Postoperative Chemoradiotherapy In Patients With Locally Advanced Gastric Cancer With Poor Pathologic Response To Neoadjuvant Chemotherapy

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Abstract

Background: This study sought to evaluate the effect of postoperative chemoradiotherapy (CRT) in patients with locally advanced gastric cancer (LAGC) who respond poorly to neoadjuvant chemotherapy (ChT).

Methods: The database of a tertiary medical center (2009-2019) was retrospectively reviewed for patients with LAGC in whom the initial treatment strategy consisted of perioperative ChT and surgery. Those who were subsequently referred for postoperative CRT because of a poor pathologic primary-tumor response (ypT3-4, ypN2-3, R1 resection) were selected for the study. CRT consisted of 45 Gy in 25 fractions of 1.8 Gy combined with capecitabine 825 mg/m² twice daily on radiotherapy days or continuous infusion of 5-fluorouracil 180 mg/m²/day. Intensity-modulated radiation was planned using computed tomography simulation.

Results: The cohort included 26 patients of median age 61 years with LAGC (clinical stage IIA-III) after surgery with D1-D2 lymphadenectomy. R0 resection was achieved in 15 (58%). Pathological stage was III in 69% (IIA-IVA); 73% had pT3-T4 tumors, and 65%, N2-N3 disease. Nineteen patients (73%) also received adjuvant ChT (same as neoadjuvant or different regimen) before postoperative CRT. Treatment was well tolerated, except in one patient with grade 4 vomiting. During a median follow-up time of 29 months (9-140 months), recurrences were documented in 14 patients (54%): 5 regional, 7 distant, 2 combined. Median progression-free survival was 23 months (10-140 months), and median overall survival was not reached. Estimated 5-year survival rates were 42% and 53%, respectively.

Conclusions: This small retrospective study suggests that in patients with LAGC who show a poor pathologic response to neoadjuvant ChT, a good outcome relative to reference arms in randomized trials can still be achieved with the addition of postoperative CRT. Further studies of the benefit of a tailored adaptive treatment approach to LAGC based on the response to neoadjuvant ChT are warranted.

Background

Gastric cancer is commonly diagnosed at an advanced stage, either with extensive locoregional involvement or involved regional lymph nodes. Complete surgical resection is curative in less than 40% of cases [1]. In patients with deep invasion of the gastric wall or regional lymph node metastases, relapse and death rates from recurrent cancer exceed 70–80%. Locoregional recurrences in the tumor bed, the anastomosis, or regional lymph nodes occur in 40–65% of patients after curative intent resection [2].

The high frequency and significant mortality of LAGC after local or regional relapse have made adjuvant radiotherapy to the tumor and surrounding tissue an attractive option. Accordingly, the U.S. Intergroup study (INT-0116) found that median relapse-free and overall survival (OS) improved in patients treated by complete gastric resection with the addition of adjuvant chemoradiotherapy (CRT) [3]. Following these results, postoperative adjuvant CRT using the so-called “Macdonald regimen” became the standard of care in the USA. The survival benefit was preserved after 11 years of follow-up [4].

Parallel to the adjuvant CRT approach, a second treatment paradigm emerged based on the administration of perioperative chemotherapy (ChT) without radiotherapy. The pivotal prospective randomized MAGIC trial showed that the addition of perioperative epirubicin, cisplatin, and fluorouracil (ECF) was associated with tumor down-staging at surgery and improved median progression-free survival (PFS) and OS compared to surgery alone [5]. These findings were supported by the FLOT4-AIO trial wherein a perioperative ECF-based regimen consisting of fluorouracil plus leucovorin, oxaliplatin, and docetaxel (FLOT) yielded an increase in median disease-free survival and OS [6].

The good results for both approaches, although difficult to compare directly owing to the different modalities and timing of treatment, initially led to their wide acceptance as standard of care. Later, concerns regarding the INT-0116 trial were raised because most patients underwent D0-D1 lymph node dissection, and the subsequent ARTIST trial showed no benefit of postoperative CRT following D2 dissection [7]. Nevertheless, the role of CRT kept evolving, because in an exploratory subgroup analysis, the ARTIST trial had demonstrated its benefit for patients with positive lymph nodes. However, the subsequent ARTIST 2 trial found no significant difference in effect between postoperative ChT and CRT [8]. Consequently, current guidelines prefer perioperative ChT, reserving postoperative CRT for patients who underwent upfront surgery with less than D2 lymph node dissection [9].

As perioperative ChT and postoperative CRT each proved to be efficacious separately, other trials strived to define the best combination of the two. In the landmark CRITICS study, patients were treated with preoperative ChT and surgery and then randomized between postoperative ChT and postoperative CRT. Unfortunately, the trial failed to meet its primary endpoint, with similar event-free survival and median OS in both arms [10].

In all the above-mentioned trials and treatment approaches, all patients received the same ChT regimen in the preoperative and postoperative settings, regardless of the pathological response of the tumor. Although lack of a pathologic response to preoperative ChT is a recognized adverse prognostic factor [11–13], there are currently no data to indicate that choosing a different postoperative regimen might be of benefit. The aim of the present study was to evaluate outcomes in patients with a poor pathologic response to preoperative ChT who received postoperative CRT according to our institutional policy.

Methods

Patients and setting

The Gastrointestinal Cancer Clinic database of a tertiary medical center was searched for patients with locally advanced (clinical stage II-III) gastric cancer (LAGC) in whom the initial planned treatment strategy was perioperative ChT followed by surgery. Included in the study were those who had a poor pathologic response to ChT, defined as ypT3-4 and/or ypN2-3 and/or R1 resection, and were referred for postoperative CRT.

The study protocol was approved by the Institutional Ethics Committee.

CRT procedure

Following a 3-hour fast, patients underwent a 2.5mm slice computed tomography simulation in the supine position with wing immobilization. Clinical target volume (CTV) consisted of the following: residual stomach and tumor bed including anastomoses or stumps, clips, areas of resected perigastric local tumor extension, and the draining lymph nodes including gastric, gastroepiploic, celiac, porta hepatis, subpyloric, gastroduodenal, splenic, suprapancreatic, and retropancreaticoduodenal nodes. For proximal lesions involving the cardia or gastroesophageal junction with any positive nodes, the lower paraesophageal nodes were included. The planning target volume (PTV) included the CTV with a 1cm margin for setup variation and organ motion. CRT consisted of 45 Gy in 25 fractions of 1.8 Gy, combined with capecitabine 825 mg/m² twice daily on radiotherapy days or continuous infusion of 5FU 180 mg/m²/day. Radiation treatment was planned using intensity-modulated radiation therapy (IMRT) in order to reduce the dose to organs at risk.

Data collection

The following clinical data were collected from the medical files: patient age, tumor location and subtype, preoperative treatment details, surgical approach and extent of lymph node dissection, pathologic outcomes, postoperative treatment details, recurrence pattern, and survival.

Statistical analysis

The statistical analysis was generated using SPSS statistical software, version 25 (IBM® SPSS® Inc., Chicago, IL) with the Essentials for R extension (R version 3.2.2). Data were summarized using standard descriptive statistics for demographic and clinical variables. OS was assessed by Kaplan-Meier analysis. Recurrence was assessed by a regression analysis with the Fine and Gray correction for death with no recurrence as a competing risk.

Results

Patient characteristics and preoperative treatment

The cohort included 26 patients. Their background and preoperative treatment characteristics are presented in Table 1. Median age was 61 years (range 34–87). A majority (73%) had proximal tumors and presented at clinical stage III (65%). Preoperative ChT regimens prescribed until 2017 were ECF-based, administered in a median of 3 cycles (range 2–6), and after 2017, either FLOT or FOLFOX (folinic acid, fluorouracil, oxaliplatin), administered in a median of 4 cycles (range 3–6).

Surgical and postoperative treatment

Treatment details are depicted in Table 2. The most common surgical approach was total gastrectomy, in 77% of patients, with D2 lymph node dissection in 61%. The median number of lymph nodes excised was

27 (range 9–49). R0 resection was achieved in only 58% of patients. All patients had a poor pathologic response; 24 (92%) had residual ypT3-4 tumors and 2 had ypT2N3 disease.

All patients except one (96%) completed CRT, for a total dose of 45Gy in 25 fractions, delivered concurrently with capecitabine in most cases (81%) or with 5-fluorouracil in the remainder (19%). The treatment was well tolerated overall, with no toxic deaths. Only one patient stopped treatment prematurely due to grade 4 diarrhea, nausea, and vomiting. The rate of grade 3–4 toxicity was low (12%), causing diarrhea, nausea and vomiting, dysphagia, and mucositis.

Recurrence and survival

Patients were followed for a median of 29 months (range 9-140 months). During this period, recurrence was documented in 14 patients (54%): 11 distant (42%) and 3 locoregional (12%), with only one in-field recurrence. Median PFS was 23 months (range 10–140) with a 5-year PFS of 42%. Median OS was not reached; 5-year OS was 54% (Fig. 1).

Discussion

The current standard of care for medically fit patients with potentially resectable LAGC is comprised of perioperative ChT with the FLOT regimen. Previous trials tested combinations of preoperative and postoperative chemotherapy and radiotherapy, providing alternative treatment options for various clinical scenarios. However, in all of the prospective trials, patients were treated in a pre-planned sequence, without taking the tumor response to preoperative treatment into account. Although the idea of modifying the treatment agent or modality in order to overcome tumor resistance is appealing, data supporting a response-adaptive treatment approach are currently lacking. Therefore, in the present study, we evaluated treatment outcomes in patients with a poor pathologic response to preoperative ChT who received postoperative CRT.

We found that with a median follow-up of 29 months (range 9-140), median PFS for the entire cohort was 23 months, and median OS was not reached. Five-year PFS and OS rates were 42% and 54%, respectively. The locoregional recurrence rate was 12%. An exploratory comparison between our results and those of pivotal earlier randomized studies [3,5,6,10] is presented in Table 3. Both 5-year and median OS in our study compared favorably with previous ones which reported a range of 36-45% and 36-50 months, respectively. Five-year PFS was reported only in the CRITICS trial and was 39%, similar to our result. Median PFS was shorter in our study than the reported range of 28-30 months. Recurrence rates should be interpreted carefully, as they were reported at different time points. However, the locoregional recurrence rate in our study seems to be in line with values reported by others (7-24%).

The favorable long-term PFS and OS results in the present trial using an adaptive approach may point to a successful salvage attempt and a better outcome than expected for poor-risk patients. The low number and proportion of locoregional recurrences in our study, with only one in-field recurrence, support the concept that salvage radiation therapy in poor responders may prevent loco-regional disease recurrence

and improve results overall. The relatively shorter median PFS in our study may be attributed mostly to patients in whom metastatic disease emerged a short while after treatment completion, reflecting the dismal prognosis of this high-risk population.

The studies cited in the above comparison included unselected patients, whereas our cohort consisted solely of poor responders to preoperative ChT. An exploratory study of the prognostic value of a pathologic response in the MAGIC trial cohort found that median OS in the CHT-treated patients with a poor pathologic response (Mandard tumor regression grade 3-5) was 20.47 months, notably shorter than reported for unselected patients in other trials. On multivariate analysis, only lymph node status was predictive of OS. The high-risk population with positive lymph nodes was well represented in our study, accounting for 73% of the patients who received preoperative ChT [13].

The main limitations of the present study are the small number of patients included, the retrospective design, and the inherent bias of limiting the cohort to high-risk poor responders who recovered from preoperative ChT and surgery and could tolerate postoperative CRT. The main strength of this study is the novel exploratory approach in a real-life clinical setting, with a complete dataset allowing for accurate evaluation of the benefit of adaptive treatment for selected patients.

In conclusion, in this small retrospective study, patients with LAGC who had a poor pathologic response to neoadjuvant ChT achieved a relatively good outcome following postoperative CRT. These results support the consideration of individualized, adaptive treatment for LAGC in highly selected patients according to pathological response to neoadjuvant ChT. This approach is still exploratory and warrants evaluation in future randomized studies in this setting.

Abbreviations

ChT, chemotherapy; CRT, chemoradiotherapy; CTV, clinical target volume; ECF, epirubicin, cisplatin, and fluorouracil; FLOT, fluorouracil plus leucovorin, oxaliplatin, and docetaxel; FOLFOX, folinic acid, fluorouracil, oxaliplatin; IMRT, intensity-modulated radiation therapy; LAGC, locally advanced gastric cancer; OS, overall survival; PFS, progression-free survival; PTV, planning target volume

Declarations

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Authors' contributions

OG conceptualization, data collection, statistical analysis, manuscript writing.

RL study conceptualization, data collection, manuscript writing.

GP data collection.

OU data collection.

BB data collection, manuscript review.

YK conceptualization, data collection, manuscript review.

All authors read and approved the final manuscript.

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Data Availability Statement

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Code availabililty

Not applicable

Ethics approval and consent to participate

This study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Ethics Committee.

Consent for publication

Not applicable.

Competing interests

The authors delcare that they have no competing interests.

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Tables

Table 1 Clinical and pretreatment characteristics of 26 patients with LAGC

Characteristics	Value
Age (years), median (range)	60 (34-87)
Tumor location	
Proximal	19 (73%)
Distal	7 (27%)
Disease type	
Diffuse	14 (54%)
Intestinal	12 (46%)
Signet ring cell histology	16 (62%)
Preoperative ChT*	
ECF/ECX/EOX	20 (77%)
FLOT/FOLFOX	6 (23%)

Values are n(%) unless otherwise indicated.

LAGC, locally advanced gastric cancer; ChT, chemotherapy;

ECF, epirubicin, cisplatin, fluorouracil; ECX, epirubicin, cisplatin,

capecitabine; EOX, epirubicin, oxalplatin, capecitabine; |FLOT,

fluorouracin, leucovorin, oxaliplatin, docetaxel; FOLFOX, folinic

acid, fluorouracil, oxaliplatin

*ECF/ECX/EOX, before 2017; FLOT/FOLFOX, after 2017

Table 2 Characteristics of surgery and postoperative treatment in 26 patients with LAGC

Characteristics	Value
Primary surgery	
Total gastrectomy	20 (77%)
Distal gastrectomy	4 (15%)
Proximal gastrectomy+distal esophagectomy	2 (8%)
Lymph node dissection	
D1	9 (35%)
D2	16 (61%)
Unknown	1 (4%)
Resection margins	
R0	15 (58%)
R1	11 (42%)
ypT stage	
2	2 (8%)
3-4	24 (92%)
ypN stage	
0	7 (27%)
2	2 (8%)
2-3	17 (65%)
Grade	
WD/MD	2 (8%)
PD	23 (88%)
Unknown	1 (4%)
PNI/LVI present	19 (73%)

Values are n (%).

LAGC, locally advanced gastric cancer; WD, well-differentiated; MD, moderately Differentiated; PD, poorly differentiated; PNI, perineural invasion; LVI, lympho-vascular invasion

Table 3 Comparison of present study to pivotal trials in the literature

Study	5-yr PFS	5-yr OS	Median PFS	Median OS (mo)	Locoregional recurrence (%)	Non-locoregional recurrence (%)
INT-0116[3]	NA	NA	30	36	24	27
MAGIC[5]	NA	36	NA	NA	14	24
CRITICS[10]	39	41	28	43	7	54
FLOT4[6]	NA	45	30	50	NA	NA
Present study	**42**	**54**	**23**	NR	**12**	**42**

OS, overall survival; PFS, progression-free survival; NA, not available, NR, not reported

Figures

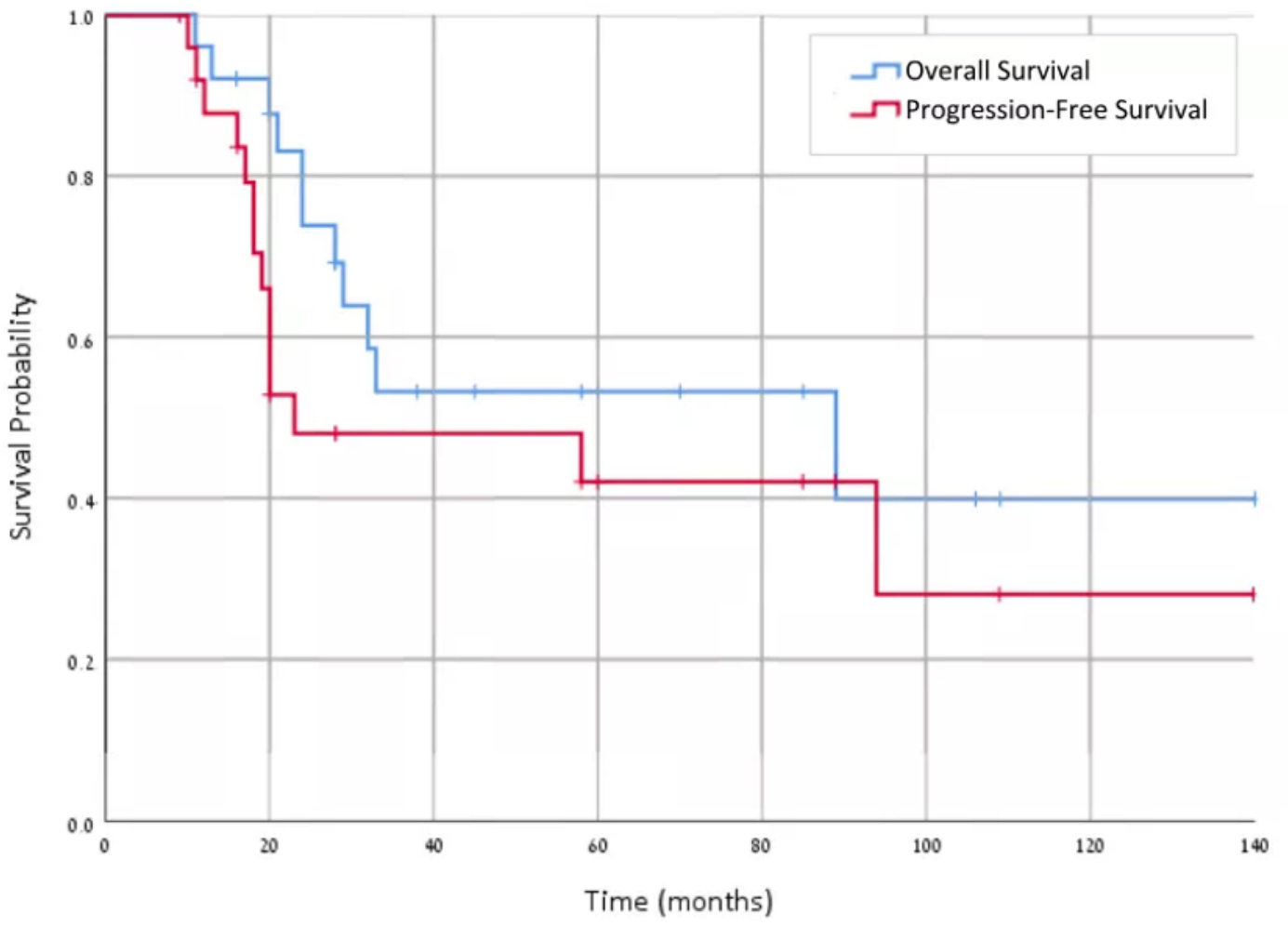

Figure 1

Overall and progression-free survival in 26 patients with LAGC