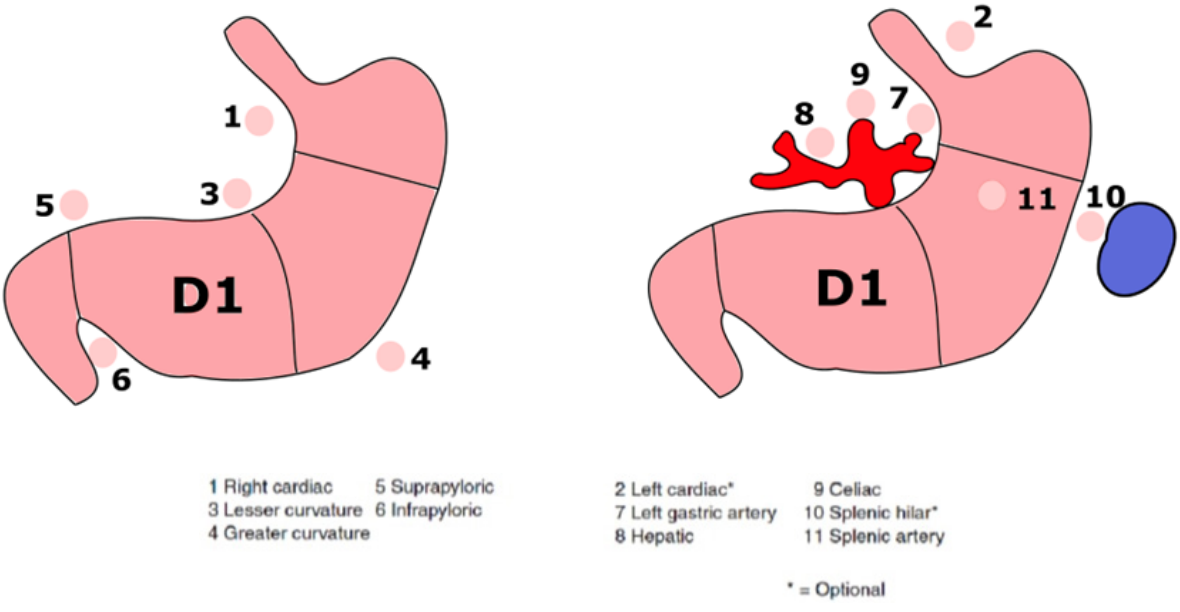

Figure 1: D1 vs D2 lymphadenectomy.

care for localised gastric cancer[1].

In 2017, the findings from the FLOT4-AIO Phase 3 trial challenged this paradigm by demonstrating the superiority of the FLOT regimen over ECF and ECX (EC + capecitabine) as neoadjuvant chemotherapy in locally advanced, resectable gastric adenocarcinoma. 716 patients with ⩾cT2 and/or cN+ disease were randomised to undergo surgical resection and either three pre-operative and three post-operative cycles of ECF/X or four pre-operative and four post-operative FLOT cycles. The results showed improved median (35 vs 50 months) and 5-year overall survival (36% vs 45%) in the FLOT group, and these patients were more likely to complete all intended therapies. Consequently, FLOT is now the recommended standard of care in the UK for patients with locally advanced gastric cancer who can tolerate a perioperative three drug combination regimen16. Mr AB is indeed undergoing a perioperative course of FLOT chemotherapy, and post-treatment imaging after the first 4 cycles revealed a reduction in avidity of his gastric tumour. The importance of involving medical oncology in patient care prior to surgery is clear.

However, some have questioned the global applicability of the FLOT regimen. For instance, grade 3 or 4 neutropenia was observed in approximately 50% of patients, thought to be due to the dose intensity of docetaxel in FLOT, which was high compared with that of Asian triplet regimens; this raises the concern of the viability of this regimen, particularly in Asian populations, who are more vulnerable to bone marrow suppression. Additionally, like the MAGIC trial, the post-operative chemotherapy completion rate was low: only 46% of the FLOT group patients completed all the allocated cycles. It may be necessary to decrease the dose intensity or the number of cycles of FLOT to increase the tolerability of the postoperative treatment[17]. Further, a more individualised postoperative treatment strategy that reflects the response to preoperative treatment may be warranted. For instance, the EORTC-1707 VESTIGAE trial is investigating the role of adjuvant immunotherapy with nivolumab and ipilimumab in patients with high risk of tumour relapse, such as positive lymph nodes at resection following neoadjuvant chemotherapy[1].

Radiotherapy

Despite the promising results of the FLOT4-AIO trial, the 5-year survival rate remains less than 50%[18]. One of the potential strategies to improve long-term survival could be the adoption of radiotherapy in perioperative chemotherapy. However, the 2018 CRITICS study found no benefit in pre-operative chemotherapy and post-operative chemoradiation compared to perioperative chemotherapy, which was thought in part to be attributed to poor patient compliance to the postoperative treatment[19]. Consequently, subsequent studies have focussed on optimising the preoperative treatment regimens. Currently underway, the TOPGEAR trial is evaluating the benefit of the addition of preoperative radiotherapy to perioperative chemotherapy[20].

A National Screening Programme

Although improving the management of gastric cancer will ultimately lead to better outcomes for patients, implementation of a national screening programme could prevent patients having to ever undergo major surgery. In the UK, 1 in 7 of gastric cancers are diagnosed at an advanced stage (T3/T4), for which chance of cure is only 40-50%[18]. In countries with high incidence of gastric cancer, such as Japan and South Korea, nation-wide screening programmes have proved effective. At present, Korean guidelines recommend endoscopy or radiographic examination to all 40-year-old individuals every 2 years, which has allowed for frequent early diagnosis[21]. However, there is some controversy as to whether the 'early cancers' that are diagnosed are actually true malignancies, rather than benign lesions[22]. Additionally, a national screening programme in lower incidence countries, such as the UK, may be cost-prohibitive. A potentially more effective approach in these countries may be to improve GP training to ensure early signs of gastric cancer are more frequently recognised. Training such as this may have allowed for Mr AB to be diagnosed at an earlier stage of his disease.

Conclusion

Although the incidence of gastric cancer is falling in the UK, survival outcomes remain poor. Indeed, patient AB only has a 40-50% chance of complete cure, despite being offered perioperative chemotherapy and surgical resection of his T3N1M0 disease with D2 lymphadenectomy. There have been great advances in the management of gastric cancer, namely the provision of evidence for the benefit of D2 over D1 resection and perioperative FLOT over ECF chemotherapy, but there is still considerable room for improvement. Earlier diagnosis of disease and a more individualised postoperative treatment strategy that reflects the response to preoperative treatment could reduce patient mortality and morbidity.

Conflicts of interest

None.

Funding

None.

Consent

The patient has consented to the publication of this case study.

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