Gastric adenocarcinoma is the 5th most frequently diagnosed cancer and the 3rd leading cause of death, worldwide (1). Historically, treatment of localized disease has been surgical resection alone. The Intergroup 0116 trial established adjuvant chemoradiotherapy (CRT) as the standard of care for resected gastric cancer (2). In parallel, the MAGIC trial demonstrated that perioperative (neoadjuvant and adjuvant) chemotherapy (CT) improves outcomes compared to surgery alone (3), establishing another standard of care. The two current approaches, broadly, for resectable gastric cancer are: upfront surgery followed by adjuvant CT and/or radiotherapy (RT) or preoperative therapy with neoadjuvant CT +/- RT followed by surgery +/- adjuvant therapy. This review will focus on published randomized trial data for both of these scenarios, as well as future directions. In addition, this review will discuss the role of RT in unresectable gastric cancer, based upon both randomized and non-randomized data. This review will not discuss gastroesophageal junction cancer in detail, as that is more commonly treated as esophageal cancer.

Gastric adenocarcinoma is a common malignancy worldwide, and treatment of localized disease has shifted from surgery alone to the addition of chemotherapy at various stages in treatment. The role of radiation in the management of gastric cancer has evolved significantly since the seminal publication of INT 0116 demonstrated a survival advantage to adjuvant chemoradiation. In this review, we summarize multiple landmark studies discussing the role of radiation in non-metastatic gastric cancer, both in resectable and unresectable patients. This review will additionally discuss the evidence for pre-operative chemoradiation, as the benefit has already been demonstrated in esophageal and rectal cancer.

Keywords: Gastric cancer; radiation therapy; adjuvant; definitive; neoadjuvant; chemoradiation

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The role of radiation treatment in resectable gastric cancer

Upfront surgery

The seminal trial demonstrating the value of adjuvant RT was the US-based Intergroup 0116 trial (2), which randomized patients with surgically resected stage Ib–IV gastric adenocarcinoma to observation or adjuvant CT/ CRT with 1 cycle of 5-fluorouracil (5-FU) and leucovorin (LV), 5-FU-based CRT, followed by an additional 2 cycles of 5-FU/LV. This trial showed significant improvements in both disease-free survival (DFS) and overall survival (OS), with median OS increased from 27 to 35 months (4). However, the trial was criticized for including patients who underwent inadequate nodal dissection, as 90% of patients had either a D0 or D1 nodal dissection, as the standard of care in Europe and Asia is a D2 dissection. A Chinese trial demonstrated improvement in PFS but not OS with CRT compared to CT alone in patients having undergone a D2 dissection (5). The Korean ARTIST trial required a
D2 dissection as part of surgical staging in their resection, and randomized patients to capecitabine and cisplatin (XP) for 6 cycles or sandwich adjuvant treatment with XP for 2 cycles, followed by capecitabine-based CRT, followed by an additional 2 cycles of XP (6). While there were no significant differences in DFS or OS between the two arms, CRT improved locoregional relapse rates, from 13% to 7% (7). On subset analyses, patients with either lymph node positive or intestinal type disease [as opposed to diffuse or mixed type under the Lauren classification (8)] showed benefit with the addition of CRT. To confirm these findings, the ARTIST-II trial will only include patients with lymph node positive disease after D2 dissection (Clinicaltrials.gov NCT01761461). These patients will be randomized to adjuvant therapy with tegafur/gimeracil/oteracil (S-1) for 8 cycles (1 year), S-1 with Oxaliplatin (SOX) for 8 cycles (6 months), or sandwich therapy with SOX for 2 cycles, S-1 based CRT, and additional SOX for 4 cycles.

At the current time, in patients undergoing upfront surgery, our institutional practice is to offer postoperative CRT to patients with T4 staging and/or lymph node positive disease. We treat all patients with positive resection margins. For patients with T2/T3 node-negative disease, CRT will be considered for those with unfavorable features, such as those undergoing a D0 or D1 lymph node dissection, <15 lymph nodes dissected, lymphovascular space invasion, especially for intestinal-type disease. We also take anatomic location of the primary into consideration. For tumors located distally, such as pre-pyloric or pyloric cancer, it is believed that RT may offer a local control benefit, given the difficulties in obtaining negative surgical margins due to proximity to pancreas and retroperitoneal duodenum.

**Preoperative CT and post-operative RT**

The seminal trial showing the value of neoadjuvant CT was the MAGIC trial, where patients were randomized to surgery alone or surgery with perioperative epirubicin, cisplatin, and 5-FU (ECF), given as 3 cycles neoadjuvantly and 3 cycles adjuvantly (3). This trial demonstrated a significant improvement in both PFS and OS with perioperative CT. While this trial did not directly use RT, it led to a second standard of care option on NCCN guidelines beyond upfront surgery and adjuvant CRT (9), and led to a question of whether CRT is necessary after perioperative ECF. The subsequent CRITICS trial combined the INT 0116 and MAGIC treatment modalities. Half of the patients received perioperative epirubicin, cisplatin, capecitabine (ECX) or epirubicin, oxaliplatin, and capecitabine (EOX) and the other half received neoadjuvant ECX/EOX ×3 cycles and adjuvant XP-based CRT (10). The trial did not show any improved oncologic outcomes with the addition of post-operative CRT compared to post-operative CT using an intention-to-treat analysis. In addition, toxicity profiles were similar between the two groups. However, only 60% of patients initiated postoperative treatment, resulting in requests for per-protocol analysis (11). In addition, subset analysis on lymph node positive patients was not performed. Given the low tolerability of postoperative therapy (either CT or CRT) after neoadjuvant ECX/EOX, the currently enrolling CRITICS-II trial will focus on evaluating various neoadjuvant therapy regimens. CRITICS-II is a 3-arm, phase II trial comparing various neoadjuvant therapy schedules, including: (I) combination CT with docetaxel, oxaliplatin, and capecitabine (DOC) for 4 cycles, (II) DOC ×2 cycles followed by CRT to 45 Gy with weekly carboplatin and paclitaxel, and (III) CRT alone (12). Neoadjuvant therapy will then be followed by surgery with mandated D2 lymph node dissection. The regimen with the best oncologic outcomes will be compared to standard of care treatment in a future trial.

In patients receiving neoadjuvant CT, we still offer postoperative CRT to patients with T3/T4 and/or node positive disease, especially patients demonstrating minimal response to pre-operative CT. We generally evaluate the tumor regression grade (TRG) on pathology and consider treating TRG 3 (extensive residual cancer with no evidence of post-operative CRT compared to post-operative CT show any improved oncologic outcomes with the addition of per-protocol analysis (11). In addition, subset analysis on lymph node positive patients was not performed. Given the low tolerability of postoperative therapy (either CT or CRT) after neoadjuvant ECX/EOX, the currently enrolling CRITICS-II trial will focus on evaluating various neoadjuvant therapy regimens. CRITICS-II is a 3-arm, phase II trial comparing various neoadjuvant therapy schedules, including: (I) combination CT with docetaxel, oxaliplatin, and capecitabine (DOC) for 4 cycles, (II) DOC ×2 cycles followed by CRT to 45 Gy with weekly carboplatin and paclitaxel, and (III) CRT alone (12). Neoadjuvant therapy will then be followed by surgery with mandated D2 lymph node dissection. The regimen with the best oncologic outcomes will be compared to standard of care treatment in a future trial.

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**Preoperative radiotherapy**

The concept of neoadjuvant CRT has been present in single institutional series for nearly two decades. An initial study dose escalated from 31.2, then 38.4, and finally 45.6 Gy along with concurrent cisplatin and 5-FU/LV, showing a 50% response rate at surgery and 3-year PFS of 50% (15). Since then, multiple phase I/II trials have shown tolerability of this treatment regimen without significant operative
risk or late effects. RT with concurrent CT, usually an alkylating platinum with 5-FU or an analogue, has resulted in pathologic complete response (pCR) rates between 10% and 26% (16-21). While preoperative CRT is listed in the NCCN guidelines as a category 2B recommendation, there are two major phase III trials, TOPGEAR and CRITICS-II, which will assist in determining its appropriateness in gastric cancer management. TOPGEAR is a 2-arm trial comparing the standard MAGIC regimen (ECF ×3 cycles, surgery, ECF ×3) to an experimental regimen of ECF ×2, preoperative CRT to 45 Gy with 5-FU or Xeloda, surgery, and ECF ×3 cycles (22). CRITICS-II has been discussed in detail in the previous section.

**The role of radiation in unresectable, non-metastatic gastric cancer**

While RT can be used for palliation of a bleeding gastric mass in the metastatic or non-metastatic setting, this review will focus on definitive-intent therapy with RT in patients with non-metastatic gastric cancer who are either medically inoperable due to significant comorbidity or surgically unresectable due to locally advanced disease. Per NCCN guidelines, medically inoperable patients are recommended for definitive CRT, while locally advanced patients are recommended for CRT or CT alone. An old GastroIntestinal Tumor Study Group (GITSG) trial evaluated 5-FU and methyl-CCNU CT +/- concurrent RT to 50 Gy showed significant early mortality in the CRT group due to treatment toxicity. However, CRT was associated with improved oncologic outcomes, with 4-year OS of 17.8% in the CRT group and 6.7% in the CT alone group (23). A similar National Cancer Database study showed that even with more contemporary CT agents and RT techniques, use of CRT improved survival (median OS 12.3 vs. 11.3 months, 2-year OS 28.3% vs. 21.5%) compared to CT alone in unresected gastric cancer (24). However, the series noted that only 30.8% of the patient cohort had received definitive CRT. Multiple recent series demonstrate a median OS between 19.8–35 months for well-selected patients with unresected (including locoregionally recurrent) gastric cancer treated with CRT (25-28). For well-selected patients with medically or surgically inoperable localized gastric cancer, without evidence of metastatic disease, CRT appears to have better oncologic outcomes than CT alone.

**Radiation treatment fields for 3-dimensional conformal RT (3D-CRT) or intensity-modulated RT (IMRT)**

Gunderson provided the initial clinical evidence for ideal development of adjuvant RT fields by delineating locations of recurrence in patients undergoing surgery alone for gastric cancer (29). With technological advances and use of computed tomography scans for better delineation of at-risk areas and sparing of normal tissue, additional guidelines were proposed for delineation of all relevant lymph node basins at risk (30). We present our institution’s method for delineation of the clinical treatment volume (CTV) in both the post-operative and pre-operative setting.

We aim to cover the following lymph node basins in all gastric cancers, irrespective of primary tumor location: perigastric, celiac, left gastric artery, common hepatic artery, splenic artery, superior mesenteric artery (SMA), suprapyloric, and subpyloric lymph nodes. Coverage of paraesophageal, splenic hilum, porta hepatis, and pancreaticoduodenal lymph nodes depends on primary tumor location.

Lesions in close proximity to the proximal stomach mandate coverage of the splenic hilum and paraesophageal lymph nodes. However, lesions of the distal stomach do not necessarily require coverage of these areas unless there is evidence of positive lymph nodes. Distal gastric primary tumors require coverage of the porta hepatis and distal SMA, along with coverage of the duodenal stump to ensure coverage of the pyloric and pancreaticoduodenal lymph nodes. Specifically, for distal tumors, we contour the celiac artery as well as common hepatic artery to the hepatic hilum. For proximal tumors, we cover the splenic hilum. We also contour the proximal 3 cm of the SMA. We include the portal vein from the confluence of the superior mesenteric vein and splenic vein to the porta hepatitis. A 1-cm geometric margin is added to these vessels to allow for coverage of perivascular lymph nodes. The aorta is contoured where it is coplanar with the other portions of CTV, and an asymmetric expansion is made, consisting of a 2-cm margin to patient’s right, left, and anterior, and a 0.2-cm posteriorly to cover paraaortic and aortocaval lymph nodes.

The tumor bed along the retroperitoneal surface should be covered in its entirety based on pre-operative imaging and surgical findings; in general, this is usually
accomplished through adding margins to the surgical clips. We favor covering the entirety of the residual stomach with an additional 1-cm margin for coverage of perigastric lymph nodes. In a proximal tumor that has been completely resected by total gastrectomy, coverage of approximately 2 to 3 cm proximal to the esophagogastric junction (EGJ) is recommended for primary CTV delineation. In a patient who has undergone a distal subtotal gastrectomy, we cover 2 cm of the residual duodenal stump. We also cover any oncologic anastomoses, such as the gastrojejunostomy (GJ) in subtotal gastrectomies and EGJ in total gastrectomies. Treatment in the post-operative setting is generally to a cumulative dose of 45 Gy delivered once daily over 5 weeks, with potential dose escalation to 54 Gy in patients with positive surgical margins.

**Pre-operative and definitive radiation treatment**

There is no consensus on the ideal target volume for pre-operative RT. The entirety of the stomach should generally be covered, although one can consider partial treatment in a well-demarcated distal tumor, using endoscopically placed surgical clips to assist in the delineation of proximal and distal extent of gross tumor volume (GTV) within the stomach. Positron emission tomography/computed tomography may also be beneficial to assist in delineation of fluorodeoxyglucose (FDG)-avid disease. Endoscopic findings should also be taken into consideration when contouring the GTV. Previous trials have covered up to 5 cm of the esophagus or duodenum for proximal and distal lesions, respectively (17). Published European guidelines recommend that for gastric cancer originating in the middle third of the stomach the entire stomach should be covered, while primaries in the proximal third can exclude cardia and fundus, as long as a 5-cm margin from GTV is included (31). We favor incorporation of histological type as well: tumors of diffuse histology should ideally have the entirety of the stomach covered regardless of primary location, while well-localized tumors of intestinal histology may be amenable to partial stomach treatment.

Per TOPGEAR protocol, the entirety of the stomach is included as CTV, with an additional 0.5–1-cm extension from the GTV outside the native stomach for T3–T4 tumors (Trevor Leong, personal communication). CRITICS-II mandates similar coverage except for very well demarcated lesions undergoing subtotal gastrectomy (Astrid Slagter, personal communication) (12). A 1-cm margin into proximal esophagus and duodenum is minimally included. For proximal tumors, the esophageal margin is increased to 4 cm; similarly, for distal tumors, the duodenal margin is increased to 4 cm. RT is delivered to a total dose of 45 Gy in both trials, given once daily over a 5-week timeframe.

These various sub-CTVs, depending on the clinical scenario, are combined to create the final CTV, at which point a 0.5- to 1-cm margin is added for setup error, creating a planning treatment volume (PTV). Setup error is dependent upon whether the patient is receiving 3D-CRT with weekly X-rays for setup or IMRT with daily image guidance using computed tomography imaging for setup. We favor treatment with IMRT when possible, as data has shown improved rates of toxicity in both pre- and postoperative treatment (32,33).

**Conclusions and future directions**

Historically, the role of RT in the adjuvant setting was significant. Recently, with improvements in systemic therapy and the use of neoadjuvant therapies, the use of RT for gastric cancer has declined. In patients undergoing upfront surgery, the results of the ARTIST-II trial are awaited to confirm a benefit of adding CRT to post-operative CT in patients undergoing a D2 nodal dissection with node-positive disease. In patients receiving neoadjuvant CT followed by surgery, the CRITICS trial has demonstrated that patients do not routinely benefit from RT. However, through future subset analyses, we may find that patients with high-risk features, such as positive surgical margins, positive lymph nodes, poor tumor response grade, and transmural disease benefit from RT.

The most interesting direction is in the use of neoadjuvant CRT, to follow the treatment trend set by other gastrointestinal cancers, mainly esophageal and rectal cancer. While there have been phase I/II trials determining the feasibility of neoadjuvant CRT, the results of the in-progress phase III TOPGEAR and CRITICS-II trials are awaited to determine if there is any oncologic benefit to treating these patients with incorporation of neoadjuvant CRT. In unresectable, non-metastatic gastric cancer, limited data shows a benefit of definitive treatment, although utilization patterns are not ideal.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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