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Radiation Therapy in the Treatment of Resectable Locally Advanced Gastric Adenocarcinoma: Present and Future

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Introduction

In the United States, patients with Gastric Adenocarcinoma (GA) confined to the stomach have a 5 year overall survival (OS) rate of approximately 67% which is reduced to 31% and 5% with nodal or distant metastatic spread, respectively [1]. The theory of adding radiation therapy (RT) to gastrectomy for improved local control is bolstered by the fact that, classically, up to 88% of resected patients will have a locoregional component of failure with 29% having locoregional failure only following surgery alone with rates dropping only modestly to 53% and 16% with the addition of adjuvant chemotherapy [2,3]. Despite this, the utility of RT in GA remains relatively unresolved despite multiple associated clinical trials (Table 1). In this review, we seek to discuss the literature underlying current treatment practice and ongoing studies with particular focus on the role of RT in resectable locally advanced disease.

Neoadjuvant Treatment

The concept of neoadjuvant chemoradiotherapy (CRT) in GA remains largely unresolved. The potential for neoadjuvant RT to provide locoregional benefit is arguably greater than that potentiated after surgery due to the fact that 1) patient performance status is often better prior to gastrectomy and thus completion of treatment is likely to be greater, 2) preoperative RT may sterilize the surgical field and thereby decrease risk of peritoneal seeding during resection, 3) the RT fields are smaller prior to gastrectomy than that for postoperative RT, therefore lead to less RT side effects and 4) providing nonsurgical treatment upfront may allow for the clinical presentation of initially micrometastatic disease, thereby allowing these patients to avoid surgical morbidities. Despite this, little data currently exists regarding neoadjuvant RT in GA with only 2 trials currently reported, both with concurrent chemotherapy and favorable results. In 2006 the Phase II RTOG 99-04 demonstrated that, in 43 assessable patients, a neoadjuvant regimen consisting of 2 cycles of cisplatin/5-FU followed by RT to 45 Gy with concurrent 5-FU/paclitaxel resulted in a 77% rate of R0 resection with 26% of patients achieving a pathologic complete response [4]. It was noted that one year OS was better in those who received a pathologic complete response to the neoadjuvant therapy. Further, post-operative morbidity was noted to be low following this regimen with only two patients suffering > grade 3 radiation toxicity, one skin and one esophagus, and five patients suffering > grade 3 toxicity due to surgery. More recently, a German study comparing 2.5 cycles of neoadjuvant cisplatin/5-FU to 2 cycles of cisplatin/5-FU followed by neoadjuvant RT to 30 Gy with concurrent cisplatin/etoposide revealed that the arm including neoadjuvant CRT resulted in increased rates of pathologic complete response, N0 nodal disease, and a near significant trend towards improvement in three-year OS (47% versus 28%, p=0.07) [5]. While post-operative morbidity was not specifically commented on in this study, perioperative mortality, length of ICU stay, and time to discharge were not significantly increased with the addition of radiation therapy.

With these favorable results and the significant promise of neoadjuvant RT, more robust clinical trials are needed to assess neoadjuvant RT in resectable gastric cancer patients. However, to our knowledge no such trials are currently in the accruing or pre-accrual phase.

Adjuvant Treatment

CRT in the adjuvant setting for GA is much better studied relative to that of neoadjuvant treatment though also remains somewhat inconclusive. Intergroup INT-0116 trial randomized 556 patients to observation versus adjuvant RT to a dose of 45 Gy with concurrent 5-FU followed by 2 additional cycles of bolus 5-FU in patients who had undergone an R0 resection for T2-4 or node-positive GA. At both initial and long-term follow-up, this trial demonstrated a significant improvement in both relapse-free survival (HR=1.51) and OS (HR=1.32) in patients receiving

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Table 1: Select clinical trials assessing the role of radiation therapy in gastric adenocarcinoma.

Trial	Arms	N	Disease-Specific Outcomes	Overall Survival	Notes
Neoadjuvant					
RTOG 9904 [4]	1) cisplatin/5FU x 2c → 45Gy/cisplatin/placlitaxel → resection	43	R0 resection: 77% pCR: 26%	Median: 23.2 m 1y OS: 72%	Improved 1y OS with pCR (82%)
Stahl et al. [5]	1) cisplatin/5FU x 2c → 30Gy/cisplatin/etoposide → resection 2) cisplatin/5FU x 2.5c → resection	126	R0 resection: 71.5% vs. 69.5 (p>0.05) pCR: 15.6% vs. 2.0% (p=0.03) pN0: 64.4% vs. 37.7% (p=0.01)	3y OS: 47% vs. 28% (p=0.07)	Arm 1 had non-significant trend toward increased post-operative mortality (p=0.26)
Adjuvant					
INT-0016/ SWOG 9008 [6]	1) resection → 45Gy/5FU → 5Fu x 2c 2) Resection → observation	556	DFS: HR=1.51 (p=<0.001)	HR=1.32 (p=0.0046)	-No benefit if diffuse histology -Possibly no benefit if HER2 amplified[38]
ARTIST [7,8]	1) resection → capecitabine/cisplatin x 2c → 45Gy/ capecitabine → capecitabine/cisplatin x 2c 2) resection → capecitabine/cisplatin x 6c	458	DFS: HR=0.74 (p=0.09) LRF: 7% vs. 13% (p=0.003) DFS (N+): HR=0.70 (p<0.05) DFS (intestinal): HR=0.44 (p<0.05)	HR=1.130 (p=0.53)	-HER2 non-amplified patients had near-significant improved DFS (HR=0.75, 95% CI=0.53-1.05)
HeCOG [10]	1) resection → docetaxel/platinum x 3c → 45Gy → docetaxel/ platinum x 3c 2) resection → docetaxel/platinum x 6c	147	PFS: 33.1 m vs. 37 m (p>0.05) 3y PFS: 48% vs. 51% (p>0.05)	Median: 44.5 m vs. 55.3 m (p>0.05) 3y OS: 57% vs. 61% (p>0.05)	-54% of patients received less than D1 resection -32% had diffuse histology
CRITICS [13]	1) epirubicin/platinum/capecitabine x 3c → resection → 45Gy/ cisplatin/capecitabine 2) epirubicin/platinum/capecitabine x 3c → resection → epirubicin/platinum/capecitabine x 3c	788	Not yet reported	5y OS: 40.9% vs. 41.3% (p=0.99)	-only 52% of patients in Arm 1 received radiation treatment

pCR: Pathological Complete Response; OS: Overall Survival; pN0: Pathologically without Nodal Disease Involvement Upon Surgical Resection; DFS: Disease-free Survival; LRF: Locoregional Failure; PFS: Progression-free Survival

adjuvant CRT with benefit present in all patients except those with diffuse histology [6]. Following these results, several trials were conceived to assess if the improved outcomes described in INT-0116 were attributable to CRT or simply represented improvement with adjuvant treatment following <D2 surgical resection [No nodal dissection (D0), resection of both greater and lesser omenta (D1) and nodal stations around the anterior portion of the common hepatic artery and celiac axis (D1+)]. The ARTIST trial randomized 458 patients following D2 (comprises a D1+ dissection with further dissection along the left gastric artery, splenic hilum, and splenic artery) gastrectomy to 6 cycles of capecitabine/cisplatin or 4 cycles of the same chemotherapy sandwiched with CRT, consisting of 45 Gy with concurrent capecitabine, between cycles 2 and 3. While this study did not demonstrate improved outcomes within the RT arm, subgroup analyses indicated a superior DFS in patients with pathologically involved nodal disease (HR=0.69) and intestinal-type histology (HR=0.44) as well as better regional nodal control following the addition of RT [7-9]. The Greek HeCOG trial, however, failed to demonstrate improved outcomes with the addition of RT (45 Gy) to 6 cycles of adjuvant docetaxel/platinum in patients with T3-4 or node-positive GA [10]. Of note, 89% of included patients had nodal disease involvement but over half (54%) underwent less than a D1 dissection and 32% had diffuse histology.

Despite disappointing results from the ARTIST and HeCOG trials, the question of adjuvant RT in GA is not resolved. While current data indicates that adjuvant RT may not be beneficial to some patients, specifically those without nodal involvement or with diffuse histology, there are significant subsets of patients who appear to derive benefit in at least DFS. As such, future study into adjuvant RT must become less of a "yes/no" question and evolve more towards a personalized medicine approach using patient and disease factors to adjust treatment recommendations. In this vein, the currently enrolling ARTIST-II trial seeks to assess DFS in patient treated with 8 cycles of S1, 8 cycles of S1 with concurrent oxaliplatin, or 6 cycles of S1/oxaliplatin sandwiched with CRT (45 Gy with concurrent S1) provided after cycle 2 in node-positive patients following D2 gastrectomy. This trial is estimated to complete in 2020 with a goal for accrual of 900 patients [11].

Perioperative Therapy

The role of RT in patients who receive perioperative chemotherapy with epirubicin, cisplatin, and infused fluorouracil (ECF) per MAGIC trial is currently in its infancy [12]. Recently, the CRITICS trial compared MAGIC-like perioperative chemotherapy, consisting of 3 cycles of epirubicin, platinum (cisplatin or oxaliplatin), and capecitabine before and after surgical resection to a similar regimen but with the adjuvant chemotherapy replaced by adjuvant CRT to 45 Gy with concurrent cisplatin and capecitabine. While we still await final results from this study, preliminary results as presented at ASCO 2016 indicate a near identical 5-year OS between the two study arms (p=0.99) though it is noteworthy that only 52% of patients randomized to the CRT therapy arm received RT [13]. Another such trial which is currently accruing patients, TOPGEAR, seeks to assess the addition of CRT (45 Gy with concurrent 5-FU) to perioperative ECF. Specifically, patients will be randomized to receive either 3 cycles of ECF or 2 cycles of ECF followed by CRT prior to resection. All patients are required to undergo at least a D1 resection and are to be treated with 3 cycles of adjuvant ECF. Total patient accrual is estimated for 752 with expected completion in 2020 [14]. Earlier this

year, interim results of the first 120 patients were reported though without any outcome data included. As expected, in the neoadjuvant setting the majority of patients (92%) completed their course of CRT with 85% of these patients successfully undergoing surgical resection (versus 90% in the ECF alone arm). While only 53% of patients in the CRT arm were able to complete all cycles of adjuvant ECF, this was not dissimilar to patients in the chemotherapy only arm (65%), indicating that the addition of neoadjuvant RT does not add significantly to treatment-related morbidity over perioperative ECF alone [15].

Future Directions

Despite multiple trials investigating RT in GA, much work yet to be done. While we await the final results of CRITICS, TOPGEAR, and ARTIST-II in the perioperative and adjuvant settings, there is still much room for further study into various treatment schemes. Particularly in light of the encouraging results of the two reported neoadjuvant trials, we encourage neoadjuvant RT to be more thoroughly analyzed, possibly with altered concurrent or induction treatments and consideration of non-conventional fractionation and treatment volumes. Additionally, investigation into the role of immunotherapy in GA is also an exciting direction of future study. One such representative trial, PROCEED, is a single arm study in which patients with adenocarcinoma of the stomach, GEJ, or esophagus will receive neoadjuvant RT(45 Gy) with concurrent carboplatin/paclitaxel and pembrolizumab with an additional 3 cycles of pembrolizumab provided adjuvantly. This study is set to open in May, 2017 with estimated completion in 2021 [16].

Conclusion

Treatment of GA remains challenging with between 50%-80% of patients succumbing to their disease within 5 years. Current standard of care is surgical resection with perioperative chemotherapy or adjuvant CRT for locally advanced stages. Information regarding prognostic and predictive factors with various therapeutic regimens, as well as the role of immunotherapy, are sure to come to light in the coming years with treatment schemes becoming increasingly complicated as we advance towards more personalized care in patients diagnosed with this malignancy.

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