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**Advancements and challenges in treating advanced gastric cancer in the West**

Leiting JL *et al.* Treatment of advanced gastric cancer

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**Abstract**

Gastric cancer is a leading cause of cancer incidence and death worldwide. Patients with advanced gastric cancer benefit from a multi-modality treatment regimen. Sound oncologic resection with negative margins and complete lymphadenectomy plays a crucial role in long-term survival for patients with resectable disease. The utilization of minimally invasive techniques for gastric cancer has been slowly increasing and is proving to be both technically and oncologically safe. Perioperative chemotherapy is the current standard of care for advanced gastric cancer. A variety of chemotherapy regimens have been used with the combination of docetaxel, oxaliplatin, 5-fluorouracil, and leucovorin being the current recommendation given its superior ability to induce a complete pathologic response and prolong survival. The use of radiation has been more controversial with its optimal place in the treatment sequence being unclear. There are current ongoing studies assessing the impact of radiation as an adjunct or in place of chemotherapy. Targeted treatments (*e.g.*, trastuzumab for HER-2 positive tumors and pembrolizumab for PD-L1 positive tumors) are showing promise and are part of a continued emphasis on individualized care. Intraperitoneal chemotherapy may also play a role in preventing peritoneal recurrences for patients with high risk lesions. The treatment of patients with advanced gastric cancer in the West continues to advance

and improve with a better understanding of optimal treatment sequences and the utilization of personalized treatment regimens.

## INTRODUCTION

Gastric cancer is the fifth most frequently diagnosed cancer and is the third leading cause of cancer death worldwide<sup>[1]</sup>. However, nearly 50% of these cases are diagnosed in Eastern Asia with over 70% of gastric cancer occurring outside of the US<sup>[2]</sup>. Overall, the incidence of gastric cancer in the US has been declining while overall survival rates have been steadily increasing<sup>[3]</sup>. Non-cardia gastric cancers have seen a decrease in incidence which has been attributed to changes in diet and treatment of chronic *Helicobacter pylori* infections which account for nearly 90% of new non-cardia gastric cancer cases<sup>[2-4]</sup>. Gastric cancers of the cardia, on the other hand, have seen an increase in incidence, and are associated with factors like obesity, Epstein-Barr virus (EBV) and gastroesophageal reflux disease (GERD)<sup>[1,3,5]</sup>. Additionally, recent studies suggest that while the incidence of gastric cancer in the U.S. is declining for those aged 40-84, the incidence of gastric cancer in the young is increasing, particularly in young Hispanic males<sup>[4]</sup>. Young gastric cancer patients are more likely to present with aggressive histologic factors such as poor differentiation, signet ring cells, diffuse histology, and linitis plastica, as well as more advanced nodal metastasis at presentation<sup>[6,7]</sup>.

Outcomes for patients with advanced gastric cancer greatly depend on whether they have resectable disease. Patients with unresectable advanced disease have very poor outcomes with median survivals of just 10-18 months<sup>[8,9]</sup>. Long-term survival for patients with resected advanced gastric cancer has improved as medical and surgical therapies have advanced. Overall survival at 5 years after a curative resection was once just 19% in the 1980's but has now improved to 40-70%<sup>[10-12]</sup>. Unfortunately, nearly half of patients with an R0 resection have a recurrence and median survival after a recurrence is just 6 months<sup>[13]</sup>. These outcomes show that there remains room for

improvement in the treatment of advanced gastric cancer. Here, we review the advancements and challenges of treating advanced gastric cancer in the West.

## SURGERY

Surgery for gastric cancer is associated with significant morbidity and mortality. A study of more than 700 American College of Surgeons (ACS) approved cancer programs in the U.S. during the 1980s reported a 30-day mortality of 7%<sup>[12]</sup>. With improvements in surgical technique, instruments, anesthesia, and peri-operative care, the morbidity and mortality associated with gastrectomy has improved in the U.S. A 2005-2010 ACS NSQIP study looking at outcomes in patients undergoing total or partial gastrectomies for gastric cancer found that 24% experienced a major morbidity and the 30-day mortality was 4%<sup>[14]</sup>. If additional procedures were required (e.g. splenectomy or pancreatectomy), major morbidity increased to nearly 30%<sup>[14]</sup>. A second NSQIP study in the same time period looking at total gastrectomies alone found similar results with 36% of patients experiencing a complication and a 30-day mortality of 5%<sup>[15]</sup>. Additionally, the 30-day mortality increased to 13% in patients who underwent a pancreatectomy in addition to a total gastrectomy<sup>[15]</sup>.

The benefit of multivisceral resection has been debated given the higher morbidity and mortality associated with these procedures, which is generally reported around 3% and 30-40% respectively<sup>[16-18]</sup>. The number of patients undergoing curative-intent resection who require a multivisceral resection is anywhere from 19-66%<sup>[16,17]</sup>. A Canadian study found that combining systemic therapy with multivisceral resections can result in a high rate of margin negative resection<sup>[19]</sup>. The 5-year survival was 34% and there were few locoregional recurrences with an acceptable morbidity and mortality<sup>[19]</sup>. A systematic review reported similar conclusions in that multivisceral resections may be helpful in achieving an R0 resection margin<sup>[20]</sup>. The US Gastric Cancer Collaborative found that patients who underwent a multivisceral resection without a pancreatectomy had higher post-operative morbidity than those who underwent a

gastrectomy alone but there was no change in mortality, while a multivisceral resection with a pancreatectomy was an independent predictor of worse overall survival<sup>17</sup>. This data would suggest that in appropriately selected patients with locally advanced gastric cancer, a multivisceral resection can be performed at high volume centers with a high rate of negative margins and an acceptable morbidity and mortality. The inclusion of pancreatectomy is an independent predictor of poor outcome and must be used selectively.

The stomach has a multidirectional and complex network of regional lymphatic vessels and nodes<sup>21</sup>. Gastric cancer has a high tendency to metastasize to these regional lymph nodes and their involvement is an important prognostic factor<sup>22</sup>. As such, lymph node retrieval is an important aspect of staging for gastric cancer and has implications in adjuvant treatment recommendations (Table 1)<sup>(22-24)</sup>. The final publication of the Dutch trial reported lower locoregional recurrence and gastric cancer-related death in patients undergoing a D2 lymphadenectomy compared to a D1 lymphadenectomy<sup>25</sup>. Similarly, an Italian trial demonstrated a survival benefit for patients with positive nodes treated with D2 gastrectomy without splenectomy and pancreatectomy<sup>26</sup>. As such, a pancreas and spleen preserving, or modified D2 lymphadenectomy, is now the standard of care at most academic institutions throughout the U.S.

Similarly, the total number of lymph nodes removed during gastrectomy is an independent predictor of survival, with an increasing number of excised lymph nodes being associated with a decreased risk of death<sup>27</sup>. As such, the recently, published AJCC 8<sup>th</sup> edition TNM-staging guidelines recommend a minimum of 16 lymph nodes be assessed in gastric cancer with 30 or more lymph nodes being desirable<sup>28</sup>. Despite this, most patients in the west do not receive an adequate lymphadenectomy. A recent NCDB study found that only 23% of patients had evaluation of the recommended 15 lymph nodes<sup>29</sup>. That same study showed that patients who were treated in National Cancer Institute-designated centers or high-volume centers were more likely to have the recommended lymph node retrieval<sup>29</sup>. A SEER analysis found that from 2004-2010,

only 42% of patients had at least 15 lymph nodes evaluated after surgery, and while being treated at a cancer program increased the odds of having 15 nodes removed, improved survival was significant with removal of 15 or more lymph nodes regardless of treatment location<sup>[30]</sup>. The ability to obtain 15 lymph nodes can be difficult if a D1 resection, rather than a D2, is utilized<sup>[31]</sup>. Recently, the National Comprehensive Cancer Network (NCCN) has recommended performing a D2 lymphadenectomy with the goal of obtaining at least 15 lymph nodes while avoiding a splenectomy<sup>[32]</sup>.

There has been a slow increase in minimally invasive surgery for gastric cancer over time. The first description of a laparoscopic gastrectomy was in 1994 from a group in Japan<sup>[33]</sup>. In the US, a SEER analysis from 2008-2013 showed that only 8% of gastrectomies were performed laparoscopically and only 2% were performed robotically<sup>[34]</sup>. There was also no significant increase in the last three years of this analysis indicating that the use of laparoscopic surgery for gastric cancer has not continued to increase<sup>[34]</sup>. This is in contrast to a nearly 26% utilization by Eastern countries<sup>[35]</sup>. Data from the NCDB showed that only 13% of cases were done laparoscopically between 1998-2011 with a conversion from laparoscopic to open in nearly 24% of cases<sup>[36]</sup>. Another study from the NCDB showed that between 2010 and 2012, there was an increase in the use of minimally invasive techniques with 4% being performed robotically and 23% undergoing laparoscopic gastrectomies<sup>[37]</sup>. This study also found that open gastrectomies are decreasing overall, with a rise in both laparoscopic and robotic gastrectomies<sup>[37]</sup>.

Two prospective trials, KLASS-01 and JCOG 0703, as well as several retrospective studies support the safety and oncologic feasibility of laparoscopic surgery for early gastric cancer (Table 1)<sup>[38,39]</sup>. Fewer studies have addressed laparoscopy in advanced gastric cancer. The KLASS-02 trial randomized patients with locally advanced gastric cancer to either laparoscopic or open distal gastrectomy<sup>[40]</sup>. Short term outcomes from this trial were recently published and demonstrated benefits in terms of lower complication rates, lower pain score, earlier return of bowel function, and shorter hospital length of stays compared to open surgery<sup>[41]</sup>. A primary concern

regarding minimally invasive surgery for advanced gastric cancer is whether adequate lymph node retrieval could be achieved. A study from the US Gastric Cancer Collaborative showed similar rates of lymph nodes retrieved between a minimally invasive cohort and an open cohort, both overall and after propensity matching<sup>[42]</sup>. From an outcomes standpoint, a NSQIP analysis of patients undergoing laparoscopic vs. open gastrectomies showed fewer complications for patients undergoing laparoscopic gastrectomies with no difference in mortality<sup>[43]</sup>. As western surgeons become more experienced and minimally invasive technology improves (e.g. 3D visualization and robotic surgery), minimally invasive surgery will likely become safer and more oncologically sound for western patients with advanced gastric cancer.

## CHEMOTHERAPY

The role of systemic chemotherapy for the treatment of advanced gastric cancer has evolved over time as we continue to search for optimal therapies and treatment sequencing that will positively influence outcomes (Table 2). The MAGIC trial was the first large prospective trial that observed improved outcomes in patients who received perioperative chemotherapy<sup>[44]</sup>. The agents used in this study were epirubicin, cisplatin, and 5-fluorouracil (ECF). This study showed improved outcomes even with only 42% of patients receiving the full six cycles of chemotherapy, with many patients being unable to complete their post-operative cycles. Patients who received pre-operative chemotherapy demonstrated significant down-staging as evidenced by smaller tumors and less lymph node involvement, but most importantly, had significantly better overall and progression-free survival<sup>[44]</sup>. Perioperative chemotherapy has since become standard of care for patients with non-metastatic stage II or higher gastric cancers. The use of perioperative chemotherapy in the U.S. has increased overtime since the MAGIC trial. In the year 2003, just 25% of patients were receiving neoadjuvant chemotherapy while in 2012 the rate increased to over 45%<sup>[45]</sup>. A later trial, the ACCORD 07, was a phase III randomized trial that again showed a significant improvement in overall and progression free survival in patients that underwent perioperative chemotherapy and

surgery compared to those that underwent surgery alone<sup>[46]</sup>. This trial used cisplatin and 5-fluorouracil without epirubicin and overall survivals were similar between the MAGIC and the ACCORD 07 trial with 5-year survivals around 30%<sup>[44,46]</sup>.

Neoadjuvant chemotherapy has several potential benefits to adjuvant chemotherapy. First, pre-operative chemotherapy is consistently better tolerated than post-operative chemotherapy in multiple trials<sup>[44,46]</sup>. Second, blood supply to the tumor is not disrupted by surgical resection and micrometastasis can be treated at the earliest possible time<sup>[47]</sup>. Down-staging or shrinkage of the tumor may lead to higher R0 resection rates, particularly in advanced gastric cancer, and it allows the assessment of response to therapy allowing postoperative therapy to be tailored to the individual response to pre-operative therapy<sup>[48]</sup>. Unfortunately, very few patients receiving pre-operative ECF are able to achieve a complete pathologic response following neoadjuvant chemotherapy<sup>[49]</sup>. Tumor regression on final surgical pathology has been reported to be an independent factor associated with improved survival in patients receiving neoadjuvant chemotherapy for a number of cancers, including gastric<sup>[50,51]</sup>. In a phase II study where patients received epirubicin, cisplatin, and capecitabine (ECX), a complete pathologic response was found in just 6%<sup>[49]</sup>. This compares to a complete response rates as high as 17-20% in phase II studies where docetaxel is part of the treatment regimen<sup>[52,53]</sup>.

The AIO-FLOT4 trial looked to compare the rates of pathological regression in patients who received neoadjuvant ECF/ECX vs. the docetaxel-based regimen FLOT (5-fluorouracil, leucovorin, oxaliplatin, and docetaxel)<sup>[54]</sup>. Results of this study showed a significant increase in complete regression with FLOT treatment when compared to ECF (16% vs. 6%). Recent phase III results of the FLOT4 randomized trial showed improved median OS of 50 months for patient receiving the FLOT regimen compared to 35 months for those on ECF/ECX with similar toxicities between the two groups<sup>[55]</sup>. The current NCCN guidelines recommend perioperative FLOT as the preferred regimen for medically fit patients with oxaliplatin and a fluoropyrimidine without docetaxel to be used in patients with a poor performance status or significant medical comorbidities<sup>[32]</sup>.



## RADIATION

The benefit of chemoradiation in patients with locally advanced gastric cancer has been controversial (Table 3). In the early 2000s, the Intergroup 0116 Trial showed that patients who underwent post-operative chemoradiation radiation therapy with 5-fluorouracil and leucovorin after a complete resection had improved long-term outcomes compared to patients who underwent surgery alone<sup>[56]</sup>. These patients did not undergo perioperative chemotherapy and the median survival in the surgery plus chemoradiation group was 36 months compared to 27 months in the surgery alone group<sup>[56]</sup>. This trial was criticized for its low (10%) utilization of D2 lymphadenectomy suggesting that chemoradiation may compensate for inadequate surgery. In contrast, a large retrospective US multi-institutional study in which patients had a median 18 lymph nodes removed showed that post-operative chemoradiation with 5-fluorouracil improved both overall and recurrence-free survival when compared to patients who received perioperative chemotherapy alone<sup>[57]</sup>. On subgroup analysis, patients with nodal disease (N1) and lymphovascular invasion derived the most benefit<sup>[57]</sup>.

Neoadjuvant chemoradiation may improve R0 resection rate and achievement of pathological complete response (pCR) in advanced gastric cancer. A phase I multi-institutional single-arm trial in the US reported a 70% R0 resection rate and a 30% pCR rate with preoperative chemoradiation consisting of two 28-day cycles of induction fluorouracil, leucovorin, and cisplatin followed by fluorouracil-based CRT to 45 Gy<sup>[58]</sup>. Pathological partial or complete response were associated with improved OSI<sup>[59]</sup>. Similarly, another multi-institutional phase II trial in the US reported a 77% R0 resection rate and 26% pCR rate following preoperative induction chemotherapy with two cycles of fluorouracil, leucovorin, and cisplatin followed by paclitaxel, fluorouracil, and concurrent 45 Gy radiotherapy<sup>[60]</sup>. A small retrospective series from Spain comparing neoadjuvant chemotherapy to neoadjuvant chemoradiation in resectable advanced gastric cancer demonstrated a significantly higher likelihood of achieving a Becker Ia-b response (58% vs 32%), a grade D nodal regression (30% vs 6%) and a favorable

pathological response (23% vs 3%). Nodal, but not primary, response was associated with a longer 5-year progression-free and overall survival<sup>61</sup>.

Whether chemoradiation offers a benefit in addition to or in place of chemotherapy is being actively prospectively investigated. The CRITICS trial randomized patients to perioperative chemotherapy vs. pre-operative chemotherapy and post-operative chemoradiation therapy and was not able to show a survival difference between the two groups<sup>11</sup>, however only 50% of patients received their intended post-operative treatment regimens in the CRITICS trial. The follow up CRITICS-II trial aims to optimize neoadjuvant therapy by comparing neoadjuvant chemotherapy alone, neoadjuvant chemotherapy followed by chemoradiation, and neoadjuvant chemoradiation alone<sup>62</sup>. Similarly, the ARTIST trial, which was designed to compare adjuvant chemotherapy to chemoradiation, failed to demonstrate a difference in disease-free and overall survival; however, subgroup analysis suggested that patients with intestinal type histology and lymph node metastasis, in particular, may benefit from chemoradiation<sup>63</sup>. A follow-up trial, ARTIST II, is currently under way addressing this question (NCT01761461). The TOPGEAR trial is another randomized prospective trial aimed at determining if pre-operative chemoradiation, in addition to perioperative chemotherapy, improves outcomes over perioperative chemotherapy alone<sup>64</sup>.

The mode of radiation administration has traditionally been through three-dimensional conformal radiotherapy (3D-CRT). The potential advantage of using intensity-modulated radiotherapy (IMRT) over 3D-CRT is the ability to limit exposure to critical surrounding structures while delivering therapeutic doses to the organs of interest<sup>65,66</sup>. One study found that overall and disease-free survival were significantly improved in patients treated with adjuvant IMRT compared to similar patients treated with adjuvant 3D-CRT<sup>67</sup>. There has been little investigation into the use of proton beam radiation for the treatment of locally advanced gastric cancer. Reasons for this include the limited availability of proton beam radiation in the U.S. and that a moderate dose of radiation over a large area may be ideal for treating the resection margins and

wide nodal basin<sup>[68]</sup>. A benefit of proton beam radiation is its ability to provide a very high dose of radiation to a single lesion with relative sparing of adjacent structures, limiting damage to surrounding tissue<sup>[69]</sup>. Given these properties, there has been more interest in using proton beam radiation for unresectable primary liver tumors like hepatocellular carcinoma, or even gastric cancer hepatic metastases<sup>[69,70]</sup>. For similar reason, stereotactic body radiotherapy (SBRT) has been under investigation for the treatment of liver tumors, though there has been a description of using SBRT for the treatment of lymph node recurrences after gastric resection<sup>[71,72]</sup>.

## FUTURE DIRECTIONS

While outcomes for patients with advanced gastric cancer have improved with medical and surgical advancement, there are still areas for improvement and exploration. The use of targeted treatments as adjuncts to traditional chemotherapeutic agents is under continued investigation (Table 4). Epidermal growth factor receptor (EGFR) is overexpressed in most gastric cancers, however the trials that used anti-EGFR antibodies such as cetuximab (EXPAND Trial), and panitumumab (REAL3 Trial) failed to improve survival<sup>[8,73]</sup>. In contrast, in the randomized phase III AVAGAST trial, bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor (VEGF), when given with cisplatin and a fluoropyrimidine was found to significantly improve progression-free survival in patients with unresectable or metastatic advanced gastric cancer though it did not improve overall survival (50% vs. 42%)<sup>[74]</sup>. However, the use of ramucirumab, a VEGFR-2 inhibitor, in the REGARD trial was able to show a significant improvement in overall survival as a second-line option for patients with metastatic disease unresponsive to first-line therapy so there may be a role for its use in the perioperative setting in the future<sup>[75]</sup>.

Another advance and future direction is using molecular analysis to better predict prognosis as well as treatment options for individual patients. One of these molecular characteristics is identification of patients with HER2 overexpression. Around 12-24% of patients with gastric cancer have been found to have HER2

overexpression with most showing associated poorer outcomes when compared to patients with normal HER2 expression<sup>[76-78]</sup>. Intestinal type gastric cancers are much more likely to have overexpression than diffuse type (32% vs. 6%)<sup>[79]</sup>. The randomized controlled ToGA trial found that in patients with HER2 overexpression, treatment with chemotherapy with trastuzumab was associated with improved overall survival when compared to patients treated with chemotherapy alone<sup>[79]</sup>. These results have led to NCCN guidelines recommending the assessment of HER2 expression and the addition of trastuzumab to all HER2 overexpressing metastatic gastric adenocarcinomas<sup>[32]</sup>.

The use of pembrolizumab, a monoclonal antibody against PD-1, in patients with PD-L1-positive cancers is another example of how individualized treatment may impact specific patients based on their tumor's molecular characteristics. In a phase I study, pembrolizumab showed promising results as a single agent in patients with PD-L1-positive metastatic or recurrent gastric cancer that had failed other treatment regimens<sup>[80]</sup>. In this cohort, 22% of patients had a partial tumor response and the 1-year survival was 42%<sup>[80]</sup>.

Additionally, there has been investigation into the adjuvant use of intraperitoneal chemotherapy. Peritoneal recurrence develops in about 60% of the patients with T3 and T4 tumors following curative-intent resection, and up to 40% of resected gastric cancer patients die as a direct result of peritoneal dissemination<sup>[13]</sup>. Few systemic chemotherapeutic agents penetrate the peritoneum well and intraperitoneal chemotherapy has less adverse effects with higher doses in the intraperitoneal regions than systemic chemotherapy<sup>[81]</sup>. A recent meta-analysis of 23 prospective randomized trials including 2,767 advanced gastric patients from Japan, China, Korea, and Austria demonstrated that adjuvant intraperitoneal chemotherapy was associated with improved 1, 2 and 3-year survival rate, as well as a 30% reduction in the incidence of peritoneal recurrence<sup>[82]</sup>. Currently, the GASTRICHIP Trial, a randomized multicenter phase III clinical study, is evaluating the effects of hyperthermic intraperitoneal chemotherapy with oxaliplatin on patients with locally

advanced gastric cancer and will hopefully provide further direction on the effectiveness of intraperitoneal chemotherapy for locally advanced gastric cancer<sup>183</sup>].

## CONCLUSIONS

Treatment for advanced gastric cancer continues to evolve with better understanding of optimal treatment regimens, treatment sequences, and surgical optimization with improved technique. Additionally, future efforts in providing individualized treatment recommendations based on molecular characteristics at the time of the initial diagnosis have the opportunity to improve long-term outcomes.

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