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Chemoradiotherapy Versus Chemotherapy for Localized Gastric Cancer: A Mini Review

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Abstract

Curative treatment for localized gastric cancer involves a multidisciplinary approach that includes surgery and chemotherapy with or without radiotherapy. In the past decades several studies have shown survival benefit of postoperative and perioperative treatments in comparison with surgery alone. Only a few trials have compared directly chemotherapy with chemoradiotherapy without a clear benefit favoring one strategy over another. In the absence of a standard approach, the choice of the best treatment is individualized and varies by geographic region and the preference of the institution where the patient is being treated. This review summarizes what is new in the treatment of localized gastric cancer and seeks to deeply analyze chemotherapy and chemoradiotherapy strategies.

Introduction

The incidence of gastric cancer has been declining over the past century; however, it is still an important cause of cancer-related death in the world and currently the most prevalent cancer in East Asia[1]. Curative strategies for localized gastric cancer (LGC) require surgery. However, even after resection, the local recurrence rate is approximately 24% to 54%[2]. Strategies to reduce the rate of locoregional recurrence have been evaluated over the last few decades, and several studies have shown a benefit from chemotherapy (CT) and chemoradiotherapy (CRT).

Despite recent advances, no treatment regimen has been clearly superior to the other, and we still do not have a standard approach for LGC patients. The objective of this study is to analyze the current evidence on the topic and to discuss future perspectives.

Postoperative strategies

The phase III Intergroup 0116 (INT-0116) trial randomized 556 patients for observation alone or 5-fluorouracil (5-FU)-based CRT. The experimental arm significantly increased overall survival (OS) (median OS of 35 vs. 27 months; P=0.0046) and disease-free survival (DFS) (27 vs. 19 months; P<0.001) compared with surgery alone (Table 1)[3]. The limitations of this study are that only 10% of patients underwent D2 dissection, and the benefit was mostly seen in locoregional relapse. Therefore, the addition of radiotherapy might have only compensated for a suboptimal surgery technique. The Cancer and Leukemia Group B (CALGB) 80101 is another phase III trial that evaluated adjuvant CRT. This trial randomized 546 patients to postoperative 5-FU-based CRT or CT with epirubicin, cisplatin, and infusional 5-FU (ECF) before and after CRT with 5-FU.

Table 1. Phase III trials of postoperative strategies.

Study	N	Experimental Arm	Control Arm	Results
Intergroup Study 0116 [3]	556	Surgery + 5-FU/LV/RT	Surgery Alone	median OS of 35 vs. 27 months (HR: 1.32; P=0.0046)
CALGB 80101 [4]	546	Surgery + ECF before and after CRT with 5-FU	Surgery + 5-FU/LV/RT	5-year OS 44% vs. 44% (HR: 0.98; P=0.69)
ACTS-GC [6]	1059	Surgery (D2 ressection) + S1	Surgery alone (D2 ressection)	5-year OS 71.7% vs 62.1 (HR 0.669; 95% CI, 0.540 to 0.828)
CLASSIC Trial [7]	1035	Surgery (D2 ressection) + capecitabina and oxaliplatina	Surgery alone (D2 ressection)	3-year DFS 74% vs 59% (HR 0.56; P<0.0001)
ARTIST Trial [8]	458	Surgery (D2 ressection) + capecitabine and cisplatin plus RT with capecitabine	Surgery (D2 ressection) + capecitabine and cisplatin	5-year OS of 75% vs. 73% (HR: 1.130; P=0.5272)

Abbreviations: 5-FU: 5-Fluorouracil; LV: leucovorin; RT: radiotherapy; OS: overall survival; DFS: disease-free survival; CRT: chemoradiotherapy; HR: hazard ratio; CI: confidence interval.

There were no survival difference, with both arms reaching 5-year OS of 44% (hazard ratio [HR]: 0.98; P=0.69) and no difference in 5-year DFS (39% for FU-based CRT and 37% for ECF arm, HR 0.96; P=0.94) (Table 1)[4].

The idea of including a targeted therapy to CRT in HER-2 positive gastric or gastroesophageal junction (GEJ) cancer was evaluated in the TOXAG study. The trial enrolled 34 patients submitted to curative gastrectomy with D2 lymph node dissection. Patients received capecetabine and oxaplatin with trastuzumab for three cycles followed by radiotherapy with capecetabine for five weeks and trastuzumab for up to a year (17 cycles). The authors concluded that the regimen was safe and tolerable and median OS was not yet reached[5].

Chemotherapy regimens have shown a survival benefit in D2-dissected patients compared to observation. The Japanese ACTS-GC trial randomized 1059 patients undergoing gastrectomy with D2 lymph node resection to receive S1 after surgery or surgery alone. The 5-year OS was 71.7% for those who received S1 versus 61.1% in the surgery alone group (HR, 0.669; 95% confidence interval [CI], 0.540 to 0.828) (Table 1)[6]. The CLASSIC trial randomized 1035 patients to receive 8 cycles of capecitabine plus oxaliplatin CT or remain under observation after surgery. The 3-year DFS was higher in the group receiving CT (74% vs 59%, HR 0.56; P<0.0001) (Table 1)[7].

Few data are available comparing head-to-head CT and CRT adjuvant strategies. The ARTIST trial compared adjuvant CT, based on capecitabine and cisplatin, with CRT in patients submitted to gastric resection and D2 lymphadenectomy. Seven-year follow-up of these patients demonstrated a lower locoregional recurrence rate for the CRT arm but a similar OS. The locoregional relapse was 13% in the CT arm and 7% in the CRT arm (P=0.0033). The 5-year OS was 75% and 73% for CRT and CT, respectively (P=0.484) (Table 1)[8].

While prospective trials failed to show any difference between CT and CRT, some nonprospective trials have reported controversial results. A meta-analysis conducted by a Chinese group evaluated 960 patients from four studies (excluding CRITICS but including ARTIST) and showed benefits in terms of DFS (HR = 0.73; $P = 0.002$) and the locoregional recurrence rate (RR = 0.50; $P = 0.0005$) for patients receiving postoperative CRT, but failed to demonstrate any significant difference in OS (HR = 0.91; $P = 0.34$)[2]. A retrospective study evaluated 21.472 patients with LGC using the Surveillance and Epidemiology and End Results (SEER) database. Patients were classified using the American Joint Committee on Cancer 6th edition. For those in Stage I, the surgery alone group had the most favorable outcomes (HR: 0.67; CI: 0.60-0.76), whereas those in stages II, III and nonmetastatic stage IV were mostly benefit by postoperative CRT[9]. Another large retrospective trial using the National Cancer Database evaluated 3.656 patients and demonstrated a small survival benefit for CRT after a propensity score-matched analysis (5-year OS of 45% vs 42% for CRT vs perioperative CT; HR 0.886; P=0.033). The benefit of CRT was mostly pronounced in patients with R1 resection and was not significantly different regarding the extent of lymphadenectomy despite the fact that most of these patients (75.4%) had suboptimal lymphadenectomy[10]. An additional two retrospective trials failed to show a significant difference between the two strategies. A Chinese trial evaluated adjuvant CRT (INT-0116 regimen) and CT alone (fluoropyrimidine alone or in combination with oxaliplatin) and found a similar median OS (51.0 vs 48.6 months for CRT and CT, respectively; P=0.251)[11]. A similar Brazilian study evaluated adjuvant CRT with the INT-0116 regimen versus adjuvant platinum-fluoropyrimidine CT. There was no difference in OS (HR 0.73; P=0.212) even after a propensity score-matched analysis (HR 0.80; P=0.47)[12].

Patient selection may play a role in detecting a difference between these strategies, if any actually exist. A subgroup analysis of the ARTIST trial[8] showed that for patients with pathological involvement of lymph nodes, the 3-year DFS was prolonged in the CRT arm compared with the CT arm (77.5% vs. 72.3%; P=0.0365). This strategy is currently being prospectively evaluated in the

ARTIST-II trial (NCT01761461). A microscopically positive margin (R1) after gastrectomy can be found in 2–20% of patients[13, 14], and there is a rationale to add postoperative radiotherapy to lower the locoregional recurrence. However, no prospective trial has evaluated this specific scenario and retrospective data have shown inconsistent results. A retrospective Dutch cohort analyzed 409 cases of patients with LGC and R1 resections. A significant difference in median OS between no-CRT and CRT groups were found (24 months vs. 13 months; for CRT and no-CRT, respectively; P = 0.003), which was confirmed by a propensity score analysis (HR 0.57; 95 % CI 0.38–0.88)[15]. Another retrospective study evaluated 114 patients with LGC with R1 gastrectomy. Patients received CRT or CT consisting of platinum-fluoropyrimidine with or without epirubicin. No difference was observed in OS. The 3-year OS rates of the CRT and CT groups were 49.6% vs 39.4%, respectively (P= 0.20)[16].

Preoperative strategies

Preoperative treatment has the potential to demonstrate in vivo tumor sensitivity, to early treat micrometastasis and to promote tumor regression leading to a higher chance of R0 resection. Recent studies evaluating preoperative CT have shown impressive results. In the MAGIC trial, which enrolled 503 patients to perioperative ECF versus observation alone, the 5-year survival rate favored the ECF arm (36.3% and 29.5% for perioperative CT and observation, respectively, HR 0.75; P=0.009) (Table 2) [17]. A French phase III trial randomized 224 to perioperative treatment with cisplatin and infusional 5-FU or surgery alone. The 5-year OS favored the experimental arm (38% vs. 24%; HR: 0.69; P=0.02) (Table 2)[18]. The FLOT4 trial enrolled 704 patients to a triplet perioperative regimen consisting of docetaxel, 5-FU and oxaliplatin (FLOT) and compared it with the MAGIC trial anthracycline-based regimen. The FLOT regimen improved OS (median OS, 35 vs. 50 months for the MAGIC regimen and FLOT, respectively; HR 0.77; P= 0.012). The 3-year OS rate was 48% with the MAGIC regimen and 57% with FLOT (Table 2)[19].

The addition of monoclonal antibodies to perioperative CT was evaluated in the MAGIC-B/ST03 trial, which randomized 1.063 patients with localized esophagogastric adenocarcinoma to perioperative CT alone consisting of epirrubicin, cisplatin and capecetabine (ECX) or the same regime plus the anti-angiogenic agent bevacizumab. Interestingly, the 5-year OS did not differ between the two arms (50.3% vs. 48.1% for ECX and ECX plus bevacizumab respectively, HR 1.08; P=0.36) (Table 2)[20].

The European Organization for Research and Treatment of Cancer (EORTC) 40954 trial evaluated the strategy of neoadjuvant treatment. This phase III trial planned to enroll 360 patients but the enrollment was closed early duo to poor accrual. A total of 144 patients with gastric or GEJ adenocarcinoma were randomized to neoadjuvant cisplatin and 5-FU CT or surgery alone. The study couldn´t demonstrate a survival benefit with neoadjuvant treatment (2-year OS rate of 72.7% with CT vs. 69.9% with surgery alone, HR 0.84; P=0.466) (Table 2)[21].

The role of radiotherapy in the perioperative strategy is still not clear. The CRITICS study randomized 788 patients receiving preoperative epirubicin, cisplatin or oxaliplatin, and capecitabine CT followed by gastric resection with D1 lymphadenectomy, to receive postoperative CT (with the same preoperative regimen) or CRT with capecitabine and cisplatin. The final data did not show a difference in OS between the two regimens (median OS was 43 vs. 37 months in the CT and CRT groups, respectively; HR 1.01; P=0.90) (Table 2)[22]. The phase III POET trial was terminated early duo to poor accrual and randomized 119 patients with GEJ adenocarcinoma to neoadjuvant CT with cisplatin and FU or neoadjuvant cisplatin and FU followed by CRT with cisplatin and etoposide. The CRT arm had a

Table 2. Phase III trial of preoperative strategies.

Study	N	Experimental Arm	Control Arm	Findings
MAGIC Trial [17]	503	ECF perioperative + Surgery	Surgery Alone	5-year OS 36.3% vs. 29.5% (HR 0.75; P=0.009)
FNCLCC/FFCD [18]	224	Cisplatin and infusional 5-FU perioperative + Surgery	Surgery Alone	5-year OS 38% vs. 24%; (HR: 0.69; P=0.02)
FLOT4-AIO Trial [19]	704	FLOT perioperative + Surgery	ECF perioperative + Surgery	Median OS 50 vs. 35 months (HR 0.77; P= 0.012)
MAGIC-B/ST03 trial [20]	1.063	ECX plus Bevacizumab perioperative	ECX	5-year OS 48.1% vs. 50.3% (HR 1.08; P=0.36)
EORTC 40954 [21]	144	Neoadjuvant cisplatin and 5-FU	Surgery Alone	2-year OS of 72.7% vs. 69.9% (HR 0.84; P=0.466)
CRITICS Trial [22]	788	ECX/EOX + Surgery + CX plus RT	ECX/EOX + Surgery + ECX/EOX	Median OS 37 vs. 43 months (HR 1.01; p=0.90)
POET Trial [23]	119	neoadjuvant cisplatin and 5-FU followed by CRT with cisplatin and etoposide	Neoadjuvant cisplatin and 5-FU	5-year OS of 39.5% vs. 24.4% (HR 0.65; P=0.055)

Abbreviations: 5-FU: 5-Fluorouracil; OS: overall survival; HR: hazard ratio, CRT: chemoradiotherapy

higher rate of pathologic complete response (14.3% vs. 1.9%, P=0.03), but the 5-year OS did not statistically differ between both arms (39.5% for CRT arm vs. 24.4% for CT arm, HR 0.65; P=0.055) (Table 2) [23].

Conclusion and future directions

Whether the addition of postoperative radiotherapy brings some benefit when added to CT is still controversial. Recent studies have shown similar OS results in patients with D2 lymph node dissection. To date, no prospective data have demonstrated that any subgroup of patients may actually benefit from CRT over CT. We are waiting for the results of ARTIST-II, which is prospectively comparing both strategies for patients with pathological lymph nodes. The rationale of offering CRT for patients with R1 surgery has not been prospectively evaluated, and retrospective data are controversial.

Perioperative CT strategies have shown impressive results in recent phase III trials. The addition of radiotherapy in this scenario is still not clear, with disappointing results from CRITICS trial. However, future trials will help clarify this question. The TOPGEAR study (NCT01924819) is a phase III trial randomizing patients with LGC to perioperative ECF alone versus preoperative ECF with chemoradiation followed by postoperative ECF. Recent published data have shown that this strategy is safe and feasible[24]. Additionally, the CRITICS II trial (NCT02931890) is currently recruiting patients and aims to compare the best neoadjuvant treatment by randomizing patients into three preoperative arms: CT alone, CT followed by CRT or CRT.

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