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ORIGINAL RESEARCH

Outcomes of gastrectomy following upfront chemotherapy in advanced gastric cancer patients with a single noncurable factor: a cohort study

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Wei Li[1]
Huiqin Jiang[1]
Yiyi Yu[1]
Yan Wang[1]
Zhiming Wang[1]
Yuehong Cui[1]
Kuntang Shen[2]
Zhenbin Shen[2]
Yong Fang[2]
Tianshu Liu[1,3]

[1]Department of Oncology, Zhongshan Hospital, Fudan University, Shanghai, China; [2]Department of General Surgery, Zhongshan Hospital, Fudan University, Shanghai, China; [3]Center of Evidence-Based Medicine, Fudan University, Shanghai, China

Purpose: Chemotherapy is the standard care for patients with incurable advanced gastric cancer. Whether or when the addition of gastrectomy to chemotherapy improves survival of advanced gastric cancer patients with a single noncurable factor remains controversial. We aimed to evaluate the superiority of gastrectomy following chemotherapy vs chemotherapy alone regarding overall survival (OS) in these patients.

Patients and methods: Patients with advanced gastric cancer from January 2008 to December 2014 were retrieved from our prospectively acquired database and retrospectively analyzed. The patients with a single noncurable factor were grouped in terms of cancer treatment: chemotherapy alone or gastrectomy following chemotherapy.

Results: Four hundred and fourteen patients (333 chemotherapy alone and 81 gastrectomy following chemotherapy) were included in this study. Kaplan–Meier survival curve showed a significant difference on median OS between chemotherapy-alone group and the gastrectomy plus chemotherapy group (10.9 vs 15.9 months, $P<0.01$). After propensity score analysis (n=126), chemotherapy plus surgery (81 patients) also showed survival benefit over chemotherapy alone (35 patients) (15.9 vs 10.0 months, $P<0.01$). Furthermore, stratified analyses indicated that patients with liver metastasis, <65 years of age, male, having normal level of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA199) upon diagnosis, or having nongastro-esophageal junction tumor benefited from surgery.

Conclusion : This study suggests that gastrectomy after chemotherapy could lead to survival benefit over chemotherapy alone in advanced gastric cancer patients with a single nonresectable factor if the disease was controllable by chemotherapy.

Keywords: gastric cancer, palliative surgery, overall survival, propensity score analysis

Introduction

Gastric cancer is one of the most common diseases affecting human health worldwide and the third leading cause of death among malignant tumors.[1] In China, most gastric cancer patients present with advanced stage disease, who are not eligible for curative surgical treatment. Chemotherapy is the standard care for these patients. For advanced gastric cancer patients, palliative surgery is considered only for the palliation of symptoms such as obstruction or uncontrollable bleeding.

With the development of surgical techniques, complications of palliative gastrectomy have decreased gradually. There are a number of studies to explore the value of palliative resection in advanced gastric cancer. Some studies indicated that certain subgroup of patients could benefit from nonradical surgery; however, in most pro-

Correspondence: Tianshu Liu
Department of Oncology, Zhongshan Hospital & Center of Evidence-Based Medicine, Fudan University, 180 Fenglin Road, Shanghai 20032, China
Tel +86 136 8197 3996
Email liu.tianshu@zs-hospital.sh.cn

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spective studies, the sample size was small and the survival time for patients undergoing gastrectomy ranged from 3 to 24 months.[2–6] A large sample study in Poland included 3,141 patients between 1990 and 2005, of whom 415 had distant metastases and underwent nonradical surgery.[7] The long-term follow-up data showed that nonradical surgery obviously improved survival time (median survival time, 10.6 vs 4.4 months; $P<0.05$). However, the data were out of date because there were no effective chemotherapeutic drugs at that moment, leading to short overall survival (OS) in chemotherapy-alone group. A number of randomized controlled trial (RCT) studies in recent years have shown that the median OS (mOS) for patients with advanced gastric cancer undergoing palliative chemotherapy is about 1 year.[8–12] Therefore, it is necessary to re-evaluate the surgical value in advanced gastric cancer.

To assess the effect of gastrectomy on such patients, we retrospectively compared the survival between those received preoperative chemotherapy combined with gastrectomy (including nonradical resection) and those underwent conventional treatment (palliative chemotherapy).

Patients and methods

Patients

We performed a retrospective review of patients between January 2008 and December 2014 from a prospectively acquired gastric cancer database of Fudan University Zhongshan Hospital. To be eligible, the patient cases had to meet the following criteria: 1) pathologically diagnosed as gastric adenocarcinoma, 2) had complete baseline computed tomography (CT) scan data, 3) in the presence of a single noncurable factor confirmed by CT and/or exploratory laparotomy, which was defined as liver metastasis (H1: equal to or less than four lesions and maximum diameter ≤5 cm), ovarian metastatic implants (unilateral or bilateral), distant lymph node metastasis including celiac lymph node, or peritoneal metastasis (P1), which meant implants from the diaphragm to the pelvic without ascites or intestinal obstruction,[13] 4) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, 5) chemotherapy as the first-line treatment after diagnosis, and received at least two cycles of chemotherapy regimens, and 6) the definition of chemotherapy combined surgery group: total gastrectomy or distal subtotal resection combined with or without resection of metastases (such as liver resection). No requirement was made on lymph node dissection.

The exclusion criteria were: 1) exploratory laparotomy revealed extensive abdominal metastasis; 2) received emergency surgery due to bleeding or obstruction; 3) received palliative surgery first after diagnosis; and 4) patients only received exploratory operation. No requirement was made for local radiotherapy, such as distant lymph node regional radiotherapy.

This study was approved by the Ethics Committee of Zhongshan Hospital, Fudan University (B2015-098) and was in compliance with the Declaration of Helsinki. All patients who were included in the database signed the informed consent to review and use their medical records.

Data collection

All eligible patients were followed-up by telephone and/or outpatient service. Those who could not connect were retrieved by the ID card number via the public health center database. The follow-up ended until the date of death or the last follow-up time, December 31, 2017.

Evaluation criteria

Tumor stage was re-evaluated according to the international TNM staging system (2010 American Joint Committee on Cancer, 7th edition).[14] The efficacy of cancer treatment was evaluated using RESIST 1.1 standard.[15] OS time was defined as the time from the date of diagnosis to the date of death.

Statistical analysis

Statistical analysis was carried out using SPSS 22.0 and Stata 13.0. The clinical characteristics of the two groups (chemotherapy with or without follow-up surgery) were compared using a chi-squared test for categorical variables. The survival curve was created using the Kaplan–Meier (K–M) method. Propensity score analysis (PSA) was used to leverage confounding factors. All statistical tests were two-sided, and the differences were considered statistically significant at a P-value <0.05.

Results

Patient characteristics and treatment

Based on the prospective gastric cancer registration database in Zhongshan Hospital, Fudan University, a total of 414 newly diagnosed patients, between January 1, 2008 and December 31, 2014, were selected for retrospective cohort analysis according to the eligibility criteria described above (Figure 1). Among them, 333 were treated with chemotherapy alone, and 81 patients underwent gastrectomy after chemotherapy. The choice of chemotherapy regimen was mainly decided by the agreement between doctors and patients or by multi-disciplinary team (MDT) based on patients' individual status. The feasibility of surgery was discussed and decided

by the MDT. The patients received either a double-drug regimen of oxaliplatin plus fluorouracil (capecitabine or S-1), or a triple-drug regimen of oxaliplatin, fluorouracil, and docetaxel/anthracyclines. Of the 333 patients in the chemotherapy-alone group, 268 (80.5%) received doublet, and 65 (19.5%) received triplet. In the surgical group, 54 (66.7%) were placed on a double-drug regimen, and 27 (33.3%) on triple-drug regimen. The patients in the chemotherapy-alone group received a median of eight chemotherapy cycles (range 4–20). All patients in surgical group were subjected to postoperative chemotherapy except one patient died 30 days after operation. The number of upfront chemotherapy cycles was two to six, and the postoperative chemotherapy cycles ranged from zero to six cycles with a median of three cycles. The total chemotherapy cycles were four to ten with a median of six for the surgical group.

The surgical procedure included subtotal gastrectomy or total gastrectomy, combined with or without resection of the metastatic sites. Among the 81 patients, 52 (64.2%) patients were subjected to R0 resection on primary gastric lesions only, and 14 (17.3%) on both gastric and metastatic lesions simultaneously. Fifteen patients were subjected to R1 resection. One patient died within 30 days after gastrectomy (OS, 3.3 months). A total of 81 patients (52 from the chemotherapy group and 29 from the surgical group) accepted local treatment (including radiofrequency and radiotherapy).

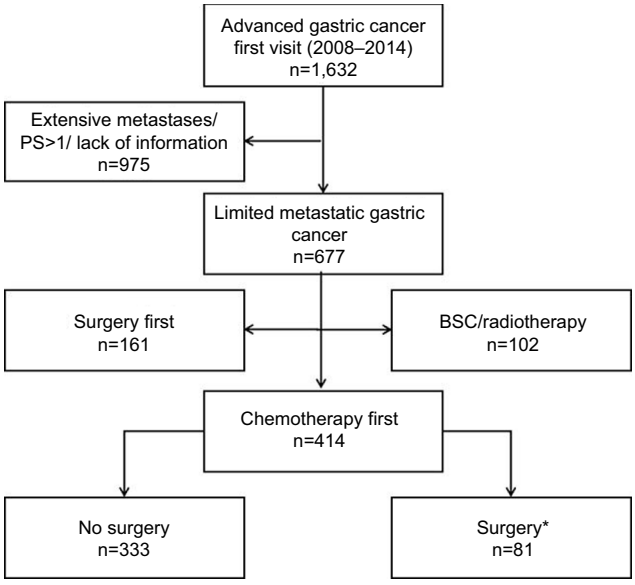

Figure 1 Flow diagram of patients involved in the analysis.
Notes: *The surgical procedure included gastrectomy, combined with or without resection of the metastatic sites.
Abbreviation: PS, propensity score; BSC, best supportive care.

Efficacy outcomes

The first efficacy evaluation result indicated a partial response (PR) rate of 33.3% (107/321), stable disease (SD) 48.9% (157/321), and progress disease (PD) 17.7% (57/321) in the chemotherapy group – a PR rate of 48.1% (39/81), SD 49.4% (40/81), and PD 2.5% (2/81) in the chemotherapy plus surgery group. Four patients in the surgical group had radiographic assessments of PR, while the surgical specimen indicated pathological complete remission.

The median follow-up time was 18 months till the last follow-up time December 31, 2017, when 309 (74.6%) patients died, including 251/333 (75.4%) patients from the chemotherapy-alone group and 58/81 (71.6%) in the surgical group. The overall median survival time was 12.5 months. There was a significant difference between the chemotherapy plus surgical group and the chemotherapy-alone group (15.9 vs 10.9 months, $P<0.01$, Figure 2A). The median survival time after surgery was 13.3 months (data not shown).

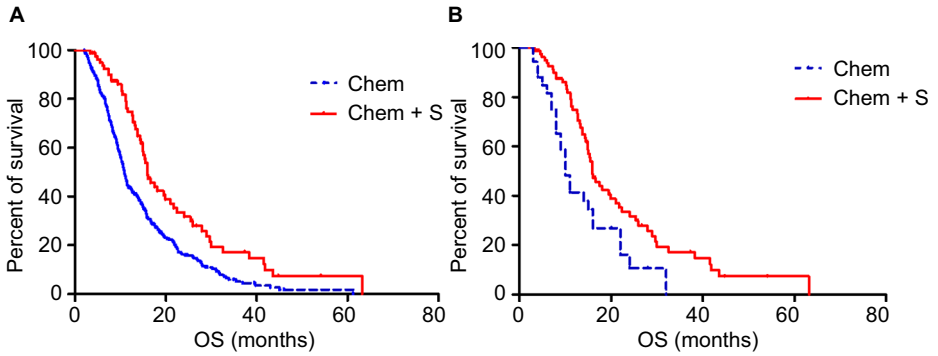

Figure 2 (**A**) Kaplan–Meier curve of overall survival in all patients (N=414, Chem + S vs Chem: 15.9 vs 10.9 months, $P<0.01$). (**B**) Kaplan–Meier curve of overall survival after PSA (N=116, Chem + S vs Chem: 15.9 vs 10.0 months, $P<0.01$).
Abbreviations: Chem, chemotherapy-alone group; Chem + S, chemotherapy plus surgery group; OS, overall survival; PSA, propensity score analysis.

Propensity score analysis

Given the difference of baseline variables between the two groups, propensity score analysis was performed to reduce the offset. The covariables included gender, age, location of tumor, T stage, location of metastasis, and CEA + CA199 level. Applying the nearest neighbor matching method (1:1) with a caliper of 0.01, we re-assessed the OS between the two groups. After correction, there was no statistical difference between the two groups in sex, age, tumor location, and CEA + CA199 level, other than the location of metastasis (Table 1). In the operation group, the proportion of patients with lymph node metastasis was higher. For K–M survival analysis after propensity score (PS) correction, there were statistical differences on mOS between the chemotherapy group and the surgical group (10.0 vs 15.9 months, $P<0.01$, Figure 2B).

Furthermore, stratified analyses were performed for included patients after PS. The results showed that patients with liver metastasis, <65 years of age, male, having normal level of CEA and CA199 upon diagnosis, or having non-gastroesophageal junction (non-GEJ) tumor benefited from gastrectomy (Figure 3).

Discussion

We retrospectively evaluated the feasibility and efficacy of induction chemotherapy followed by surgery for advance gastric cancer patients with a single noncurable factor. The median OS was 15.9 months for patients underwent surgery and 10.9 months for patients administered chemotherapy alone. After PSA to reduce the offset between the two groups, the median OS of surgery patients was still higher than chemotherapy-alone patients (15.9 vs 10.0 months). AIO-FLOT3 study was conducted recently to assess the survival benefit of neoadjuvant chemotherapy followed by surgical resection on patients with limited metastatic gastric or GEJ cancer.[16] The patients in group B with limited metastatic cancer (N=60), similar to our study population, received chemotherapy first and proceeded to surgical resection if restaging showed a chance of R0 resection of the primary tumor and a macroscopic complete resection of the metastatic lesions. The median OS was 31.3 months for those received surgery (36/60) vs 15.9 months for the rest (24/60), suggesting the feasibility of surgery after chemotherapy. The results were in accordance to our data, although the median OS in our study was much shorter. Differences may come from the distinct people included in those groups: the group B patients in AIO-FLOT3 study could be converted into a R0 resection after chemotherapy, while the patients in our study were difficult to achieve the goal of conversion and were not forced to have a radical surgery.

The REGATTA study compared the survival of patients with gastric adenocarcinoma with a single noncurable factor, who received either chemotherapy alone or chemotherapy after palliative surgery. Unfortunately, the authors failed to observe any improvement of OS by gastrectomy (mOS of 16.6 vs 14.3 months).[13] However, our study showed that chemotherapy followed by surgery had survival benefit over chemotherapy alone for patients with advanced gastric cancer.

Table 1 Clinical characteristics before and after matching on propensity score

Variables		Before matching		*P*-value	After matching		*P*-value
		Chemotherapy, n=333 (%)	Chemotherapy + surgery, n=81 (%)		Chemotherapy, n=35 (%)	Chemotherapy + surgery, n=81 (%)	
Gender	Male	202 (60.7)	63 (77.8)	0.00	22 (62.9)	63 (77.8)	0.10
	Female	131 (39.3)	18 (22.2)		13 (37.1)	18 (22.2)	
Age	≤65	240 (72.1)	49 (60.5)	0.04	22 (62.9)	49 (60.5)	0.84
	>65	93 (27.9)	32 (39.5)		13 (37.1)	32 (39.5)	
Primary site	GEJ	56 (16.8)	12 (14.8)	0.32	4 (11.4)	12 (14.8)	1.00
	Stomach	277 (83.2)	69 (85.2)		31 (88.6)	69 (85.2)	
Metastatic site	Liver	121 (36.3)	10 (12.2)	0.00	10 (28.6)	10 (12.2)	0.01
	Peritoneum	186 (55.9)	8 (9.8)		8 (22.8)	8 (9.8)	
	Lymph node	20 (6.0)	60 (74.1)		17 (48.6)	60 (74.1)	
	Others (ovary)	6 (1.8)	3 (3.7)		0	3 (3.7)	
CEA + CA199 level[a]	0	51 (15.3)	8 (9.8)	0.30	5 (14.3)	8 (9.8)	0.79
	1	147 (44.1)	42 (51.9)		17 (48.6)	42 (51.9)	
	2	133 (39.9)	30 (37.0)		13 (37.1)	30 (37.0)	
	NA	2 (0.6%)	0		0	0	

Notes: [a]Both CEA and CA199 levels within the reference value were assigned as 0, either one higher than the reference value as 1, both higher than the reference value as 2. The reference value: CEA ≤5 ng/mL and CA199 ≤37 U/mL.

Abbreviations: GEJ, gastroesophageal junction; NA, not available.

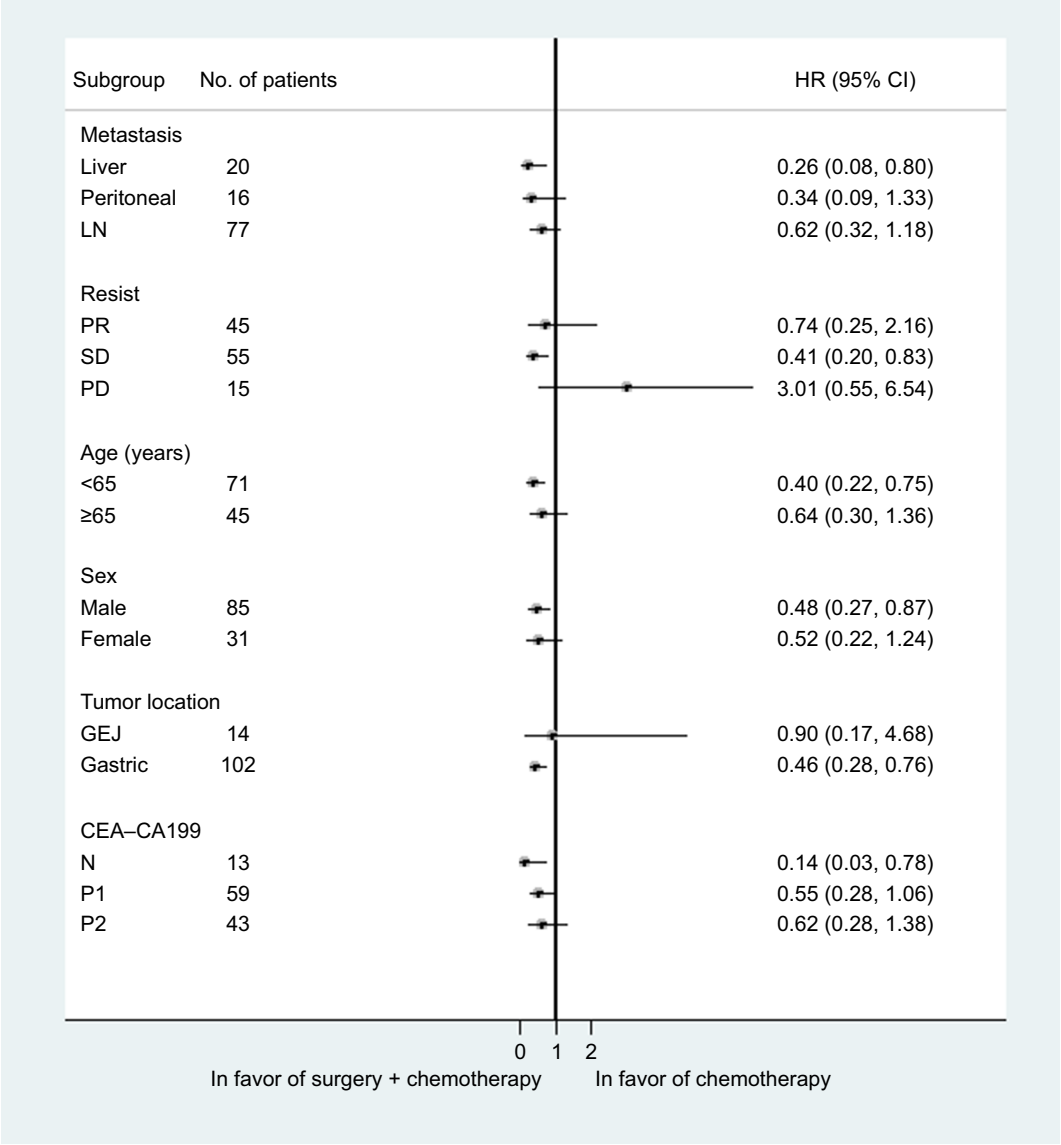

Figure 3 Forest plots for subgroup analyses.
Note: HRs for death in the patients accepted chemotherapy + surgery are shown with 95% CI.
Abbreviations: GEJ, gastroesophageal junction; PD, progress disease; PR, partial response; SD, stable disease; LN, lymph node; HR, hazard ratio.

The disparity can be raised from following conditions: 1) Patients in the REGATTA trial did not receive preoperative chemotherapy. Some patients may progress during early treatment, and chemotherapy can be used to exclude these patients who are not eligible for surgery. 2) Patients were more tolerant to chemotherapy before gastrectomy. In REGATTA study, only half of the patients, with tumors located in the upper one-third of stomach and receiving total gastrectomy, completed the chemotherapy cycles.

Notably, patients with liver metastases had a remarkable survival benefit from surgery in our study, which may be related to nearly tumor-free status after simultaneous surgery or radiofrequency ablation of liver metastases. This result was consistent with previous studies.[17,18] In the

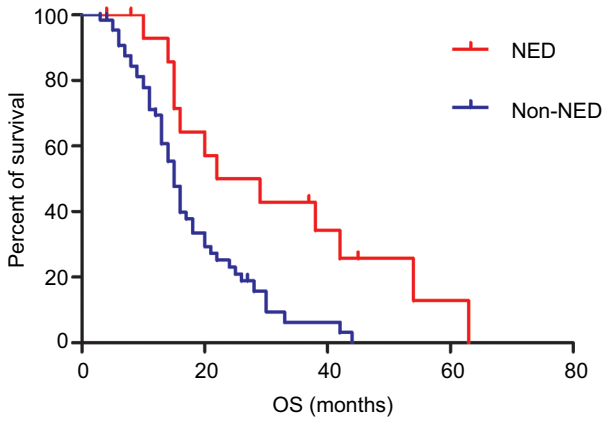

Figure 4 Kaplan–Meier curve of overall survival in patients underwent surgical procedures: attaining NED status vs non-NED status (N=81, $P<0.01$).
Abbreviations: NED, no evidence of disease; OS, overall survival.

surgical group, 16 patients attained no evidence of disease (NED) status after treatment. These patients had a better survival benefit than others (25.5 vs 15.0 months, $P<0.01$, Figure 4). The concept is well accepted in colorectal cancer that patients have better survival benefits by attaining NED status.[19–21] Our study showed a similar result in gastric cancer.

Interestingly, in the SD subgroup, surgery seemed to achieve the best benefit at the first interim evaluation, whereas no significant benefit for PR patients receiving operation (Figure 3). This may be because chemotherapy was the key contributor to survival benefit for PR patients, which weakens the role of operation. Moreover, patients who received surgery during disease progression showed a poor prognosis, suggesting that salvage surgery was not recommended for patients after primary chemotherapy. In terms of the tumor sites, patients with gastric cancer but not the GEJ tumor benefited significantly from surgery. It is speculated that GEJ patients underwent a total gastrectomy, leading to a poor tolerance to assigned chemotherapy.

Previous studies have reported that levels of CEA and CA199 may be as one of the predictors of surgical benefit.[22] We sought to differentiate patients according to CEA and CA199 levels and found that patients with normal CEA and CA199 levels benefited most from surgery, while those in the CEA and CA199 elevation groups had less benefits. Although the underlying mechanism is unknown, a possible explanation is that the levels of CEA and CA199 reflect tumor burden and are associated with prognosis after treatment.[23]

As a real-world study, there are some limitations in this study, such as the inconsistency between the two groups of patients and the disunity of the chemotherapy regimen. However, our study suggests that palliative surgery is not completely undesirable in advance gastric cancer and can be carefully considered for patients with stable disease after chemotherapy. Patients could receive more tangible benefits by attaining NED status through comprehensive treatment including surgery.

Conclusion

The present study suggests that gastrectomy after chemotherapy may lead to survival benefits in gastric cancer patients with a single nonresectable factor. Patients with liver metastasis, <65 years of age, male, normal level of CEA and CA199 upon diagnosis, or non-GEJ tumor are recommended to undergo conversion surgery. Especially, patients attaining NED status through comprehensive treatment have a significantly prolonged survival. This result needs to be further confirmed through RCT studies.

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Disclosure

The authors report no conflicts of interest in this work.

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