



Evidence based radiation therapy for locally advanced resectable and unresectable gastric cancer

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Abstract

Despite the fact that gastric cancer is decreasing in incidence in the United States, it remains one of the most commonly diagnosed and most fatal cancers worldwide. In localised disease, surgery remains the cornerstone of treatment. Nevertheless, the low overall survival rates at 5 years due to locoregional and distant recurrences has led to a large debate regarding the role of radiation therapy and chemotherapy in addition to curative resection. Recent data have shown that, even with improved surgical techniques, locoregional failure rates in these patients ranged between 57% and 88%. Failures were noted in the gastric bed, regional nodes, gastric remnant, anastomosis and duodenal stump, all of which can be encompassed in a regional radiation field, indicating the need of further locoregional treatment. In this article, a comprehensive literature review of the reliable medical databases of PubMed and Cochrane is made and we present all available information on the role of radiation therapy in the preoperative and postoperative setting of gastric cancer. Data reported show that in locally advanced gastric cancer the addition of radiation therapy post surgery has significantly improved disease-free survival as well as overall survival. Moreover, in unresectable gastric cancer, the combination of radiation therapy with chemotherapy has significantly improved

mean and overall survival rates. The role of radiation therapy in patients with resectable gastric cancer is being further evaluated in ongoing phase III trials.

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INTRODUCTION

Gastric cancer is still the third most frequent cause of cancer mortality^[1]. More prevalent in Asian countries, adenocarcinoma of the stomach remains a significant oncological problem^[2,3]. Although surgery still represents the cornerstone of management, adjuvant strategies have seemed to offer survival advantages in prospective randomized trials. Two adjuvant approaches are now regarded as viable options in the management of localized, resectable gastric cancer^[4]. In a study conducted by Cunningham *et al*^[5], the authors concluded that perioperative chemotherapy (epirubicin, cisplatin and fluorouracil) improved the progression-free and overall survival rates among patients suffering from the disease. Macdonald *et al*^[6] on the other hand, observed that postoperative

chemoradiotherapy (fluorouracil and leucovorin plus external-beam radiotherapy to the site of the gastric resection and the draining lymph nodes) significantly improved the disease-free and overall survival rates among patients treated with resected adenocarcinoma of the stomach. The review by McCloskey and Yang in this issue of *Gastrointestinal Cancer Research*^[7] elegantly and succinctly highlights the role of radiation therapy employed preoperatively or postoperatively in the multimodality treatment of nonmetastatic resectable gastric cancer. The objective of the study is to accumulate and present all available information regarding the role of radiation therapy in the treatment of gastric cancer.

IDENTIFICATION OF ELIGIBLE STUDIES

We searched MEDLINE and the Cochrane Central Register of Controlled Trials (last search in December 2010) using combinations of terms such as: locally advanced gastric cancer, resectable gastric cancer, unresectable gastric cancer, treatment and radiation therapy. We also checked the abstracts from major international cancer meetings such as the American Society of Clinical Oncology (ASCO) and Gastro-Intestinal Cancer Symposiums during the last decade. We considered all English meta-analyses, randomized controlled trials, research trials providing evidence about the effectiveness of radiation therapy on gastric cancer treatment and future directions of ongoing research as eligible. Due to the fact of the large experience accumulated during the last few years on the use of radiation therapy for treating patients with resectable and unresectable gastric cancer, we believe it is of interest to present a review and summary of the results of the most relevant clinical trials on this issue. We have incorporated full papers published in peer-reviewed journals as well as those recently reported at major international cancer meetings such as ASCO and the Gastro-Intestinal Cancer Symposium.

DATA EXTRACTION

We extracted information from each eligible study. The data recorded included author's name, year of publication, number of patients included in the study, combination(s) of treatment used, doses of radiation therapy, disease free survival, median time to progression and overall survival.

RADIATION THERAPY IN RESECTABLE GASTRIC CANCER

Postoperative radiation or chemo-radiation therapy

Following surgical resection of early stage gastric cancer, 5 year survival rates of 80% or higher can be achieved, while the same rate is 30% or less for patients with extensive lymph node involvement^[8,9]. The suboptimal outcome after surgery alone for gastric cancer indicates the necessity of adjuvant treatment for locally or locore-

gionally advanced adenocarcinoma of the stomach. Adjuvant treatment for gastric cancer could involve radiation therapy, chemotherapy or combined chemoradiotherapy. Postoperative radiation therapy alone is not indicated for gastric cancer after complete surgical resection. A prospective randomized trial reported by the British Stomach Cancer Group (BSCG)^[10,11] compared surgery alone versus surgery followed by postoperative chemotherapy or postoperative radiation. The results showed postoperative radiation therapy improved local-regional control but provided no survival benefit for patients, suggesting that combining with chemotherapy may be helpful to improve survival rates.

Postoperative concurrent chemo-radiation is indicated for resected high-risk stage II-III B gastric cancer patients. The efficacy of combined chemo-radiation therapy has been demonstrated in randomized trials of various sizes. The Mayo clinic performed the first trial to evaluate postoperative chemoradiotherapy versus surgery alone, and 62 patients were enrolled. Local control was achieved in 61% of patients treated with adjuvant chemo-radiation and 45% in the surgery alone group. The 5 year survival also favored the adjuvant therapy group (20% *vs* 4%)^[12]. The randomized phase III trial Intergroup 0116 compared postoperative chemo-radiation with observation. This study demonstrated an overall survival benefit in combined adjuvant therapy. Patients who received postoperative therapy had a significant improvement in median survival (26 mo *vs* 35 mo at 7-year follow up, $P = 0.006$) and 3 year overall survival (50% *vs* 41%, $P = 0.005$). Local and regional failure decreased in the chemo-radiation group (19% *vs* 29% and 65% *vs* 72%). However, only 10% of patients received planned surgical resection (i.e., D2 dissection)^[6,13]. Adjuvant chemoradiation therapy is recommended after D2 resection for patients with locally or locoregionally advanced gastric cancer; however, randomized trial data is lacking. A large retrospective adjuvant chemoradiation analysis from Korea indicated an overall survival benefit for postoperative therapy compared to surgery alone: the 5-year survival rates were 57% *vs* 51%, respectively, in favor of postoperative treatment ($P = 0.005$). Local control was significantly improved with postoperative chemoradiation therapy (15% *vs* 22%, $P = 0.005$); however, no difference in distant metastasis (38%) was observed^[14]. The results of these randomised phase III trials are summarised in Table 1.

Preoperative chemo-radiation or radiation therapy

Preoperative chemo-radiation therapy cannot be routinely offered for resectable gastric cancer at this stage as the efficacy of such a strategy has not been confirmed by phase III randomized trials. Research on neoadjuvant chemo-radiation for patients with gastric cancer is limited to phase II trials. The RTOG 99-04 trial included 49 patients treated with two cycles of induction 5-fluorouracil (5-FU), leucovorin and cisplatin followed by irradiation (45 Gy) with concurrent continuous 5-FU and weekly paclitaxel preoperatively. The results revealed 27% pathological

Table 1 Randomized trials for postoperative chemo-radiotherapy in resectable gastric cancer

Author, year published	Nr Pt	Treatment arms	Local control	Overall survival
Moertel <i>et al</i> ^[12] , 1984	62	Arm 1 (23 patients): Observation only Arm 2 (39 patients): 5-FU (15 mg/kg by rapid intravenous injection × 3) plus radiation (3750 rad in 24 fractions)	The alive without recurrence distributions were significantly different for the two groups ($P = 0.024$) and favored treatment assignment.	The five year survival rate for patients randomized to treatment was 23%, and for those randomized to no treatment, 4% ($P < 0.05$).
Kim <i>et al</i> ^[15] , 2005	990	Arm 1 (446 patients): no adjuvant treatment Arm 2 (544 patients): 400 mg/m ² of 5-FU plus 20 mg/m ² of LV for 5 d, followed by 4500 cGy of RT for 5 wk, with 5-FU and LV on the first 4 and the last 3 d of RT. Two additional cycles of the chemotherapy were given 4 wk after the completion of RT	The CRT was associated with increases in the median duration of relapse-free survival (75.6 mo <i>vs</i> 52.7 mo; hazard ratio for relapse, 0.80, $P = 0.016$).	Overall survival was significantly longer in the CRT arm: 95.3 mo <i>vs</i> 62.6 mo (hazard ratio for death of 0.80, $P = 0.02$)

Nr: Number; Pt: Patients; 5-FU: 5-fluorouracil; LV: Leucovorin; CRT: Chemo-radiotherapy.

Table 2 Phase II trials for preoperative chemo-radiotherapy in resectable gastric cancer

Author, year published	Nr Pt	Treatment schedule	PathCR rate	Quality of surgery
Ajani <i>et al</i> ^[16] , 2006	49	Patients received two cycles of induction 5-FU, LV and CIS followed by concurrent CRT (infusional 5-FU and weekly paclitaxel). Resection was attempted 5 to 6 wk after CRT	27%	The R0 resection rate was 77%
Ajani <i>et al</i> ^[17] , 2004	33	Patients received two cycles of induction 5-FU, LV and CIS followed by concurrent CRT (infusional 5-FU).	30%	The R0 resection rate was 70%
Ajani <i>et al</i> ^[18] , 2005	41	Patients received two cycles of induction 5-FU, LV and CIS followed by concurrent CRT (infusional 5-FU and weekly paclitaxel).	25%	The R0 resection rate was 78%

Nr: Number; Pt: Patients; 5-FU: 5-fluorouracil; LV: Leucovorin; CIS: Cisplatin; CRT: Chemo-radiotherapy; PathCR: Pathologic complete response; R0: Microscopically negative surgical margins.

complete response (PathCR) and 77% microscopically negative surgical margins (R0) resection rates^[15,16].

Two phase II studies from the M. D. Anderson Cancer Center also indicated the possible effect of neoadjuvant chemo-radiation therapy. One enrolled 33 patients treated with induction chemotherapy of 5-FU, leucovorin and cisplatin followed by chemo-radiation of 45 Gy in 25 fractions concurrently with 5-FU. The pathological complete and partial response was observed in 64% of patients^[17]. The second study included 41 resectable gastric cancer patients treated with two cycles of induction chemotherapy of 5-FU, paclitaxel and cisplatin followed by 45 Gy irradiation with concurrent 5-FU and paclitaxel. The 25% pathological CR and 78% R0 resection rate was achieved^[18]. Table 2 summarizes the results of these phase II trials.

Although there are no published phase III trials aimed at studying the effect of preoperative chemo-radiation on gastric cancer, two randomized trials of esophageal cancer included either gastric cardia or gastroesophageal (GE) junction lesions. The randomized trial by Walsh *et al*^[19] assigned 113 patients with lesions of the esophagus and gastric cardia, comparing immediate surgery to preoperative 5-FU/cisplatin-based chemotherapy and radiation therapy (to a total dose of 40 Gy in 15 daily fractions) followed by surgical resection. A significant survival improvement was demonstrated with combined therapy in 3-year survival of 32% *vs* 6% of the surgery alone

arm. The prospective randomized Cancer and Leukemia Group B (CALGB) 9871 was a phase III trial of preoperative chemo-radiation (5-FU/cisplatin and 50.4 Gy in 28 fractions) *vs* surgery alone for treatment of esophageal carcinoma. Patients with GE junction lesions were included in the trial. It was closed due to poor accrual of 56 patients for a targeted patient enrollment of 500. Although accrual was well below that planned, the observed 5-year survival of 39% in the preoperative therapy arm *vs* 16% in the surgery alone arm suggests that combined modality is an appropriate treatment for this disease^[20]. It is important to note that the numbers of patients with gastric cardia lesions are limited in both studies, and the results of the trials cannot be directly applied to gastric cancer treatment.

Radiation therapy is not routinely indicated in the treatment of resectable gastric cancer. As the effects of adjuvant chemotherapy and radiation therapy, as well as perioperative chemotherapy, have been confirmed by well designed multi-institutional randomized trials, preoperative radiation is not recommended as standard practice for potentially resectable gastric cancer. Prospective randomized trials from Russia and one from China have demonstrated the effect of preoperative radiotherapy in the treatment of resectable gastric cancer; however, regimens including dose and fractionation used in the studies were not standardized. Further investigations with randomized trials are needed to confirm the efficacy of neo-

adjuvant radiation therapy before it can be recommended as part of standard treatment.

Three prospective randomized Russian trials have evaluated radiotherapy alone (20 Gy in four fractions in the first two trials and 32 Gy in the third trial) in potentially resectable gastric cancer. Although survival advantage was observed in these trials with preoperative therapy, there were some methodological uncertainties and their applicability to gastric cancer in other countries is not clear^[21,22,23].

A well designed randomized trial from China compared preoperative radiation (40 Gy in 20 fractions) with surgery alone in patients with clinically resectable gastric cardia disease. A significant improvement in survival and local regional disease control were observed with the preoperative radiation arm to the surgery only arm. The 5-year survival rate was 30% *vs* 20%, $P = 0.0094$, with local relapse rates of 39% *vs* 52%, $P < 0.025$. However, only patients with adenocarcinoma of gastric cardia were included in this single institutional randomized trial^[24].

In a phase III trial from Georgetown University, 293 patients with gastric cancer (resectable and unresectable) were randomized to preoperative radiation therapy, preoperative radiation with postoperative hyperthermia or gastrectomy alone. The results of this trial showed that preoperative radiation therapy of 20 Gy delivered in four fractions (5 Gy per fraction) did not improve overall survival compared to surgery alone. However, patients with unresectable gastric cancer benefited significantly from preoperative radiotherapy with or without hyperthermia^[25].

RADIATION THERAPY IN LOCALLY ADVANCED UNRESECTABLE GASTRIC CANCER

Combined radiation and chemotherapy may be considered for patients with unresectable gastric cancer or for patients with residual tumor after surgical resection. Data from randomized studies of combined chemoradiation in patients with locally unresectable gastric cancer were inconsistent.

In an early randomized study reported by the Mayo Clinic, combined therapy of radiotherapy (35-37.5 Gy over 4-5 wk) and chemotherapy (5-FU) were given to patients with unresectable gastric cancer after surgery and compared to surgery alone. Mean and overall survival rates were significantly improved in the combined modality group (13 mo *vs* 5.9 mo and 12% *vs* 0% for 5-year survival)^[26]. Two randomized trials conducted by Gastro-Intestinal Tumor Study Group (GITSG) compared the effect of combined chemoradiotherapy and chemotherapy in patients with locally advanced unresectable gastric cancer. The first trial compared chemotherapy (5-FU and MeCCNU) and split course radiation (50 Gy delivered in split courses spaced 2 wk apart) with chemotherapy alone in patients with locally unresectable gastric cancer. Approximately 25% of patients who received chemoradiation died or deteriorated earlier within the first 10 wk of treatment. However, further follow-

up revealed that a significant improvement in 4-year survival was observed in the combined modality group (18% *vs* 6%)^[27]. In the second study from GITSG, radiation was delivered in a continuous course, doxorubicin was added to the chemotherapy regimen and chemotherapy was delivered before combined modality therapy. However, close to 50% of the patients in the combined treatment group did not receive planned therapy and the outcome of the combined therapy group did not show improvement of survival^[28]. A retrospective analysis of 60 patients with unresectable, incompletely resected or recurrent gastric or gastroesophageal junction adenocarcinoma was reported by the Mayo Clinic. The results indicated that in patients with recurrent disease, the number of sites involved and the use of external beam radiation and intraoperative radiation therapy to a total dose of more than 54 Gy were of borderline significance in regard to survival^[29]. The median survival time for the entire group of patients was 11.6 mo, similar to those reported in the randomized trials.

CONCLUSION

Prognosis of gastric cancer remains dismal, especially in western countries where the incidence of early gastric cancer is very rare^[1,30]. High relapse rates (stage dependent up to 80%) indicate the need for adjuvant therapy after surgery. The finding that postoperative chemoradiation improved survival in patients with resectable gastric cancer was met with both excitement and apprehension among oncologists who treat gastrointestinal malignancies. The INT0116^[6] demonstrated the advantage of postoperative radiochemotherapy for the first time. The Cunningham *et al*^[5] study demonstrated a survival benefit of a neoadjuvant-adjuvant chemotherapy regimen alone for the first time, followed by a second randomized trial from Japan^[31]. Extent of surgery and absolute survival numbers, however, differed significantly between these studies^[32]. It is therefore unclear if chemotherapy alone^[32,33] or radio- chemotherapy is the most beneficial approach for locoregionally advanced gastric cancer in a perioperative setting^[34]. The answer to this question, as well as which chemotherapy regimen combined with radiation therapy (RT) is better for resectable stomach cancer patients, is the subject of two ongoing phase III trials. The first trial (Intergroup trial CALGB 80101) is a randomized multicenter study which purpose is to compare overall survival, disease free survival and local and distant recurrence rates in patients with resected gastric adenocarcinoma treated with epirubicin, cisplatin and infusional 5-fluorouracil (ECF) *vs* 5-FU bolus and leucovorin calcium before and after 5-FU plus radiotherapy. Interim toxicity results have recently been presented in the Gastrointestinal Cancers Symposium^[35] and the authors have concluded that a postoperative regimen of ECF before and after 5-FU and concurrent RT appears to offer a comparable, or possibly a superior (Grade 4/5), toxicity profile to the chemoradiation regimen utilized in

Table 3 Ongoing phase III trials for resectable gastric cancer

Study	Sponsor	Estimated Enrollment	Arms	Primary endpoint
Adjuvant chemotherapy or chemoradiotherapy in resectable gastric cancer (CRITICS)	Dutch colorectal cancer group	788	1 CRT(Experimental): cisplatin 20 mg/m ² (IV, q 1 w, 5 wk), capecitabine 575 mg/m ² (bid, oral, on radiotherapy days). Radiation therapy: 45 Gy in 25 fractions (5 d/wk). 2 C (Active comparator): 3 courses q 3 w: epirubicin 50 mg/m ² (IV, day 1), cisplatin 60 mg/m ² (IV, day 1), capecitabine 1000 mg/m ² (bid, oral, day 1-14). All patients receive 3 cycles of the C in arm 2 before surgery.	Whether chemoradiotherapy after preoperative chemotherapy and adequate surgery leads to improved survival in comparison with postoperative chemotherapy.
Chemotherapy and radiation therapy after surgery in treating patients with stomach or esophageal cancer	Cancer and leukemia group B	824	1 (Active comparator): Patients receive leucovorin calcium IV and fluorouracil (5-FU) IV on days 1-5 of courses 1, 3 and 4. Courses repeat every 28 d. During course 2, patients undergo radiotherapy 5 d a week and receive 5-FU IV continuously for 5 wk. Patients rest for 28-35 d between course 2 and 3. 2 (Experimental): Patients receive epirubicin IV over 3-15 min and cisplatin IV over 1 h on day 1 and 5-FU IV continuously on days 1-21 during course 1. Beginning 1 wk later, patients undergo radiotherapy 5 d a week and 5-FU IV continuously for 5 wk. Patients rest for 28-35 d before beginning course 2 of chemotherapy. Patients then receive epirubicin, cisplatin and 5-FU as in course 1. Treatment repeats every 21 d for 2 courses.	Compare overall survival in patients with resected gastric adenocarcinoma treated with epirubicin, cisplatin and infusional 5-FU vs 5-FU bolus and leucovorin calcium before and after 5-FU plus radiotherapy.

5-FU: 5-fluorouracil; LV: Leucovorin; CRT: Chemo-radiotherapy; C: Chemotherapy; q 1 w: Given every one week; bid: Given two times per day; q 3 w: Given every three weeks; IV: Intravenous.

INT 0116. The second study is a multicenter randomized phase III trial of neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy in resectable gastric cancer (CRITICS Study). This phase III prospectively randomized study investigates whether chemoradiotherapy (45 Gy in 5 wk with daily cisplatin and capecitabine) after preoperative chemotherapy [3 × ECC (epirubicin, cisplatin, capecitabine)] and adequate (D1+) surgery leads to improved survival in comparison with postoperative chemotherapy (3 × ECC). Furthermore, toxicity of both treatment regimens will be explored. The trial has an estimated enrollment of 788 patients and an estimated study completion date in December 2013. No interim results have been published yet. The study design of the ongoing phase III trials are summarized in Table 3.

Since locoregional failure rates in patients with locally advanced resectable gastric cancer are quite high, it seems that the results of the ongoing trials will strengthen the necessity of radiation therapy as an integral part of their treatment.

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