Review Article

Postoperative chemoradiotherapy *vs*. preoperative chemoradiotherapy for locally advanced (operable) gastric cancer: clarifying the role and technique of radiotherapy

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Background: Worldwide, almost one million new cases of stomach cancer were diagnosed in 2012, making it the fifth most common cancer, and the third leading cause of cancer deaths. The current tumor node metastasis (TNM) staging system represents a consensus between the East and the West, and will serve as a strong foundation upon which to build future evidence. In this review article, we first discuss the definition and optimal surgery for locally advanced gastric cancer, followed by the general principles when considering a pre *vs*. postoperative radiotherapy (RT) strategy. We then provide a synthesis of the existing randomized trial evidence in an attempt clarify the role of pre and postoperative RT in the management of locally advanced gastric cancer.

Methods: A Medline search 1966-Jun 2014 was undertaken. Randomized trials including patients with locally advanced gastric cancer (using established definitions), comparing RT [with or without chemotherapy (CT)], with surgery alone or other treatment modalities were included. Systematic reviews and evidence based practice guidelines that include this body of primary studies were preferentially discussed. Medline, Cochrane Library, Clinicaltrial.gov, Guidelines Clearinghouse were searched.

Results: Sixteen randomized trials, three systematic reviews and one practice guideline were included as the evidence base. In this group of studies, two reports compared postoperative chemoradiotherapy (CRT) with surgery alone. Driven predominantly by INT0116, they established the role of postoperative CRT to provide a survival benefit in a patient group that underwent surgery with predominantly D0-1 dissections. Preoperative RT (four studies) showed promise for survival benefit but the risks of bias in these trials were high. Postoperative CRT compared with CT alone (eight trials) showed no survival benefit with the addition of radiation although some evidence of activity can be observed with improved local regional control.

Conclusions and future directions: Technical expertise to enable the delivery of high quality RT to complex target volumes as is required in gastric cancer, and surgical standards to ensure the delivery of high quality surgery, have matured in recent years. Six trials with large sample sizes are currently ongoing to better define the role of preoperative CRT (two studies) and postoperative CRT (four studies), when used in conjunction with high quality surgery and RT, and contemporary CT regimens. The moderate likelihood of locoregional recurrences and the favorable therapeutic ratio with using RT preoperatively in other settings, provide optimism that preoperative CRT would have a pivotal role to play in locally advanced gastric cancer. Active accrual into ongoing trials is strongly encouraged.

Keywords: Gastric cancer; radiotherapy (RT); multimodality; locally advanced cancer

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Introduction

Worldwide, almost one million new cases of stomach cancer were estimated to have occurred in 2012, making it the fifth most common cancer, and the third leading causing of cancer deaths (1). The 7th edition of the tumor node metastasis (TNM) staging system, revised based on the evidence that exists around prognostic factors and current treatment strategies, emphasizes the importance of depth of invasion and the number of locoregional nodes involved as major prognostic factors. For the first time, this represents a consensus approach of Eastern and Western countries (2,3). To facilitate reporting and provide guidance for patients with gastroesophageal (GE) junction cancers, they are now classified under esophageal cancer, although it is important to remind ourselves that many clinical trials designed for gastric cancers include a significant proportion of GE junction tumors and many esophageal cancer trials also included some proximal gastric cancers, complicating the interpretation of the literature and its application in clinical practice.

There are many heterogeneous subgroups under the broad heading of gastric cancers. Tumors arising from different anatomical locations have access to different routes of spread. Tumors with different histological (e.g., diffuse *vs*. others) and molecular [e.g., human epidermal growth factor receptor-2 (HER2)] (4) characteristics have different etiology (5), prognosis (4,6), and response to therapy (7). Patients from Asia, North America and Europe differ in terms of their toxicity profiles and response to treatments (8).

The objective of this review is to provide the rationale, evidence and technical considerations comparing the use of pre and postoperative radiotherapy (RT) in gastric cancer.

What is locally advanced gastric cancer?

While what constitutes early gastric cancer is relatively well defined (9), there is considerable variability in what is considered locally advanced disease. DE Sol *et al*. (10) provided a summary of definitions extracted from recent trials highlighting this variation. A minority of authors use the term to describe the locoregional extent of disease irrespective of whether distant disease is present, while the more common approach refers to patients with no evidence of metastatic disease (M0), where invasion of muscularis and beyond is present, with or without nodal involvement. For example, the pivotal randomized trial reported by Macdonald *et al*. (11) in the management of gastric cancer that resulted in the generalized adoption of postoperative chemoradiotherapy (CRT) employs the definition of stage Ib-IV (M0) as advanced cancers.

For the majority of investigators, the term locally advanced gastric cancer is a general term that is used to describe patients with a modest survival with surgery alone. For the purpose of this review, we will focus our deliberations with this definition in mind, where the risk of recurrence would justify the use of adjuvant or neoadjuvant therapies. In TNM terms, patients with locoregional disease, with T stage of submucosal involvement or higher or node positive disease (T2-4, N1-3, M0; TNM v7) are being staged as locally advanced gastric cancer, with a five-year overall survival (OS) rate following complete resection in the range of 57% (3).

Anatomical definition of lymph node stations for gastric cancer was described by the Japanese Gastric Cancer Association and has been widely adopted. Nodal stations 1-12 (1: paracardial nodes to 12: hepatoduodenal ligament nodes) and 14v (lymph nodes along inferior mesenteric vein) are defined as regional gastric lymph nodes, while metastasis to any other nodes are classified as M1 (12). While the prognostic value of the number of involved nodes is of critical importance, the anatomic extent of metastatic nodes also conveys prognostic significance, with extra-perigastric nodal stations conveying a worse prognosis than the perigastric nodes (13,14).

What is optimal surgery?

A discussion on the role of neoadjuvant or adjuvant therapy is incomplete without a brief consideration of the clinical impact of the type and extent of surgery, the central curative modality for patients with gastric cancer. While the fundamental surgical principles of achieving a complete resection with negative margins, and the more recently adopted quality indicator of a minimum of nodes resected (e.g., 16) (15) are uniformly accepted, significant variations in approach exist in other areas of surgical decision-making.

The extent of gastric resection is based on oncologic principles. The location, extent and type of gastric cancer will dictate the extent of resection. Diffuse type cancers require a total gastrectomy, regardless of the location of the gross tumor. Total gastrectomy is required for large tumors or tumors of the lesser curve or body of the stomach. Antral cancers may be adequately resected with a distal gastrectomy if a 5 cm margin can be achieved. Proximal

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gastric cancers are generally resected by a total gastrectomy because of the poor functional result due to intractable reflux esophagitis when the distal stomach is anastomosed to the esophagus. Locally advanced proximal cancers often require resection of the spleen and tail of pancreas because of direct extension of the primary tumor. If the tumor involves the distal esophagus, a 5 cm margin or more on the esophagus is required to reduce anastomotic recurrences. Rarely, a proximal gastrectomy with reconstruction using a short segment of pedicle jejunum is used for small tumors of the proximal stomach, allowing preservation of the antrum.

The major factor of ongoing debate is the extent of lymph node dissection. D1 dissection generally describes the removal of nodal stations 1-7 (perigastric nodes including pericardial, lesser curvature, greater curvature, supra and infrapyloric, along the trunk of L gastric artery) while D2 dissection refers to the removal of lymph node stations up to 12 (D1 and splenic hilar, hepatoduodenal ligament) (12). The effect of an extended lymphadenectomy provides greater clearance of locoregional nodes and potentially better sampling of the nodes. Extended *vs*. limited (D2 *vs*. D1) dissections were compared in several randomized trials and summarized most recently using a systematic review by Jiang *et al*. (16). Data from eight randomized trials conducted in Asia, Europe and Africa involving over 2,000 patients were included. Five-year OS was similar between the two approaches. However, postoperative mortality rates were significantly higher for patients treated with D2 dissection [D2 *vs*. D1, 18% *vs*. 11%; relative risk (RR) 0.58, 95% confidence interval (CI): 0.47-0.71]. Other morbidities (e.g., anastomotic leak, pancreatic leak, reoperation rates, wound infection, pulmonary complications and postoperative mortality) all favored D1 dissection, (D2 *vs*. D1, 37% *vs*. 21%; RR 0.62, 95% CI: 0.5-0.76), while perioperative hemorrhage risks were equivalent. Subgroup analysis would suggest that D2 dissection, without spleen and pancreas resection, is better tolerated with a trend towards lower gastric cancer mortality (D2 *vs*. D1, 41% *vs*. 48%; RR 1.19, 95% CI: 0.98-1.44).

Notwithstanding these conclusions, the modest cure rate achievable for most locally advanced cancers despite complete surgical resections (R0), the desire to optimize surgery by adhering to sound oncological principles, the subgroup data that suggest superior survival when D2 dissection is used (without routine splenectomies and pancreatectomies) provide the justification to advocate for gastrectomy with D2 dissections, in expert hands, as the optimal surgical standard. Indeed, using a RAND/UCLA appropriateness study design, an expert panel considered D2 lymphadenectomy in all patients with tumors >T1N0. The panel also found the use of total gastrectomy for all patients and distal gastrectomies for patients with distal gastric cancers as appropriate (17).

Whether the factors leading to variations in surgical decisions were related to patient comorbidities, tumor extent or surgical expertise, different quality and extent of surgery is expected to have an impact on survival, treatment related morbidity and mortality and postoperative functional status. For patients with significant morbidities in the postoperative setting, many would not be suitable for additional adjunctive therapies even if there were indications to consider them. Judicial use of prognostic factors and clinical experience is the cornerstone for choosing the best approaches for individual patients.

What is the role of RT?

RT, a locoregional treatment, is likely to be most impactful if there is a significant risk of local regional recurrence despite optimal surgery. This may occur as a result of seeding of the tumor bed, challenges in achieving good resection margin clearance, or microscopic residual lymphatic involvement. The rationale for the optimal timing of RT, pre *vs*. postoperative, and the optimal way of combining systemic therapies with RT hinges on a complex relationship between the modalities, additive or synergistic, and the effect on anticipated toxicities and relative therapeutic ratio. These factors will be discussed in the following section, followed by a discussion of the existing evidence, and ongoing trials.

How effective is the state of the art surgery in securing local control?

Locoregional recurrence rates are often subject to detection and reporting biases. They are most likely to exist when locoregional recurrence pattern is not planned as an important outcome and where follow-up practices are not standardized. Consequently, some studies report on the site of first recurrence only, while others on recurrences at any time if they were followed. Geographic misses in relation to the extent of surgery, and the extent of RT, is labor intensive and generally not available to guide modifications on treatment delivery. Notwithstanding these biases, locoregional recurrence rates in the surgery alone arm are on the order of 20% (18) to 70% (19) depending on the

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Table 1 Pattern of recurrence following surgery alone (selected randomized trials)

RCTs	N	Local regional recurrence	
Hartgrink *et al*. (Dutch) (20)	D2 *vs*. D1 dissection	D2	D1
	331 *vs*. 380[†]	31.8% (95/299)	42.2% (154/365)*
Zhang *et al*. (21)	Preoperative RT *vs*. surgery alone	Preoperative RT	Surgery
	171 *vs*. 199	38.6%	51.7% (P<0.025)
Cunningham *et al*. (18)	Preoperative CT *vs*. surgery alone	Perioperative CT	Surgery
	250 *vs*. 253	14.4% (36/250)	20.6% (52/253)[§]
Macdonald *et al*. (19,22)	Postoperative CRT *vs*. surgery alone	Postoperative CRT	Surgery
	120 *vs*. 177	65.0% (78/120)[∫]	71.8% (127/177)

[†], Number achieving curative resection; *, denominator equals total treated curatively minus postoperative deaths; [§], denominator equals patients assigned to the group; [∫], patients could have relapses at multiple sites, total number of relapses greater than number of patients. RCT, randomised controlled trial; RT, radiotherapy; CT, chemotherapy; CRT, chemoradiotherapy.

Table 2 Pros and cons of pre *vs*. postoperative radiotherapy

Factor	Preoperative	Postoperative
Patient population	Decision based on clinical staging	Decision based on pathological staging
Toxicity burden	Toxicity of preoperative therapy may preclude surgery	Toxicity of surgery may preclude the use of postoperative therapy
Timing of surgery	Need to be delayed until completion of surgery	For all patients as first modality
Treatment volume	Generally smaller	Generally larger
Dose effect	Require less dose for the same local control benefit	Require more dose for the same local control benefit

quality and extent of the surgery. Even if we restrict our focus to trials with a high compliance for D2 dissections, locoregional recurrence remains a significant problem with a range of 32-42% (20). This pattern of locoregional recurrence would suggest a high potential that RT can have a major role in optimizing the management of patients with locally advanced gastric cancer (*Table 1*).

Pros and cons of pre *vs*. postoperative RT—general principles

The issue of whether RT is best employed in the preoperative or postoperative setting [with or without chemotherapy (CT)] has been the subject of debate in the management of many cancers such as rectum (23), sarcoma (24), and esophageal cancer (25) to name a few. Some general principles apply (*Table 2*).

The accuracy of clinical staging, typically based on diagnostic tests, plays an important role in identifying the appropriate patients for preoperative therapy, avoiding over treatment of early stage patients and the futile use of curative strategies in those who are harboring more advanced metastatic disease. For gastric cancer patients, the use of gastric protocols in the CT acquisition, incorporation of endoscopic ultrasound, laparoscopy and peritoneal washings are practices that are increasingly sophisticated to allow accurate preoperative staging.

The toxicity burden of multimodal therapies may differ based on the symptom profile and premorbid condition of the patient. Careful consideration of patients' baseline condition and suitability for combined modality is necessary to avoid unacceptable treatment related morbidity and mortality. Borderline patients taken through preoperative therapy may delay or preclude the definitive surgery. Some patients with acute complications from the primary (e.g., uncontrolled bleeding, obstruction) demand immediate surgery even if preoperative therapy may have a role to play. Postoperative therapy typically needs to be given within a finite period following surgery (e.g., 10 weeks) beyond which the anticipated benefits are expected to diminish.

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Table 3 Summary of randomized trials, systematic reviews and meta-analysis comparing pre or postoperative (CT) RT with other strategies

RCT	Number of studies	References
Postoperative CRT *vs*. surgery alone	2	(22,26)
Preoperative RT *vs*. surgery alone	4	(27-29,46)
Postoperative RT *vs*. postoperative CT	1	(30)
IORT *vs*. surgery	1	(31)
Postoperative CRT *vs*. postoperative CT	8	(32-39)
Systematic reviews and meta-analyses	4	(40-43)
Guidelines	1	(44)

RCT, randomised controlled trial; CRT, chemoradiotherapy; RT, radiotherapy; CT, chemotherapy; IORT, intraoperative radiotherapy.

In the original Macdonald trial 17% of patients stopped treatment because of toxicity, while major (≥ grade 3) toxicity occurred in 33% of patients.

The design of the RT target volume requiring treatment is generally smaller in the preoperative setting. The presence of the tumor typically displaces and minimizes the need to encompass normal structures (e.g., small bowel). In contrast, postoperative treatment typically requires inclusion of normal structures that would fill to original tumor site, and difficult to avoid when the tumor bed needs to be included. Surgery can open previously uninvolved planes that become potential routes of spread. Anastomosis and reconstructions may result in regions of interest located adjacent to sensitive structures (e.g., duodenal blind loop and its relationship to the L kidney, esophagogastric anastomosis), requiring expansion of treatment fields or suboptimal coverage of critical structures.

Finally, preoperative strategies generally require lower doses to achieve the same local control effect, with obvious benefits on the long term anticipated effect following treatment. This phenomenon is likely attributable to the increase in hypoxic tissues in the postoperative state.

What is the evidence?

In an attempt to clarify the role of RT for gastric cancer, for the purpose of this review, emphasis is placed on randomized trials that target the current definition (TNM 7th edition) of gastric cancer. Where GE or esophageal cancers represent >30% of the participants, the trials were excluded (unless subgroup data is available for gastric cancers). Similarly, systematic reviews, and meta-analyses that collate the evidence that emphasizes this body of primary studies are preferentially discussed. Clinicaltrial.gov was search for ongoing trials. Medline and Cochrane databases were searched. Guidelines Clearinghouse was searched for current evidence based guidelines (last searched Jun 2014).

A total of 16 randomized trials (11,21,26-39), four systematic reviews (40-43) addressing the role of RT in gastric cancer were identified with the most recent one published in 2014 (40). A single practice guideline (44) that is relevant to our question is listed under the National Guidelines Clearinghouse (45) and is included. A summary of the relevant references in the different study designs is included (*Table 3*).

Preoperative RT vs. surgery alone (Tables 4,5)

Preoperative RT is the subject of investigation in four randomized trials. The studies were performed in Russia, Ukraine and China and published between 1994 and 2002. The quality of reporting is generally poor with limited information on the quality of the surgery, adequacy of nodal dissection and extent of tumor involvement especially when contrasted against contemporary standards. With the exception of the study from China with a sample size of 370 patients, the studies were small (and likely underpowered). None of the studies provided a justification for the sample size design. The dose fractionation used was hypofractionated (2 Gy in 5 fractions) with the addition of intraoperative RT. In one (28), and the addition of hyperthermia in another study (29). The study from China employed a dose fractionation of 40 Gy in 20 fractions. The techniques used were all simple with anterior posterior *vs*. posterior anterior beam arrangement (APPA) techniques to upper abdominal fields that have generally been replaced by more sophisticated planning techniques.

Notwithstanding the significant risk of bias inherent within these trials, the study by Zhang *et al*. (21), the largest within this group, observed a survival benefit of approximately 7% (10 years OS: 20% preoperative RT *vs*. 13% surgery alone; P<0.05), using a modest dose of 40 Gy in 20 fractions.

A meta-analysis performed by Fiorica *et al*. (41) in

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Table 4 Randomized trials comparing preoperative RT *vs.* surgery alone—study characteristics

Author	Year	Site	Eligibility	Characteristics	N		Surgery	Study arm		
					Preoperative RT	Surgery alone		RT dose	RT volume	Technique
Skoropad (27)	2002	Russia	Stomach Ca Adenocarcinoma	Esophagus involvement 22 preoperative RT, 16 surgery Diffuse NA SII/IV: 31 preoperative RT, 33 surgery R0 not stated, R1 preoperative RT 3, surgery 4 D1 100% Total gastrectomy 27 preoperative RT, 20 surgery No. nodes removed: NA No. nodes involved: NA	77 [51][§]	75 [51][§]	D1 dissection*	20 Gy in 5 fractions	Whole stomach, regional nodes along curvatures, celiac axis and branches 20×20 cm^2 field size with no shielding	APPA
Skoropad (28)	2000	Russia	Stomach Ca (esophageal involvement <3 cm included) Adenocarcinoma	Esophagus involvement not stated Diffuse NA T3-4 20 preoperative RT, 21 surgery N+ 17 preoperative RT, 13 surgery R0 not stated R1 3 preoperative RT, 3 surgery D1 100% Total gastrectomy 19 preoperative RT, 16 surgery No. nodes removed: NA No. nodes involved: NA	59 [40][§]	53 [38][§]	D1*	Preoperative RT 20 Gy in 5 fractions and IORT 20 Gy in 1 fraction	Preoperative RT: primary tumor and regional nodes (10×12 to 14-16 cm fields) IORT: tumor bed and celiac axis approximate 6-10 cm field	APPA (Co60) IORT: direction electron beam (8-22 MeV)
Zhang (21)	1998	China	Stomach Ca (cardia)	Esophagus involvement not stated Diffuse NA (one case SCC) SIII/IV preoperative RT 71.2% surgery 89.4% R0 not stated D2 not stated Total gastrectomy: NA No. nodes removed: NA No. nodes involved: NA	171	199	NA	40 Gy in 20 fractions	Cardia, lower segment of esophagus, fundus, lesser curve, hepatogastric ligament, superior border at 4-5 cm from cranial extent of tumor	APPA
Shchepotin (29)	1994	Ukraine	Stomach Ca	Esophagus involvement not stated Diffuse NA T2,3,4: 3%, 65%, 32% N+: 65% R0 not stated D1 not stated Total gastrectomy: 51% No. nodes removed: NA No. nodes involved: NA	98 preoperative RT 96 preoperative RTHT	100	NA	20 Gy in 5 fractions HT: tumor temperature to 42 ℃ daily ×4 days, 2 hours postoperative RT	Not specified	APPA

[§], patients were randomized to be explored, and if curative resection possible, to receive protocol treatment. Numbers in square brackets are patients eligible after exploration; *D1, complete dissection of perigastric nodes in all patients; RT, radiotherapy; Ca, cancer; NA, not available; R1, positive resection margins; APPA, anterior posterior *vs.* posterior anterior beam arrangement; IORT, intraoperative radiotherapy; SCC, squamous cell carcinoma; RTHT, radiotherapy and hyperthermia.

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Table 5 Randomized trials comparing preoperative RT *vs.* surgery alone—outcomes

Author	Year	N[†]		FU	OS[¶]			Regional RFS			Toxicity[‡]		
		RT + surgery	Surgery	Median	RT + surgery	Surgery	P	RT + surgery	Surgery	P	RT + surgery	Surgery	P
Skoropad (27)	2002	77 [51][§]	75 [51][§]	NA	5-year: 59%, 10-year: 32%	5-year: 30%, 10-year: 18%	NS	NA	NA	–	Percentage with complications: 57%	Percentage with complications: 49%	NS
Skoropad (28)	2000	59 [40][§]	53 [38][§]	NA	5-year: 50%	5-year: 50%	NS	NA	NA	–	Percentage with complications: 35%	Percentage with complications: 50%	–
Zhang (21)	1998	171	199	10.6 years	5-year: 30%, 10-year: 20%	5-year: 20%, 10-year: 13%	<0.01	5-year 38.6%	5-year 51.7%	<0.025	Operative death: 1%, anastomotic leak: 1.8%	Operative death: 2.5%, anastomotic leak: 4%	NS NS
Shchepotin (29)	1994	98 preoperative RT, 96 preoperative RTHT	100	NA	5-year: 45% (preoperative RT), 51% (preoperative RTHT)	5-year: 30%	<0.05	NA	NA	–	NA	NA	–

[†], none of the studies provided a sample size justification; [¶], none of the studies provided RFS as an outcome of interest; [‡], not all toxicity data presented are represented, only key representative parameters presented; [§], patients were randomized to be explored, and if curative resection possible, to receive protocol treatment. Numbers in square brackets are patients eligible after exploration. RT, radiotherapy; FU, 5-fluorouracil; OS, overall survival; CI, confidence interval; RFS, relapse free survival; NA, not available; NS, not specified; RTHT, radiotherapy and hyperthermia.

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2007 provided summary statistics across the relevant trials showing a survival benefit with RT alone with a odds ratio (OR) 0.54, 95% CI: 0.43-0.68 (41). A more recent update by Pang *et al*. in 2014 using a different set of selection criteria arrived at a similar observation and conclusions (40).

While the primary preoperative RT studies were conducted with less sophisticated RT techniques and quality of surgery, the observation remains potentially compelling that modest doses of local regional RT delivered prospectively can complement surgery to provide a survival advantage. It is tantalizing to hypothesize that with optimal combination quality surgery and CT; more significant gains can be accomplished.

Postoperative CRT vs. surgery

The pivotal postoperative CRT *vs*. surgery trial (INT0116) was first reported by Macdonald *et al*. (11) resulting in the general adoption of postoperative CRT in addition to surgery as the standard treatment for gastric cancer in North American and Europe. Updated results were subsequently published (22) with a median follow up of more than 10 years, confirming the original observation of OS benefit of 9% with a hazard ratio (HR) 1.32 (95% CI: 1.1-1.6; P=0.0046). Relapse free survival (RFS) was 11% with a HR of 1.51 (95% CI: 1.25-1.83; P<0.001). The pattern of recurrence, with 24% fewer relapses occurring in patients in the CRT arm, confirmed the degree of benefit predicted through the original pattern of failure analysis by Gunderson *et al*. in 1982 (47). Subgroup analysis showed patients with diffuse histology (typically associated with poorer prognosis occurring in younger, female patients) appear to benefit less, while patients with more nodes (N4+ *vs*. others) derived greater benefit. The authors suggested extreme caution in their interpretation given the small numbers within some of the subgroups (22). Moertel *et al*. (48) also in this category is of historic interest only and is not discussed further.

Postoperative RT vs. postoperative CT

Hallissey *et al*. (30) reported on the second British stomach cancer trial comparing postoperative RT alone with postoperative CT. Patients were randomized to one of three arms, surgery alone, postoperative RT (45 Gy in 25 fractions, boost 5 Gy) *vs*. postoperative CT [mitomycin, doxorubicin and 5-fluorouracil (5FU)]. Proportion of patients with GE junction tumor was not stated. No survival advantage can be seen for 5 years OS (surgery *vs*. pRT *vs*. pCT: 20% *vs*. 12% *vs*. 19%).

Postoperative CRT vs. postoperative CT (Tables 6,7)

Six studies were designed to examine the incremental role of RT when added to postoperative CT and is the most frequently studied strategy in recent years, with four published in 2012 and two in 2010. In four of the studies, only patients who had a D2 dissection were included (32,33,35,37). Similarly, the RT used was most consistent with contemporary practice. All studies used a dose fractionation of 45 Gy in 25 fractions. All studies employed treatment targets consistent with standard practice (anastomosis, duodenal stump, local regional nodes, residual stomach, and tumor bed) with some modifications. Kim (32) and Lee (33) and Kwon (32,33,37) all excluded tumor bed treatments with the exception of T4 lesions. Coverage of the stomach remnant is more flexible permitting variations in favor of reducing dose to normal structures (e.g., kidneys). Two studies used intensity-modulated radiation therapy (IMRT) (34,35), one conformal RT (37) while three used older techniques (APPA) (32,33,36).

The different CT regimens used and the discussion around the optimal one is presented in the next section.

All but one study was underpowered. Three studies closed prematurely and lack the power to detect the difference they were looking for (32,36,37) and two (34,35) were small and almost certainly also underpowered. The ARTIST trial reported by Lee *et al*. (33) was the only study that successfully completed accrual and dominated this group of studies with 458 participants. It also suffered from sample size issues, with an unexpectedly high proportion of earlier stage tumors resulting in a lower event (recurrence) rate than anticipated.

There is some evidence to support improvements in local regional control (32,35) although the largest study (ARTIST) (33) did not find this benefit. While local regional control was extremely high (92% CT, 95% CRT) in the ARTIST trial, local RFS ranged from 63% CT to 84% CRT supporting the potential in improving outcomes by RT. No difference in survival, RFS and local regional relapse free was observed.

Choice of systemic regimen

5FU has been the mainstay chemotherapeutic agent when

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Table 6 Randomized trials comparing postoperative CRT *vs.* postoperative CT—study characteristics

Author	Year	Site	Eligibility	Characteristics*	N		Surgery	Control arm		Study arm		
					CRT	CT		CRT	CT	RT dose	RT volume	Technique
Kim (32)	2012	Korea	Stomach Ca (no GE jc) Adenocarcinoma SIII-IV (M0) AJCC 2002 R0 D2	No GE jc Diffuse: 56% T2,3,4: 59%, 57%, 7% R0: 100% D2: 100% Total gastrectomy: 51% Nodes removed (mean): 41 CT, 46.5 CRT Nodes involved (mean): 9 CT, 8 CRT	46	44	R0 D2	FL	FL	45 Gy in 25 fractions	Standard RT except —tumor bed for T4 only —modifiy stomach remnant coverage to maintain renal tolerance	APPA
Lee (33) (ARTIST)	2012	Korea	Stomach Ca Adenocarcinoma SII-IV (M0) AJCC 2002 R0 D2	No GE jc documented Diffuse: 60% SIV (M0): 12% R0: 100% D2: 100% Total gastrectomy: NA Nodes removed (median): 40 Nodes involved (median): 3	230	228	R0 D2	XP	XP	45 Gy in 25 fractions	Standard RT except —tumor bed for T4 only —stomach remnant not routinely included	APPA
Yu (34)	2012	China	Stomach Ca Adenocarcinoma T3-4 and/or N+ R status Ns D1 or 2	No GE jc documented Histology type: NS T2,3,4: 11%, 62%, 28% R0: NA D2: 69% Total gastrectomy: NA Nodes removed: NA	34	34	R Ns D1-2	FL	FL	45 Gy in 28 fractions	Standard RT No other modifications described	IMRT
Zhu (35)	2012	China	Stomach Ca (GE jc included) Adenocarcinoma T3-4 ± N+ UICC 7th editon R0 D2	GE jc: 9% CT, 16% CRT Histology type: NA SIV (M0): 15% R0: 100% D2: 100% Total gastrectomy: NS Nodes removed: NS Nodes involved ≥7: 21%	56	59	R0 D2	FL	FL	45 Gy in 25 fractions	Standard RT	IMRT

Table 6 (*continued*)

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Table 6 (*continued*)

Author	Year	Site	Eligibility	Characteristics*	N		Surgery	Control arm		Study arm		
					CRT	CT		CRT	CT	RT dose	RT volume	Technique
Bamias (36)	2010	Greece	Stomach Ca (GEjc included) Adenocarcinoma T3 ± N+ (AJCC 2002) R0 D status Ns	GE jc: Ns (esophagogastrectomy 7%) Diffuse: 32% CRT, 59% CT T2,3,4: 3%, 18%, 75% R0: 100% D0: 56% D1+2: 44% Total gastrectomy: 40% Nodes removed (median): 14 Nodes involved (median): 4	72	71	R0 D0-2	XP	DP	45 Gy in 25 fractions	Standard RT —proximal T3 include medial L hemidiaphragm —proximal lesions may exclude pancreaticoduodenal nodes —antral lesions exclude splenic hilar	APPA
Kwon (37)	2010	Korea	Stomach Ca Adenocarcinoma SIIIa-IV (M0) (AJCC 2002) R0 D2	No GE jc documented Diffuse: 65% CRT, 43% CT SIV (M0): 23% CRT, 10% CT R0: 100% D2: 100% Total gastrectomy: Ns Nodes removed (median): Na Nodes involved (median): Na	31	30	R0 D2	FP	FP	45 Gy in 25 fractions	Standard RT —preoperative tumor bed included	Conformal RT
Dent (38)	1979	S. Africa	Stomach Ca Adenocarcinoma All stages Resection not stated									

*, when key characteristics are equally distributed between the arms, total for the whole study is presented. Where imbalance is noted, data by treatment arm is presented. CRT, chemoradiotherapy; CT, chemotherapy; RT, radiotherapy; Ca, cancer; GE jc, gastroesophageal junction cancers; AJCC, American Joint Committee on Cancer; R0, complete resection of disease *en bloc*, negative resection margins; D status (D0/1/2), describes extent of nodal dissection; FL, 5 cycles: (fluorouracil 425 mg/m^2, leucovorin 20 mg/m^2) ×4 days, 4 weeks interval (as used in INT 0116); FL with RT, (fluorouracil 425 mg/m^2, leucovoring 20mg/m^2) ×5 days ×1 cycle, RT (45 Gy in 25 days, 5 days/week) with 2 cycles of FL (fluorouracil 400 mg/m^2, leucovorin 20 mg/m^2 days 1-4, days 29-31), FL (fluorouracil 425 mg/m^2, leucovorin 20 mg/m^2, 4 weeks interval) ×2 cycles; standard RT volumes, anastomosis, duodenal stump, regional nodes, residual stomach, tumor bed; APPA, anterior posterior versus posterior anterior beam arrangement; NA, not available; XP, 6 cycles: capecitabine 1 g/m^2 bid days 1-14, cisplatin 60 mg/m^2 day 1 every 3 weeks; XP with RT arms, XP (2 cycles), capecitabine 825 mg/m^2 bid daily during RT, XP (2 cycles); NS, not specified; IMRT, intensity-modulated radiation therapy; UICC, Union for International Cancer Control; DP, docetaxel 75 mg/m^2 day 1, cisplatin 75 mg/m^2 (or carboplatin AUC 5) days 1, 3, weekly, ×6 cycles; DP during RT, same as CT alone, RT 3-4 weeks after cycle 3; FP, 5-fluorouracil 1 g/m^2 continuous infusion days 1-5, cisplatin 60 mg/m^2 day 1 ×6 cycles; FP with XRT, 5-fluorouracil 1 g/m^2 continuous infusion days 1-5, cisplatin 60 mg/m^2 day 1, 3 weeks gap, 1 cycle, day 28 XRT ×5 weeks with capecitabine 1,650 mg/m^2 daily in 2 doses, 4 weeks post RT, FP ×3.

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Table 7 Randomized trials comparing postoperative CRT *vs.* postoperative CT—outcomes

Author	Year	N		Planned sample size	FU	OS			DFS			Local regional RFS			Toxicity[¶]			Notes
		CRT	CT		Median	CRT (95% CI)	CT (95% CI)	P	CRT (95% CI)	CT (95% CI)	P	CRT (95% CI)	CT (95% CI)	P	CRT	CT	P	
Kim (32)	2012	46	44	140 To detect a 20% difference (from 30% CT to 50% CRT) in 5 years DFS, with power 80%, one-sided alpha 0.05	86.7 months [60-117]	5-year: 65.2% (51.4-79)	5-year: 54.6% (39.8-69.3)	0.67	5-year: 60.9% (36.8-75)	5-year: 50% (35.2-64.8)	0.25	5-year: 84.4% (72.7-96.1)	5-year: 62.7% (47.6-77.7)	0.04	≥ Grade 3 GI: 17.4% ≥ Grade 3 hemorrhage: 19.6%	≥ Grade 3 GI: 11% ≥ Grade 3 hemorrhage: 25%	NS NS	Study closed after accrual of 90 patients over 4 years due to slow accrual Subgroup analysis suggests stage III patients benefited more
Lee (33) (ARTIST)	2012	230	228	448 To detect a HR 1.45 of DFS (from recurrence rate of 23% CT *vs.* 16% CRT) with power of 80% and two-sided alpha of 0.05	53.2 months [37-77]	NA	NA	NA	3-year: 78%	3-year: 74%	0.09	3-year: 95%	3-year: 92%	0.35	Treatment modifications: 35%, death*: 1	Treatment modifications: 52%, death*: 1	–	Final analysis was scheduled for when 227 events has occurred. The actual analysis was done when 127 events has occurred due to the lower event rate (due to the lower event rate as a result of large % of stage Ib/II patients) Subgroup analysis suggest N+ patients benefited more
Yu (34)	2012	34	34	NA	NA (all patients completed 3 years FU)	3-year: 67.7%	3-year: 44.1%	0.04	3-year: 55.8%	3-year: 29.4%	0.02	NA	NA	NA	Grade 1-2 anorexia: 74% Grade 1-2 N+V: 82% Grade 1-2 neutropenia: 71%	Grade 1-2 anorexia: 44% Grade 1-2 N+V: 74% Grade 1-2 neutropenia: 44%	<0.05 >0.05 <0.05	

Table 7 (*continued*)

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Table 7 (*continued*)

Author	Year	N		Planned sample size	FU	OS			DFS			Local regional RFS			Toxicity[¶]			Notes
		CRT	CT		Median	CRT (95% CI)	CT (95% CI)	P	CRT (95% CI)	CT (95% CI)	P	CRT (95% CI)	CT (95% CI)	P	CRT	CT	P	
Zhu (35)	2012	56	59	NS (OS was primary endpoint)	42.5 months (all patients alive completed 5 years FU)	5-year: 48.4%, HR 1.24 (0.9-1.65)	5-year: 41.8%	0.1	5-year: 45.2%, HR 1.35 (1-1.78)	5-year: 35.8%	0.03	5-year: 15.6%	5-year: 24.2%	0.04	≥ Grade 3 vomit: 1.6% ≥ Grade 3 diarrhea: 1.6% ≥ Grade 3 leucopenia: 7.5%	≥ Grade 3 vomit: 0 ≥ Grade 3 diarrhea: 0 ≥ Grade 3 leucopenia: 7.3%	– – –	
Bamias (36)	2010	72	71	200 To detect an increase in survival of 20% (35% CT, 55% CRT), power of 80% and alpha 0.05	53.7 months (0.1-77.8)	3-year: 57%	3-year: 61%	NS	3-year: 48%	3-year: 51%	NS	–	–	–	≥ Grade 3 febrile neutropenia: 7% ≥ Grade 3 diarrhea: 4%	≥ Grade 3 febrile neutropenia: 9% ≥ Grade 3 diarrhea: 7%	NA –	Study close after accrual of 147 over 3 years due to decreasing accrual
Kwon (37)	2010	31	30	170 To detect a 20% increase in DFS (30% CT, 50% CRT, HR 1.7) with a power of 80% and two-sided alpha of 0.05	77.2 months (2.4-92.8)	5-year: 70.1%	5-year: 70%	NS	5-year: 76.7%	5-year: 59.1%	0.2	5-year: 87.1%	5-year: 76.7%	0.4	≥ Grade 3 neutropenia: 48% ≥ Grade 3 diarrhea: 3.2%	≥ Grade 3 neutropenia: 17% ≥ Grade 3 diarrhea: 0%	– –	Study close after accrual of 61 over 2.5 years due to slow accrual

[¶], not all side effects reported are included. Diarrhea, neutropenia and nausea and vomiting are preferentially presented, as they are typically the most common; *, one patient (CRT) died of neutropenic sepsis, one patient (CT) died of pneumonia. CRT, chemoradiotherapy; CT, chemotherapy; FU, 5-fluorouracil; OS, overall survival; CI, confidence interval; DFS, disease free survival; RFS, relapse free survival; GI, gastrointestinal; NS, not specified; HR, hazard ratio; NA, not available.

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used concurrently with radiation, either in bolus form at the beginning and end of radiation (11,32,34,35), continuous infusional form (49), or in oral form as capecitabine (33,37). However, the CT before and after the radiation has been more varied. Other than 5FU (11,32,34,35), the following other CT regimens have been used: epirubicin, cisplatin and 5FU (ECF) (49), capecitabine and cisplatin (33), 5FU and cisplatin (37), as well as cisplatin and docetaxel (36).

Two additional important trials need to be considered when addressing the choice of systemic backbone when combined with RT. The MAGIC trial (18) established the survival benefit provided by ECF perioperative CT compared with surgery alone. A survival benefit was clearly established (5 years OS, 36% CT *vs*. 23% surgery alone; HR 0.75, 95% CI: 0.6-0.83; P=0.009), as well as an advantage in progression free survival (HR 0.66; 95% CI: 0.53-0.71; P<0.001). The CALBG trial (49) was the only phase III trial that compared the optimal CT when used in conjunction with postoperative radiation. The control arm used 5FU as in the Macdonald protocol, while the experimental arm used ECF CT before and after RT. Both arms used infusional 5FU during radiation (as opposed to bolus 5FU at the beginning and end of RT). Both groups had similar OS, and therefore the trial did not meet its primary endpoint. However, toxicity was reported to be less in the ECF arm, and the final publication is awaited.

At Princess Margaret, we still use 5FU as per the Macdonald protocol, as this has the best and longest standing evidence. However, others have switched to infusional 5FU during RT, as is often done in other gastrointestinal cancers such as rectal cancer, and some other centers have used ECF before and after radiation.

In the ongoing trials, TOPGEAR (50) is designed with perioperative ECF (6 cycles) *vs*. the same regimen replacing the 3rd cycle of ECF with RT with 5FU or capecitabine. CRITICS (51) employs a similar strategy using epirubicin, cisplatin and capecitabine (ECC) ×3 cycles, *vs*. the same regimen with RT and concomitant cisplatin and capecitabine. Zhou (52) and Xie (53) *et al*. use 2 cycles of capecitabine and oxaliplatin (CapOx), Kang *et al*. use cisplatin and capecitabine in one study (54), and S1 and oxaliplatin in ARTIST II (55). Biological agents are actively being investigated especially in North America (*Table 8*).

Summary

Taken together, these trials showed an interest in the use of preoperative RT (reported between 1994 and 2002), although perhaps given the quality of the evidence and the variable results, the findings were not translated into adoption of this strategy into clinical practice. The Macdonald study [2002] single handedly changed clinical practice to the adoption of postoperative CRT with a 9% survival benefit. Recent efforts (reported between 2010 and 2012), employing contemporary surgery, RT and "standard" CT, were focused on establishing the incremental benefit of adding RT to CT in the postoperative setting, found improved local control, but no survival benefit. A single small dated study [1994] would suggest postoperative RT alone to be ineffective.

Preoperative RT alone offered some tantalizing evidence that it can also improve survival but the power of inference is lower. The significant local regional rates that are expected from locally advanced disease despite improved surgical quality (including safe delivery of D2 dissections) are powerful reasons to motivate a strong support for current studies that are designed to establish the effectiveness of preoperative CRT when used together with optimized CT and surgery.

Technical considerations of RT

Choice of dose fractionation

The typical dose fractionation of 45 Gy in 25 fractions is employed quite uniformly across current practice and in ongoing clinical trials, given the relatively large target volume (driven by the distribution of local regional nodes predominantly), and the intimate relationship with critical normal structures and their normal tissue tolerances.

Choice of target volume

The choice of target volume is based on the principle to include all the local regional nodes at risk and the threat posed by direct microscopic extension.

Nodal regions encompassed would parallel what would be captured in an extended D2 dissection, where perigastric, celiac axis, pancreaticoduodenal, porta hepatis, are targeted. Paraaortic nodes are included where this corresponds to the cranial caudal extent of the overall target volume. Splenic hilar nodes are included in proximal tumors.

To account for the risk of recurrence arising through direct extension of the primary, a margin surrounding the primary (in the preoperative setting), or a margin around

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Table 8 Ongoing clinical trials

PI/Study name	Study location(s)	Clinicaltrial.gov	Patient population	Sample size	Control arm	Study arm	Study start date	Projected completion date
Preoperative								
Leong TOPGEAR (50)	Australia, Europe, Canada	01924819	Stomach Ca GE jc if <2 cm of esophagus involvement T1-2N1 (T2N0 excluded), T3-4N + M0 D2 dissection recommended	750	ECF[§]	ECF RT: 45 Gy in 25 fractions	2009	2020
Zhou (52)	China	01815853	Stomach Ca T4anyNM0 Dissection requirement: NA	620	Cap/Ox[‡]	CapOx RT: 45 Gy in 25 fractions	2012	2022
Postoperative								
CRITICS (51)	Netherlands	00407186	Stomach Ca SIb-IVaM0 ≥ D1 dissection	788	ECC[∫]	ECC RT: 45 Gy in 25 fractions	2006	2014
Kang (54)	Korea	00323830	SIb, II, III, IV (T4N3M1nodes) D2 dissection	458	XP[¶]	XP RT: NA	2004	2011
Kang (55) ARTIST II	Korea	01761461	Gastric or gastroesophageal Ca SII/III, N + M0 ≥ D2 dissection	1,000	S1/Ox	S1/Ox RT	2013	2016
Xie (53)	China	01711242	Stomach Ca T3-4, N + M0 D2 dissection	300	Cap/Ox	CapOx RT: 45 Gy in 25 fractions	2012	2017

[§], ECF: epirubicin 50 mg/m^2 day 1, cisplatin 60 mg/m^2 day 1, 5FU 200 mg/m^2/day continuous intravenous infusion days 1-21, ×3 cycles preoperative, 3 cycles postoperative. (5FU can be replaced by capecitabine 625 mg/m^2 twice daily); ECF/RT, cycle 3 ECF replaced by RT 45 Gy in 25 fractions, 5FU 200 mg/m^2/d days 1-35 (5FU can be replaced by capecitabine 625 mg/m^2 twice daily); [‡], CapOx: capecitabine 1 g/m^2 days 1-14, oxaliplatin 130 mg/m^2 day 1, ×2 cycles every 21 days; CapOx/RT, same chemo + RT 45 Gy in 25 fractions; [∫], ECC: epirubicin 50 mg/m^2 day 1, cisplatin 60 mg/m^2 day 1, capecitabine 1 g/m^2 bid days 1-14, every 3 weeks, c3 cycles; ECC/RT, after ECC ×3 cycles, 45 Gy in 25 fractions with cisplatin 20 mg/m^2 weekly, capecitabine 575 mg/m^2 bid daily during RT; [¶], XP: capecitabine, cisplatin; S1/Ox, S and oxaliplatin; Ca, cancer; GE jc, gastroesophageal junction cancers; 5FU, 5-fluorouracil; RT, radiotherapy; NA, not available.

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the perioperative tumor bed, residual stomach and excision margins on the tumor side, i.e., the anastomosis, and blind loop of the duodenum are used in the postoperative setting. The proximal hemi diaphragm is targeted for the same reasons in proximal tumors. In general terms, a clinical target volume (CTV) margin of 0.5-1 cm around the vasculature is used to capture the nodal groups. A margin of 0-0.5 cm around the primary for T1-2 lesions, and a margin of 0.5-1 cm for T3-4 primaries are typically used.

Certain modifications of these principles are generally permitted to reduce dose to normal structures under specific circumstances. For patients who have undergone a D2 dissection with adequate nodal sampling, omitting the preoperative tumor bed when the tumor is T3 or less, and omission of the entire residual stomach, are acceptable variations introduced in recent trials (32,33) with no adverse consequences reported.

At the conclusion of TOPGEAR, this study would have accrued 750 patients whereby half of the patients would have received preoperative CRT according to the method of target definition, with a thoughtful quality assurance program and is anticipated to provide high quality evidence on the appropriateness and effectiveness of the contouring guidelines used in this study.

Choice of treatment technique

When preoperative CRT was first introduced, the Macdonald trial described the use of APPA or three field techniques (19). This is quickly superseded by the adoption of conformal techniques, intensity modulated and volumetric arc techniques.

With more sophisticated treatment approaches, special considerations need to be made during planning and treatment delivery to ensure reproducible and accurate targeting. Dietary guidelines are an attempt to ensure minimal and consistent stomach volumes throughout the planning and treatment period. At our institution, a cup of coffee and a slice of toast (or its equivalent) only 2 hours prior to RT is routinely recommended. Daily image guidance incorporating cone beam computed tomography is necessary to provide verification of fields designed with more sophisticated planning techniques with sharper dose gradients (e.g., conformal, IMRT) to avoid normal structures. Renal perfusion scan can provide differential renal function and is useful for refining beam geometry and permissible dose to the kidneys. Four dimensional-computed tomography scans provide individualized assessment of respiratory organ motion assessment and planning target volume (PTV) margins (56).

A recent systematic review on comparison between standard and conformal three dimensional (3D) techniques supported superior normal tissue sparing with 3D CRT (57). More sophisticated techniques such as IMRT and tomotherapy, provide refinement in dosimetric advantages which could benefit particularly challenging cases although clinically significant differences at a population level is more difficult to demonstrate (58,59).

Ongoing phase III studies

Globally, five randomized trials (50-53,55) are currently actively accruing, and one has completed accrual (54) and awaiting follow-up. Two studies examining the role of neoadjuvant RT when added to CT, and four studies addressed the role of RT in the adjuvant setting when added to CT.

Postoperative CT ± RT

Kang *et al*. (54) has completed accrual in 2011 on a study in Korea comparing capecitabine, cisplatin (XP), with or without RT having recruited 458 patients, results pending. A second study by the same group (55) aims to accrue 1,000 patients, comparing S1/oxaliplatin with or without RT, scheduled to complete accrual in 2016. Xie *et al*. (53) is conducting a study in China targeting 300 patients comparing capecitabine/oxaliplatin with or without RT, scheduled to completed in 2017.

CRITICS (Clinicaltrials.gov NCT00407186) (51) is designed to compare perioperative CT with postoperative CRT uses 45 Gy in 25 fractions (with cisplatin and capecitabine), together with high quality surgery, pathology and RT quality control. This study initiated accrual in 2006 and is scheduled to complete accrual of its sample size of 788 patients.

Preoperative CT ± RT

Zhou *et al*. is conducting a study in China comparing capcitabine/oxaliplatin in the preoperative setting in 620 patients, targeting completion of accrual in 2022 (52).

TOPGEAR (Clinicaltrial.gov NCT01924819) (50) is designed to deliver 45 Gy in 25 fractions, with 5FU in the preoperative setting during what would be the 3rd cycle of MAGIC CT. D2 dissection is strongly recommended. This study initiated accrual in 2009, and is scheduled to complete accrual of its sample size of 752 patients in 2020.

The design of this study is built upon three phase II

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studies providing promising safety data. Postoperative use of CRT using ECF was tested in a phase II study demonstrating tolerability (60) ECF ×1 cycle followed by CRT (45 Gy in 25 fractions with concurrent 5FU) was tested in the phase II setting through TROG 03.02. The definition of the RT target volumes and normal tissue dose limits and general planning approach provided evidence of initial safety and feasibility. In this study, compliance rate of 94% was achieved, and grade 3-4 gastrointestinal (GI) toxicity was 28% and neutropenia 65%, febrile neutropenia 5.6% (60). Ajani *et al*. (61) reported on the first of two multi-institutional phase II neoadjuvant study (n=34) using 5FU/folinic acid (FA)/cis-diamminedichloroplatinum (CDDP) followed by CRT (45 Gy in 24 fractions with concurrent continuous intravenous infusion 5FU). The R0 resection rate was 70% and the pathological complete response (pCR) rate was 30% while median survival was 34 months. The second phase II study (62) (RTOG 99-04) (n=49) used 5FU/FA/CDDP ×2 cycles preoperative, followed by CRT (45 Gy with concurrent continuous intravenous infusion 5FU/paclitaxel). The R0 resection rate was 77%, pCR 26%. Both studies reported an acceptable toxicity profile.

Conclusions

Differences in patterns of practice have resulted in different strategies to enhance the outcome of surgery between the East and the West. TNM staging system version 7 published in 2010 represent a consensus between these two worlds and would likely lay the foundation for advances that would capitalize on these variations. The philosophy that quality is important, especially in technical based modalities such as RT and surgery is critical, if optimal effect of combined modality is to be defined.

The technical ability to deliver RT to large complex volumes while minimizing exposure to normal structures has matured. Postoperative CRT improves the cure rate by approximately 9%, attributable to the effect of RT on securing local control when the majority of patients are managed by D0-1 dissections. Ongoing trials are expected to provide the answer to the question, what is the role of incorporating RT and CT to optimal surgery in both the preoperative or postoperative setting over the next 5-10 years. Based on sound principles, there is particular optimism that preoperative CRT may have a critical role to play. Assuming safety and effectiveness is confirmed in the neoadjuvant setting, future trials would need to be initiated to clarify the role between pre and postoperative RT.

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