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REVIEW ARTICLE

Evidence-based Management of Gastric Cancer

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ABSTRACT

Gastric carcinoma is one of the most common cancers worldwide. Patients in the early stages of the disease experience non-specific symptoms. This contributes greatly to delayed diagnoses and poor prognoses, as reflected by low survival rates. Although surgical resection is currently the only curative treatment option, the management of gastric cancer has been rapidly evolving. The emergence of new chemotherapeutic agents and targeted biological therapies used as adjuvant treatments has contributed greatly to improved survival. In this patient group, there is clinical evidence favouring various types of adjuvant therapy in addition to surgery. However, there appears to be regional discordance in recommendations and clinical practice. Evidence from the United States supports the use of adjuvant chemoradiation. In a United Kingdom study, survival benefits were demonstrated with perioperative chemotherapy. In Asia, clinical evidence supports the use of postoperative chemotherapy. This underscores the lack of consensus between adjuvant gastric cancer treatment modalities. This paper presents the evidence for these various approaches to adjuvant treatments for gastric cancer. Importantly, data supporting the use of novel biological agents as part of multimodal treatment of unresectable gastric cancer are also reviewed.

Key Words: *Antineoplastic agents; Capecitabine; Chemotherapy, adjuvant; Stomach neoplasms; Trastuzumab*

中文摘要

胃癌的循證治療

傅耀彤

胃癌是最常見的癌症之一，在癌症初期不會有特定的症狀，導致耽擱診斷和不良預後，這從低生存率可反映出來。雖然胃切除術為當前唯一的根治性治療選擇，但近年胃癌的治療方案進展迅速。作為輔助治療，近年新化療藥和標靶生物療法的出現大大改善了胃癌存活率。有關胃癌的治療方法，臨床證據傾向支持除手術外不同類型的輔助治療。然而，有關的治療建議和臨床應用似乎有地區性分別——美國研究支持使用輔助合併化放療，而英國一項研究則指出圍術期化療有助改善存活率；在亞洲，臨床證據支持術後化療。這更加說明在胃癌輔助治療方式上未取得一致意見。本文列舉各種胃癌輔助治療的方式，重要的是，本文同時也回顧分析新的生物制劑作為對不能手術切除患者的多模式治療的一部份。

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INTRODUCTION

Gastric cancer is one of the most common cancers worldwide. Over the last decade, it has consistently been one of the 10 most common types of cancers in Hong Kong,[1] where it was responsible for about 5% of cancer deaths in Hong Kong in 2009,[2] and it is more common in males. Moreover, the number of local persons with the disease has decreased considerably over the last 30 years.[2] Nevertheless, the 10-year survival for patients with gastric cancer of all stages remains low (at only 20%).[3] As patients with early stages of gastric cancer have mainly non-specific symptoms, this often delays patient diagnosis leading to a poor prognosis.

It is well known that radical surgical resection is the only curative modality for early-stage gastric cancer. Achieving en-bloc removal of the primary tumour and the nodal basins at risk of metastasis are the goals of resection. Historical data and recent studies suggest that standardised extended (D2) lymphadenectomy leads to better results than standardised limited (D1) lymphadenectomy.[4]

The Dutch D1D2 trial was a nationwide prospectively randomised clinical trial, undertaken to compare D2 with D1 lymphadenectomy in patients with resectable primary adenocarcinoma of the stomach, in terms of disease recurrence and survival after treatment with curative intent.[4] After a median follow-up of 15 years, D2 lymphadenectomy was associated with lower local regional recurrence and gastric cancer–related death rates than D1 surgery. This study also indicated that tumour staging had little to do with choice of D1 or D2 lymphadenectomy. As a safer, spleen-preserving D2 resection technique is currently available in high-volume centres, D2 lymphadenectomy is the recommended surgical approach for patients with resectable gastric cancer.

While surgery is the mainstay of treatment, the management of gastric cancer has been rapidly evolving with the emergence of new cytotoxic drugs and targeted biological agents. However, none of these approaches can definitively alter the natural history of this disease. In spite of potentially curative resections, the majority of patients with gastric cancer die of disease relapse.[5]

Clinical trials have been conducted to determine the types and efficacy of adjuvant therapies to surgery in this patient group. There appear to be some regional discrepancies in recommendations and clinical practice. This paper presents the evidence pertaining to different approaches to adjuvant treatments for gastric cancer.

ADJUVANT TREATMENTS FOR RESECTABLE GASTRIC TUMOURS

Postoperative Chemoradiation

Fiorica et al[6] conducted a meta-analysis to assess the effectiveness of surgery combined with preoperative radiotherapy or postoperative chemoradiotherapy in the reduction of all-cause mortality in patients with resectable gastric carcinoma. In such patients, they inferred that adjuvant chemoradiotherapy significantly reduced 3-year and 5-year all-cause mortality, but the magnitude of the benefit was relatively small. Available evidence is inadequate to determine whether postoperative chemoradiotherapy is superior to preoperative radiotherapy. Gastric cancer frequently manifests with local and systemic recurrence after curative surgical resection. Hence, postoperative therapy with chemoradiation was explored.

The Southwest Oncology Group (SWOG) 9008/INT0116 trial[7] conducted in the United States was a prospectively randomised phase III trial of postoperative adjuvant therapy utilising 5-fluorouracil (5-FU) / leucovorin plus external beam radiation in 582 eligible cases of resected stage IB-IV(M0) stomach and gastroesophageal junction cancers. This study provided evidence favouring postoperative chemoradiotherapy for all gastric cancer patients at risk of recurrence who had undergone curative resection. The INT0116 study provided the basis for the current National Comprehensive Care Network (NCCN) clinical practice recommendations.[8]

The INT0116 study revealed a high level of toxicity associated with chemoradiation. Three patients (1%) died from the toxic effects of the chemoradiotherapy; grade-3 toxic effects occurred in 41% of the patients in the chemo-radiotherapy group, and grade-4 toxic effects in 32%.[7]

Notably only 10% of patients in this study had D2 resections, which are recommended as the standard of care in the East (e.g. Japan). In 2009, a 10-year follow-up of the INT0116 study was reported.[9] This demonstrated consistent survival improvements in stage IB-IV (M0) gastric cancer patients treated with postoperative chemoradiation. All patient subsets benefited from this treatment, with the exception of those with diffuse histology, which occurs more

commonly in women. In line with that observed in clinical practice, this long-term follow-up found no increase in late toxic effects.

Adjuvant Chemotherapy or Chemoradiotherapy in Resectable Gastric Cancer (CRITICS) is an ongoing randomised phase III trial to evaluate the efficacy and safety of chemoradiation (in comparison to chemotherapy alone) as adjuvant treatment after surgery for gastric cancer.[10] In CRITICS, all patients also receive neo-adjuvant chemotherapy prior to at least D1 surgery. This study aims to recruit 788 patients. The expected study completion is in 2013. Hopefully it will contribute to evidence regarding the efficacy of chemoradiotherapy after D1 as well as D2 lymphadenectomy.

Conversely, the Korean Adjuvant Chemoradiation Therapy in Stomach Cancer (ARTIST) trial is an ongoing study comparing capecitabine/cisplatin (n = 228) vs capecitabine/cisplatin + radiotherapy (n = 230) in curatively D2 resected gastric cancer patients, in terms of disease-free survival (DFS) and overall survival (OS).[11] To date, only safety data from this study have been reported. Data collection has been completed and the pending results will reveal the role of chemoradiation after both D1 and D2 surgery.

Adjuvant Chemotherapy

The premise behind both peri- or pre-operative chemotherapy is similar to that of preoperative chemoradiation. All these modalities aim to downstage the primary tumour and eliminate micrometastases. Meta-analyses looking at the use of adjuvant chemotherapy in gastric cancer found that most studies were under-powered and of suboptimal quality.[12-15] Small survival benefits were demonstrated, although they appeared to be more apparent in Japanese than western studies.

Paoletti et al[5] performed an individual patient-level meta-analysis of all randomised controlled trials to quantify the potential benefit of chemotherapy after complete resection over surgery alone in terms of OS and DFS; the role of mono- and combined chemotherapy regimens were also studied. In total, 17 trials were identified for this meta-analysis (n = 3838). Adjuvant chemotherapy was associated with a statistically significant benefit in terms of OS (hazard ratio [HR] = 0.82; p <0.001) and DFS (HR = 0.82; p <0.001). No significant heterogeneity for OS across trials (p = 0.52) or the four regimen groups (p = 0.13) was observed. Five-year OS increased from 49.6% to 55.3% with chemotherapy. It should be noted that treatment effects were consistent, irrespective of geographical location and time trends.[5]

Perioperative Chemotherapy

The UK Medical Research Council Adjuvant Gastric (MAGIC) trial[16] found that pre- and post-operative chemotherapy (with epirubicin, cisplatin, and infused fluorouracil; the ECF regimen) decreased tumour size and stage in patients with operable gastric cancers. Significant improvements in both progression-free survival (PFS) and OS were observed. Patients who received perioperative chemotherapy had statistically significant downstaging of their disease, but this did not translate to increased resectability. The European Society for Medical Oncology's (ESMO) clinical practice guidelines for gastric cancer contained perioperative chemotherapy recommendations based on this evidence.[17]

Results from the FNLCC ACCORD 07-FFCD 9703 trial[18] reconfirmed the results of the MAGIC trial and underscored the benefits of perioperative chemotherapy. Patients with resectable gastric or gastroesophageal junction adenocarcinoma (n = 224) were randomised to receive either surgery alone, or two cycles of preoperative cisplatin and 5-FU followed by surgery. Four cycles of adjuvant chemotherapy were given to those in the latter group who responded to preoperative chemotherapy, or had stable disease and high-risk histopathology. OS was significantly longer in the perioperative chemotherapy arm than the surgery-alone arm (38% vs 24%; HR = 0.69; p = 0.021). The five-year DFS and R0 resection rates were also significantly increased by perioperative chemotherapy.

Neoadjuvant Chemotherapy

A recent meta-analysis studied the value of neoadjuvant chemotherapy for advanced gastric cancer.[19] All published controlled trials of neoadjuvant chemotherapy compared with no therapy before surgery for advanced gastric cancer were included. Patients with advanced gastric cancer (n = 2271) enrolled in 14 trials were divided into the neoadjuvant chemotherapy group (n = 1054) and control group (n = 1217). Patients were followed up for a median of 54 months. Neoadjuvant chemotherapy significantly improved survival rates (odds ratio [OR] = 1.27), tumour stage (OR = 1.71), and resection rates (OR = 1.51) of patients with advanced gastric cancer.

Postoperative Chemotherapy

The Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) trial was conducted in Japan.[20] In this study, adjuvant chemotherapy (with oral fluoropyrimidine derivative, S-1) significantly improved OS.[21] Five-year follow-up data showed postoperative adjuvant therapy improved OS and relapse-free survival in patients with stage II or III gastric cancer, who had undergone D2 gastrectomy.[21]

It should be noted that even after D2 dissection, many patients still had lymph node and peritoneal relapse. This may indicate that postoperative chemotherapy only prevented lymph node and peritoneal, rather than failures by haematological spread. Surprisingly, results of ACTS-GC seemed to indicate less benefit from adjuvant chemotherapy in patients with higher-stage disease and more extensive lymph node involvement.

CLASSIC is a randomised, open-label, phase III international study of XELOX (capecitabine 1000 mg/m^2 twice a day, days 1-14, every three weeks, and oxaliplatin 130 mg/m^2, day 1, every three weeks x 8 cycles) versus controls, following D2 gastrectomy.[22] This multinational study involved patients from South Korea, China, and Taiwan. The XELOX (n = 520, intention-to-treat [ITT] population) and the observation arms (n = 515, ITT population) were both chemotherapy- and radiotherapy-naïve.

The results of CLASSIC were reported after a pre-planned interim analysis of only two-thirds of patients, due to the highly significant and clinically meaningful patient outcomes observed with XELOX. The primary endpoint of this study was met at the interim analysis, as three-year DFS was 74% in the XELOX arm compared with only 60% in the observation arm (Table 1). This constituted a 44% reduction in the risk for disease progression (p<0.0001). Moreover, the significant DFS benefit conferred by XELOX was observed for all disease stages.[22]

Although longer follow-up is needed to discern the possible effect of adjuvant XELOX on OS, the preliminary analysis conducted at a median follow-up of 34 months showed a trend towards superiority with XELOX (p=0.0775; Table 1).[22] XELOX-related grade 3/4 adverse events occurred in 49% of the safety population, whilst serious XELOX-related grade 3/4 adverse events occurred in 7%.[22] This study demonstrated the superior efficacy of adjuvant XELOX compared to observation alone, following D2 gastrectomy.

TREATMENTS FOR ADVANCED UNRESECTABLE GASTRIC TUMOURS

Chemotherapy (5-Fluorouracil or Capecitabine Backbone)

At present, the combination of 5-FU and a platinum analogue is a widely accepted standard regimen worldwide. Recent clinical studies have shown that 5-FU can be replaced by S-1 (based only on supportive data from Japan) or capecitabine, and cisplatin by oxaliplatin.[23]

The ML17032 study was a randomised, open-label, phase III study, conducted to compare capecitabine plus cisplatin with 5-FU plus cisplatin as first-line treatment for advanced gastric cancer. In this study, patients received cisplatin (80 mg/m^2 intravenously day 1) plus oral capecitabine (1000 mg/m^2 twice a day, days 1-14) [XP]; or 5-FU (800 mg/m^2/day by continuous infusion, days 1-5) [FP] every three weeks. The primary end-point was to confirm non-inferiority of XP versus FP for PFS.[24]

A total of 316 patients were randomised to XP (n = 160) or FP (n = 156). In the per-protocol population, median PFS for XP (n = 139) versus FP (n = 137) was 5.6 versus 5.0 months. The primary end-point was met with an unadjusted HR of 0.81 (p <0.001 vs non-inferiority margin of 1.25). Median OS was 10.5 versus 9.3 months for XP versus FP (unadjusted HR = 0.85, p = 0.008 vs non-inferiority margin of 1.25).[24] The most common

Table 1. Efficacy results of the XELOX arm in the intention-to-treat population of the CLASSIC trial.[22]

			95% CI	Wald χ^2 test
DFS		HR = 0.56	0.44-0.72	p<0.0001
3-year DFS rate (%)	XELOX	74	70-79	-
	Observation	60	54-65	-
OS		HR = 0.74	0.53-1.03	p=0.0775

Abbreviations: CI = confidence interval; HR = overall hazard ratio; DFS = disease-free survival; XELOX = capecitabine + oxaliplatin chemotherapy; OS = overall survival.

treatment-related grade 3/4 adverse events in XP versus FP patients were neutropenia, vomiting, and stomatitis.

The ML17032 study confirmed that a cisplatin-based regimen with oral capecitabine yielded significant non-inferiority for PFS versus cisplatin plus 5-FU in this patient group. Based on this study, capecitabine can be considered an effective alternative to 5-FU when used with cisplatin as standard chemotherapy for the treatment of advanced gastric cancer.[24]

The REAL-2 study was a non-inferiority study which evaluated capecitabine and oxaliplatin as alternatives to infused fluorouracil and cisplatin, respectively, for untreated advanced oesophagogastric cancer.[25]

In total, 1002 patients were randomly assigned to one of the following treatment arms:

- epirubicin and cisplatin plus either fluorouracil (ECF) or capecitabine (ECX),
- or triplet epirubicin and oxaliplatin plus either fluorouracil (EOF) or capecitabine (EOX).

For the capecitabine-fluorouracil comparison, HR for death in the capecitabine group was 0.86, while the HR for the oxaliplatin group was 0.92 for the oxaliplatin-cisplatin group. OS was significantly longer with EOX than with ECF (p = 0.02) [Table 2]. PFS and response rates did not differ significantly between regimens.[25]

There were no differences in toxicities between patients on capecitabine and those on fluorouracil. As compared to cisplatin, oxaliplatin was associated with a lower frequency of grade 3 or 4 neutropenia, alopecia, renal toxicity, and thromboembolism, but with a slightly higher frequency of grade 3 or 4 diarrhoea and neuropathy.[25]

In conclusion, REAL-2 showed that both capecitabine and oxaliplatin are as effective as fluorouracil and cisplatin, respectively, in patients with previously untreated oesophagogastric cancer.

Table 2. Median and 1-year survival rates.[25]

Treatment*	Median survival (months)	Survival rate at 1 year (%)
ECF	9.9	37.7
ECX	9.9	40.8
EOF	9.3	40.4
EOX	11.2	46.8

* ECF = epirubicin + cisplatin + fluorouracil; ECX = epirubicin + cisplatin + capecitabine; EOF = epirubicin + oxaliplatin + fluorouracil; EOX = epirubicin + oxaliplatin + capecitabine.

Molecular Targeted Therapy (as Add-on to Standard Chemotherapy)

ToGA (Trastuzumab for Gastric Cancer), a recently published study, was an open-label, international, phase III, randomised controlled trial undertaken in 122 centres in 24 countries.[26] This landmark study was the first that demonstrated the efficacy of adding a biological agent to standard chemotherapy to improve survival outcomes in this patient population. These findings emphasised the biological and clinical importance of human epidermal growth factor receptor 2 (HER2) protein as a therapeutic target.[27]

ToGA involved patients with gastric or gastroesophageal junction cancer with tumours demonstrating overexpression of the HER2 protein. Participants were randomly assigned in a 1:1 ratio to receive a chemotherapy regimen consisting of capecitabine plus cisplatin or fluorouracil plus cisplatin given every three weeks for six cycles or chemotherapy in combination with intravenous trastuzumab.[26] In total, 594 patients were randomly assigned to one of two treatment arms[26]—trastuzumab plus chemotherapy (n_1 = 298), or chemotherapy alone (n_2 = 296). Of these, 584 were included in the primary analysis (n_1 = 294; n_2 = 290).

Median follow-up was 19 months in the trastuzumab plus chemotherapy group and 17 months in the chemotherapy alone group. Median OS was 14 months in those assigned to trastuzumab plus chemotherapy compared with 11 months in those assigned to chemotherapy alone (p = 0.0046).[26] A subgroup analysis indicated that trastuzumab was most effective in prolonging survival in patients with HER2 immunohistochemistry (IHC) 3+ tumours (HR = 0.66). In HER2-positive patients with IHC 2-3+ subgroup, the median OS was 16.0 months in the trastuzumab arm, compared with 12 months in the chemotherapy-alone arm (HR = 0.65). The most common adverse events in both groups were nausea, vomiting, and neutropenia. Rates of overall grade 3 or 4 adverse events and cardiac adverse events did not differ between groups.

ToGA has shown that trastuzumab, a monoclonal antibody directed against the extracellular domain of HER2,[27] can enhance the efficacy of standard chemotherapy in patients with enhanced, unresectable gastric tumours.

Clinical Case

A 60-year-old female patient with HER2 IHC 3+

adenocarcinoma of the stomach presented with mediastinal and supraclavicular fossa lymph node involvement. This patient was treated for eight cycles with trastuzumab plus chemotherapy (capecitabine plus cisplatin) per the ToGA study[26] followed by a drug holiday.

By cycle five (six months after starting treatment), significant improvement (tumour shrinkage; Figure) was observed on computed tomography.

This remarkable radiological response was obtained despite repeated dose reduction and cycle delays due to bone marrow suppression. Otherwise, this patient tolerated this chemotherapy regimen very well. In spite of limited clinical experience, this case study demonstrated that this chemotherapy regimen with trastuzumab was well-tolerated and effective in the setting of metastases.

CONCLUSIONS

Gastric cancer remains one of the most clinically challenging cancers among all gastrointestinal malignancies. Complete surgical resection offers the chance of cure for localised gastric cancer. Local and distant recurrences are common, however.

Adjuvant chemoradiation significantly improves survival as demonstrated by the US Intergroup INT0116 study.[7] While adjuvant chemoradiation is accepted as standard practice by NCCN,[8] ESMO in their current clinical practice guidelines indicated that there is some evidence suggesting postoperative chemoradiation may further improve outcomes following D2 dissection. Toxicity concerns remain, however.[17]

The MAGIC trial showed survival benefits with perioperative chemotherapy.[16] Pre- and post-operative chemotherapy have also been explored with encouraging results. The ACTS-GC study showed the survival benefits of postoperative chemotherapy in an Asian population.[20,21] Together, these three landmark trials (INT0116, MAGIC, and ACTS-GC) underline the lack of consensus between adjuvant gastric cancer treatment modalities around the world. Further studies involving both Asian and western patient populations are required to change clinical practice.[28,29]

In patients with inoperable metastatic disease, the REAL-2 study provided evidence that chemotherapy with capecitabine plus oxaliplatin is as effective as the fluorouracil plus cisplatin regimen.[25] The ML17032

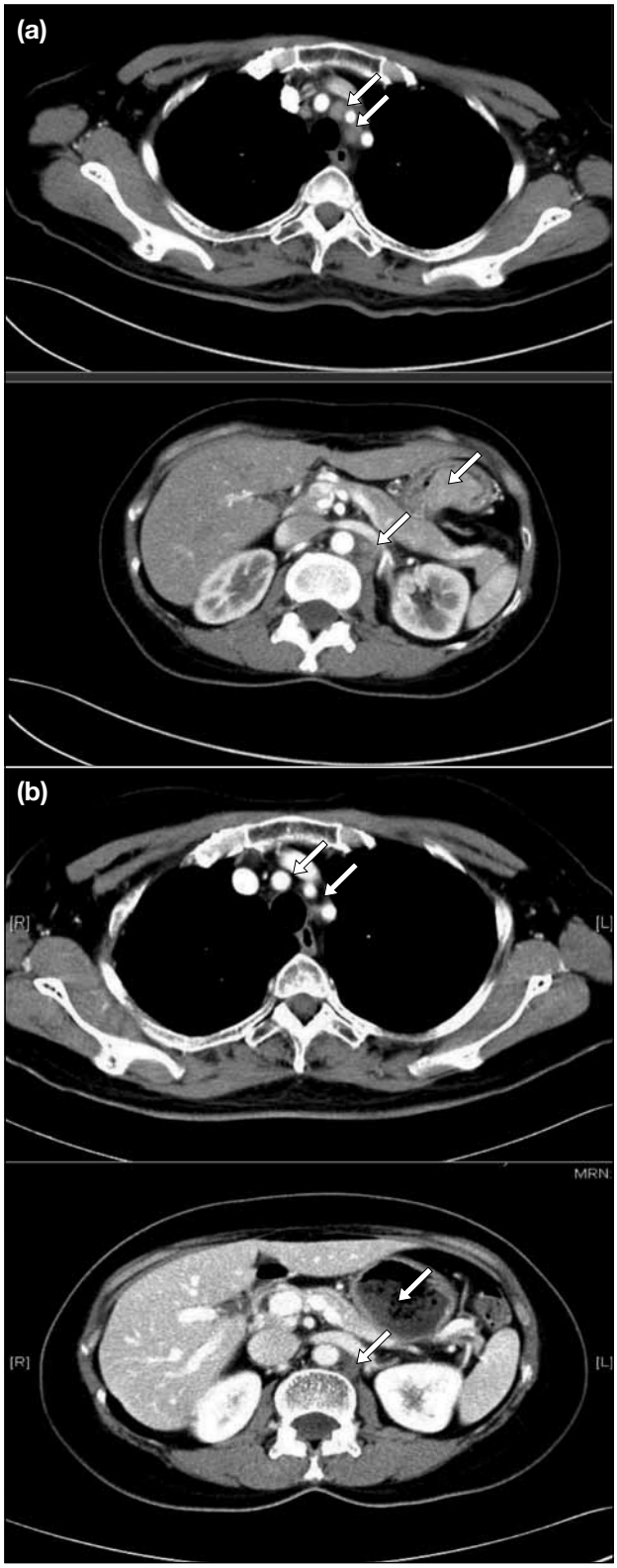

Figure. Tumour shrinkage of a patient treated with trastuzumab plus chemotherapy (capecitabine plus cisplatin) per the ToGA study shown on computed tomography (CT).
(a) Baseline CT scan in October 2010 prior to treatment. (b) CT scan in April 2011 following five cycles of trastuzumab plus chemotherapy (capecitabine plus cisplatin) per the ToGA study.

study showed that capecitabine plus cisplatin is an effective alternative to 5-FU plus cisplatin as standard chemotherapy for this patient group.[24]

In addition, novel molecular targeting agents have been incorporated into the multimodality treatment of unresectable gastric cancer. Trastuzumab, in addition to standard chemotherapy, significantly improved the OS of patients with metastatic HER2-positive gastric tumours both within clinical trials and practice settings.[26]

The management of gastric cancer has been rapidly evolving over the past decade. Integrating targeted agents in gastric cancer treatment offers a new alternative to the management of this devastating disease.

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