The efficacy and safety of continuous intra-arterial infusion neoadjuvant chemotherapy with surgery for locally advanced gastric cancer: a preliminary pilot study

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Background: Neoadjuvant chemotherapy (NAC) followed by R0 resection is regarded as a standard treatment strategy for locally advanced gastric cancer (GC); however, the response to systemic chemotherapy remains unsatisfactory. Continuous intra-arterial infusion chemotherapy (CAIC) is a new method, compared with systematic chemotherapy, it can deliver chemotherapy drugs more accurately, so as to achieve higher surgical conversion rate. This study aimed to explore the efficacy and safety of CAIC in locally advanced GC patients.

Methods: In this retrospective pilot study, four patients with histologically confirmed locally advanced GC were identified from a tertiary hospital between May 2018 and December 2018. Clinic stage was belonged to T4N1-3M0 in all cases with potential probability for surgery. All cases received three cycles of NAC by CAIC with oxaliplatin (100 mg on day 1) plus oral S-1 (80 mg/m^2/day twice daily for 14 days) (SOX). Contrast-enhanced computed tomography (CT) scans and pathological examinations were performed to evaluate chemotherapeutic response based on the tumor regression grade (TRG) and post-neoadjuvant pathological Tumor Node Metastasis (ypTNM) staging. All cases were regularly followed up with face-to-face interviews at outpatient, abdominal enhanced CT scan and serum tumor markers were be requested at 3-month intervals for up to 1 year postoperatively.

Results: The obstruction was significantly alleviated after three cycles of CAIC. Contrast-enhanced CT scans showed decreased tumor volume to some extent, along with lymph node shrinkage after treatment. Radical (R0) resection was achieved in all cases. Histopathological analysis showed tumor downstaging in three cases and upstaging in one case. The tumor response to treatment demonstrated TRG1a in one case, TRG1b in one case, and TRG2 in two cases, with an overall tumor regression rate of 100%. No obvious adverse events or perioperative complications were observed during or following treatment. All cases were alive without tumor recurrence or progression after the 1-year postoperative follow-up.

Conclusions: Our study may shed light on super-selective CAIC as an effective method for improving the NAC response in locally advanced GC. Future studies with a larger sample sizes and long-term outcomes are required for a final conclusion.

Keywords: Locally advanced gastric cancer; continuous intra-arterial infusion; neoadjuvant chemotherapy (NAC); SOX regimen

Introduction

Gastric cancer (GC) is one of the leading causes of malignancy-related morbidity and mortality worldwide (1), and especially in East Asia. Most GC patients are already at an advanced stage when diagnosed (2). Although surgical resection is the only curative treatment for GC, many patients with advanced disease fail to achieve R0 resection after surgery alone. Preoperative or neoadjuvant chemotherapy (NAC) has been regarded as the standard of care for patients with locally advanced GC, especially in terms of tumor downstaging, improved radical (R0) resection, and survival outcomes (3,4). Previous studies of preoperative systemic chemotherapy have reported a complete or subtotal pathological response rate of 3.3–37%, and an overall pathologic response rate of 42.2–89.7% (5-9). Various chemotherapy regimens and routines have been studied for the perioperative treatment of patients with advanced GC. However, due to the inaccuracy of chemotherapeutic drug delivery and the inability to maintain local high drug concentration, chemotherapy response remained unsatisfactory. The development of more effective and less toxic treatment options for GC remains a priority to enhance the surgical opportunities and survival outcomes of patients.

Intra-arterial infusion chemotherapy (CAIC) can increase the local drug concentration around the tumor sites, thereby offering potentially greater efficacy and less toxicity. Chemotherapy administered via intra-arterial infusion has been reported to result in a 20–30% higher response rate in advanced GC patients when compared with systemic chemotherapy (10). Regional arterial infusion chemotherapy (RAIC) is a form of CAIC in GC that involves injecting chemotherapeutic drugs directly into the tumor site via the tumor-feeding artery. Compared with systematic chemotherapy, RAIC can improve the tumor response and reduce the toxicity of drugs (11). Unlike RAIC, CAIC involves direct and continuous delivery of chemotherapeutic drugs into the tumor site through a tumor-feeding artery for a longer period of time. CAIC has been reported to provide survival benefits in patients with advanced hepatic cancer (12). However, few studies have been carried out with respect to neoadjuvant CAIC in GC. Also, as a useful tool for intraoperative navigation, C-arm computed tomography angiography (CACTA) has been used to assist in super-selective catheterization during CAIC for various types of cancer, including hepatic cancer (13,14). Thus, the purpose of this study was to evaluate the efficacy and safety of CACTA-guided super-selective CAIC in locally advanced GC patients. We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-304/rc).

Methods

Patients and study design

In this retrospective study, patients with locally advanced GC were identified from the Second Affiliated Hospital of Zhejiang University School of Medicine between May 2018 and December 2018. Eligible patients were those aged 18 years or above, had histologically confirmed GC, and received three cycles of preoperative CAIC followed by surgery. Details regarding patient demographics, preoperative chemotherapy, radiographic re-evaluation, operation, pathology reports, adverse effects, and postoperative outcomes were collected via chart review of the patients' medical records. The patients were then prospectively followed up for recurrence or progression of the disease at 3-month intervals for at least 1 year after surgery. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the independent Institutional Review Board of the Second Affiliated Hospital of Zhejiang University School of Medicine (No.2021-1051). Written informed consent was obtained from each patient.

Preoperative staging and treatments

Preoperative staging was evaluated with contrast-enhanced CT according to the 8th edition of the Tumor Node Metastasis (TNM) classification (15). All patients received oral S-1 (80 mg/m^2 twice daily for 14 days) plus CAIC with oxaliplatin (100 mg for 5 hours on day one) for three cycles, with each cycle lasting for 3 weeks. A modified fluorouracil, leucovorin and oxaliplatin (FOLFOX6) regimen was initially administrated due to the obstruction symptoms, and was replaced by S-1 plus Oxaliplatin (SOX) once the symptoms were alleviated. The modified FOLFOX6 consisted of a CAIC of oxaliplatin (100 mg/m^2) on day 1, followed by an intravenous injection of leucovorin (400 mg/m^2) on day 1, an intravenous injection of 5-fluorouracil (400 mg/m^2), and then a continuous intravenous infusion of 5-fluorouracil (2,400 mg/m^2) for 46 hours on day 1 every 3 weeks. After three cycles of NAC, the patients received total or subtotal gastrectomy with D2

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lymphadenectomy.

Intra-arterial oxaliplatin was administered via the femoral artery using the Seldinger's technique. Briefly, a 2.4 F microcatheter (Merit Maestro microcatheter, Merit Medical, Utah, USA) was directed to a super-selective tumor feeding artery based on CACT in angiography. Oxaliplatin mixed with 250 mL of 5% glucose solution was then infused into the super-selective artery (50 mL/h). If more than one artery were involved in tumor feeding, the most important one was selected for intra-arterial infusion. A specific artery was selected accordingly in each cycle (*Figure 1*). All patients were re-evaluated for the feasibility of surgery via contrast-enhanced CT after three cycles of treatment. Distal gastrectomy with D2 lymphadenectomy was then performed.

Tumor response and adverse effects

Resected tumor specimens were examined for surgical margin status (R0, R1, and R2) and post-neoadjuvant pathological TNM (ypTNM) staging. The pathological response was graded according to the Becker regression criteria (16): (I) tumor regression grade (TRG)1a: complete pathological regression without any residual tumor cells; (II) TRG1b, subtotal regression with <10% residual tumor cells; (III) TRG2, partial regression with 10–50% residual tumor cells; and (IV) TRG3, minor or no regression with >50% residual tumor cells. The adverse events were collected from the patients' medical records.

Follow-up

Every 3 months, all patients received face-to-face interviews at outpatient to know whether there were discomfort symptoms such as nausea, vomiting, abdominal distension, abdominal pain and obstruction. At the same time, they received abdominal enhanced CT and serum tumor markers to find out whether the tumor had recurrence and metastasis. The postoperative follow-up was requested for more than 1 year in all patients.

Results

Baseline patient characteristics

From May 2018 to December 2018, a total of four patients were included in this study, all of whom completed the 1-year postoperative follow-up. The baseline demographics and clinical characteristics of the patients are summarized in *Table 1*. All patients were diagnosed with stage IIIA/IIIB gastric adenocarcinoma with obstruction that required jejunal feeding.

Clinical and pathological findings

The patients' obstructions were significantly alleviated. A liquid diet was possible 3–5 days after the first cycle of treatment. All patients resumed oral intake after three cycles of treatment. CT scan showed shrinkage in tumor volume and enlarged lymph nodes, as well as marked edema of the gastric wall adjacent to the tumor area (*Figures 1,2*). Also, compensatory enlargement of the non-target tumor feeding arteries was observed, along with atrophy of the target artery and decreased tumor staining on CAIC (*Figures 3,4*).

The surgical and pathological findings of the patients are shown in *Table 2*. R0 resection was achieved in all patients. Histopathological assessment showed tumor downstaging in three patients and upstaging in one patient. As for the pathological response, two patients achieved a complete (TRG1a) or subtotal (TRG1b) response, while the other two patients achieved a partial response (TRG2).

Meanwhile, no adverse events or perioperative complications were observed during or after treatment. All patients were alive without tumor recurrence or progression after the 1-year postoperative follow-up.

To sum up, the obstructive symptoms of all patients were relieved, tumor downstaging was evaluated by CT scan (4/4) and histopathology (3/4), conversion rate of R0 resection was 100%. The pathological response in all patient was 100%, including a complete/subtotal regression rate of 50%. There was no recurrence or metastasis after 1-year follow-up.

Discussion

Local intra-arterial administration of chemotherapeutic agents has been reported to produce 10-fold higher serum concentrations than systemic intravenous chemotherapy (2). The intra-arterial route is associated with a higher overall chemotherapy response rate than that of the systemic intravenous route. In our study, the tumor feeding artery of the included patients was defined using the CACTA technique. A microcatheter was then used to accurately deliver the chemotherapeutic drugs to the targeted arteries, so as to keep high local concentrations. Furthermore, the microcatheter was retained for a long time period
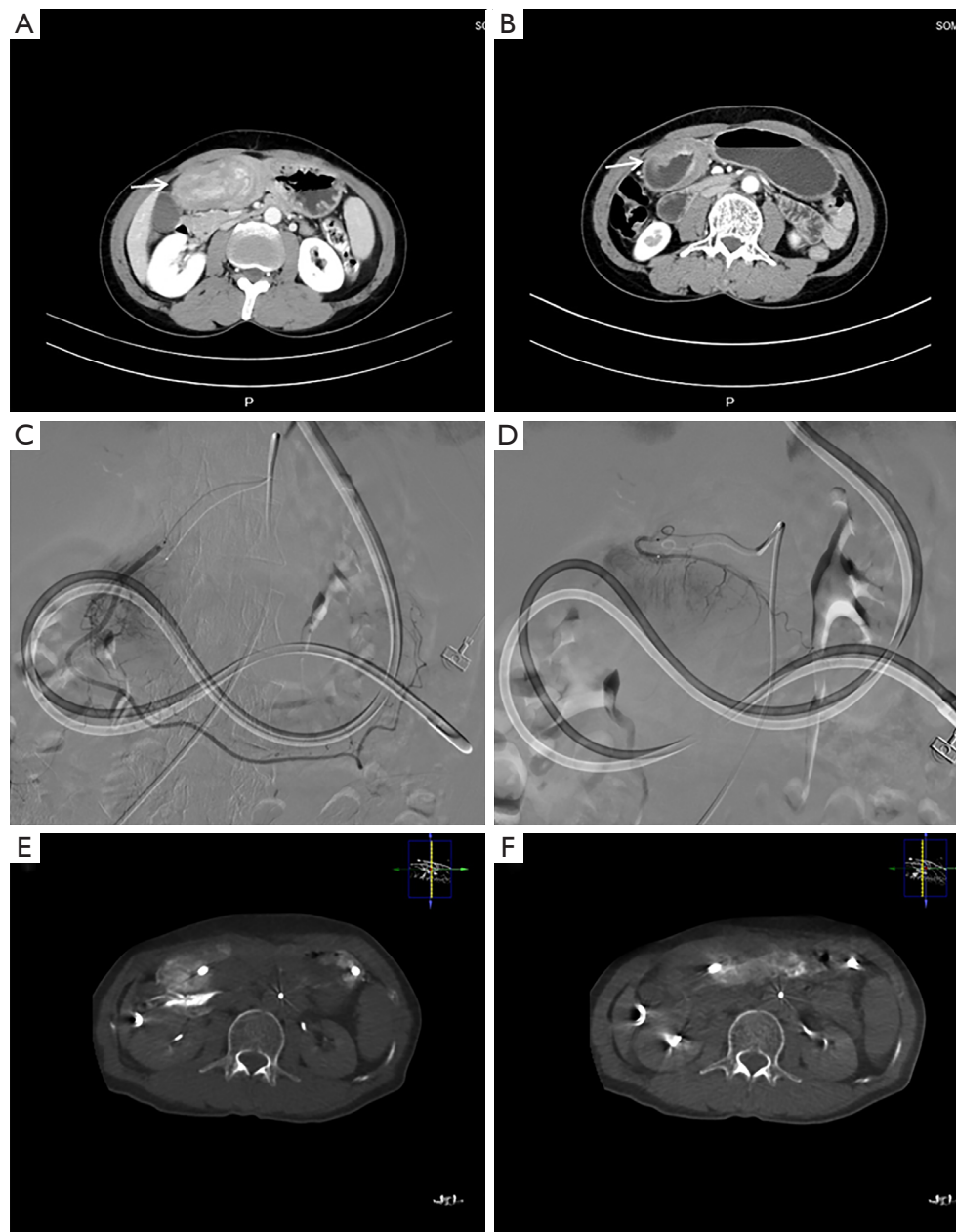
Figure 1 The CACTA-guided super-selective continuous intra-arterial infusion chemotherapy and radiologic response after three treatment cycles (Case 2). A tumor located in the gastric antrum (A, white arrow), tumor feeding artery with gastroduodenal artery (C), and right gastric artery (D) were confirmed by intraoperative CACTA technology (E,F). The tumor was obviously regressed after three cycles of continuous intra-arterial infusion chemotherapy, along with the marked edema of the surrounding gastric wall (B, white arrow). CACTA, C-arm CT angiography.

(5 hours) to steadily perfuse chemotherapeutic drugs that can continuously act on tumor cells, while at the same time reducing the discomfort and incompliance of patients encountered during the CAIC.

The contrast-enhanced CT scan showed varying degrees of tumor volume reduction, which is a potential independent prognostic factor for advanced GC patients who had received NAC (17). Also, as a significant

Table 1 Patient demographics and clinical characteristics

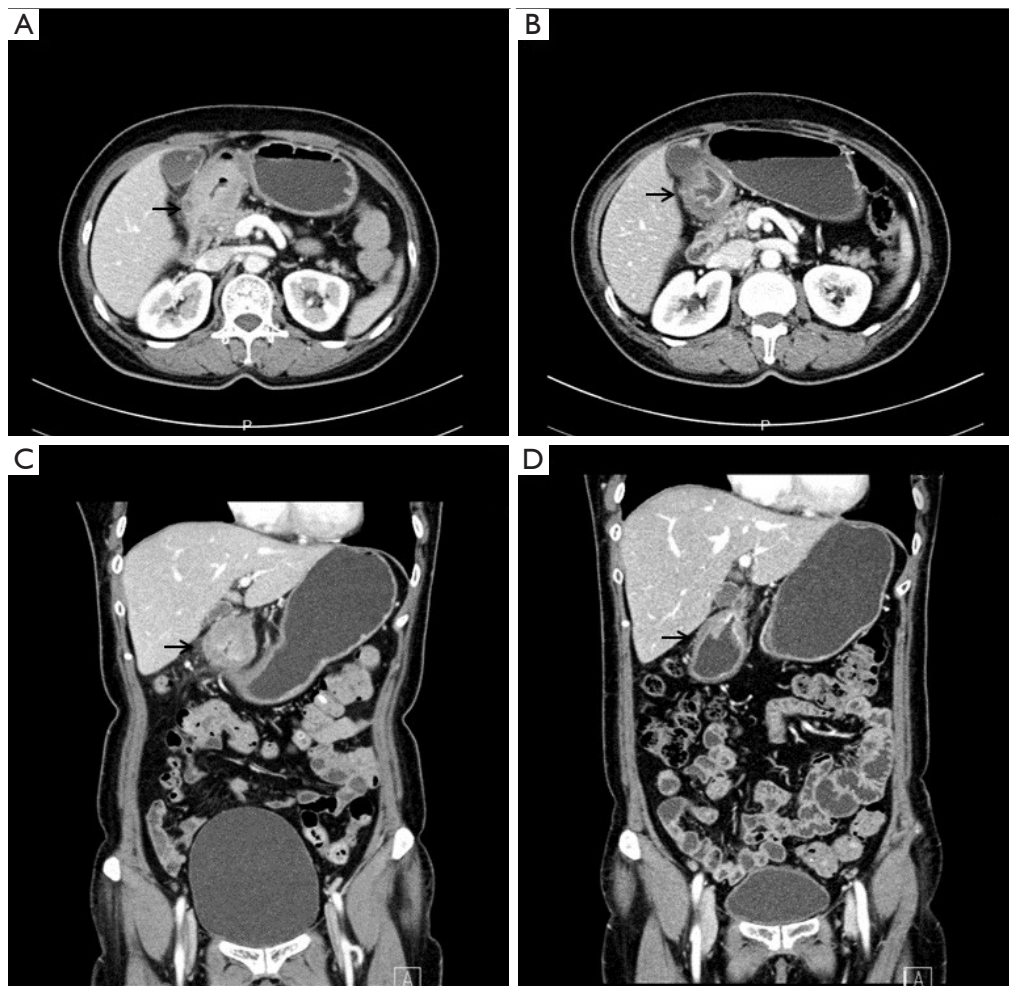| Variables	Case 1	Case 2	Case 3	Case 4
Age, years	57	59	65	71
Sex	Female	Female	Male	Male
Tumor location	Gastric antrum	Gastric antrum	Gastric angle	Gastric antrum
Tumor invasion	cT_{4a}	cT_{4a}	cT_{4a}	cT_{4a}
LNM	cN_{3a}	cN_1	cN_1	cN_2
cTNM staging	IIIB	IIIA	IIIA	IIIA
Obstruction	Yes	Yes	Yes	Yes

LNM, lymph node metastasis.

Figure 2 The patient (Case 1) had a tumor located in the greater and lesser curvatures of the gastric antrum (A,C, black arrow). CT scan showed a markedly reduced tumor volume after three cycles of continuous intra-arterial infusion chemotherapy and obvious edema of the gastric wall adjacent to the tumor area without enhancement (B,D, black arrow). Postoperative pathological examination showed complete tumor regression. CT, computed tomography.

Figure 3 The patient (Case 3) had a tumor located in the gastric angle. The first angiography showed the gastroduodenal artery as the tumor feeding artery and strong tumor staining (A, white arrow). After three cycles of continuous intra-arterial infusion chemotherapy, the image showed atrophy of the target arteries and a remarkable decrease in tumor staining (B, white arrow).
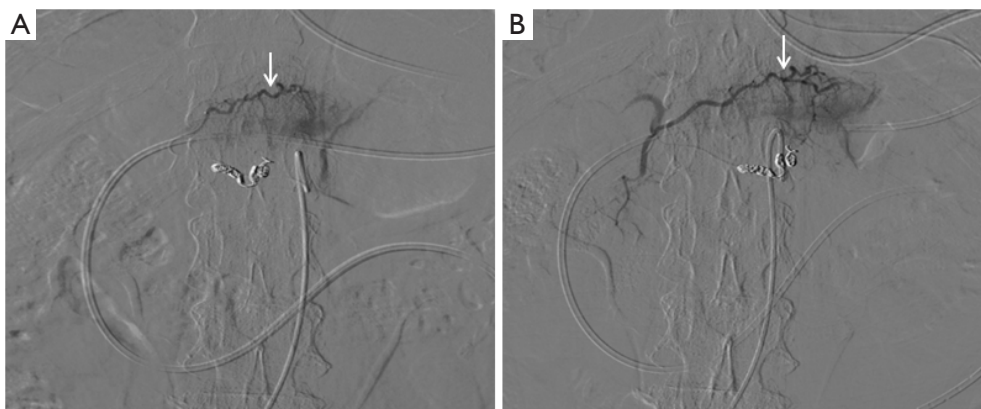

Figure 4 The patient (Case 4) had a tumor located in the gastric antrum. The first angiography showed the gastroduodenal artery as the primary tumor feeding artery, and the right gastric artery was also involved in tumor feeding (A, white arrow). After continuous intra-arterial infusion chemotherapy via the gastroduodenal artery, the second angiography showed compensatory enlargement of the right gastric artery that was not used for continuous intra-arterial infusion chemotherapy, and an increase in tumor staining (B, white arrow).

Table 2 Surgical and pathological findings

Variables	Case 1	Case 2	Case 3	Case 4
Surgical margin	R0	R0	R0	R0
Tumor invasion	T_0	T_{4a}	T_{4a}	T_{4a}
LNM	N_0	N_0	N_0	N_2
Distant metastasis	M_0	M_0	M_0	M_1
ypTNM stage	0	II	II	IV
TRG	TRG1a	TRG1b	TRG2	TRG2

LNM, lymph node metastasis; TRG, tumor regression grade; ypTNM, post-neoadjuvant pathological Tumor Node Metastasis.

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determinant of prognosis (18), tumor downstaging was also observed in three cases after CAIC. Tumor upstaging was noted in one case, since a nodule on the abdominal wall was not observed on CT scan, although the tumor and lymph node classification remained unchanged. TRG after preoperative chemotherapy has been established as an important prognostic factor in patients with advanced GC for tumor downstaging, recurrence, and patient survival (5). In this study, the TRG after CAIC were TRG1a (n=1), TRG1b (n=1), and TRG2 (n=2), with a complete/subtotal regression rate of 50% and an overall regression rate of 100%.

A higher overall pathological response rate [91.3% (42/46); 100% (78/78)] was observed in previous studies of advanced GC patients who received combined intravenous and intra-arterial neoadjuvant chemotherapies with FLEP (5-FU, leucovorin, etoposide, and cisplatin) or FLEEOX (5-FU, leucovorin, etoposide, oxaliplatin, and epirubicin) (19,20). However, a comparatively lower response rate was also noted in patients who received RAIC with EOX (56.1%, 46/82; epirubicin, oxaliplatin, and capecitabine) or EOF (42.4%, 72/170; epirubicin, oxaliplatin, fluorouracil, and calcium folinate) regimens (11,21). The potential reasons for this may be partially explained by the different regimens and methods of RAIC, as well as the criteria and cutoff levels used for pathologic response [Becker criteria, Mandard criteria, Japanese Classification of Gastric Carcinoma (JCGC) histological criteria]. Notably, the complete or subtotal pathologic response rates were only 11.54% and 30.43%, respectively, in the above-mentioned two studies of combined intravenous and intra-arterial neoadjuvant chemotherapies. The data were well within the range reported in patients treated with preoperative systemic NAC (19,20). In addition to the comparatively lower complete/subtotal pathologic response rates, the combined intravenous and intra-arterial procedures are complicated, which may limit their practical use as well as patient compliance. Based on what has been discussed above, super-selective CAIC showed promising efficacy in the neoadjuvant treatment of locally advanced GC patients.

Moreover, no obvious drug-related adverse events or perioperative complications were observed in multiple processes of CAIC in this study. This unexpected performance may be partly attributable to the lower dosage of the chemotherapy agents (approximately 1/2–2/3 of the recommended dose for systematic NAC) administrated locally into the tumor sites. Additionally, the CACTA-

based micrometer system used for the super-selection of specific feeding arteries for long-term continuous infusion chemotherapy. These measures can not only ensure local drug concentration for tumor eradication, but also minimize the effect on the normal arteries. Taken together, our study showed good tolerance of CAIC in neoadjuvant treatment of locally advanced GC. The super-selective CAIC may serve as a promising alternative to systemic NAC in locally advanced GC patients.

Obstruction is commonly observed in advanced GC. Patients with obstruction often present with deeper cancer invasion and more lymph node metastases. Also, the survival rates of these patients are significantly lower compared with those without obstruction (12). The definitive role of chemotherapy as an initial treatment for relieving obstruction remains unclear (22). In this study, all four GC patients had obstruction that required jejunal feeding at baseline. The clinical symptoms were evidently improved after three treatment cycles, and oral intake was resumed in all patients. These results suggested that CAIC may be a potential alternative treatment option for GC patients with obstruction.

This study also has some limitations that should be noted. Firstly, only a few cases were included in this preliminary study. Secondly, radiologic response was not evaluable due to the marked edema of the gastric wall adjacent to the tumor area, which posed a major challenge in assessing the tumor response after treatment. Despite this, contrast-enhanced CT scanning showed shrinkage in tumor size and lymph nodes. Meanwhile, compensatory enlargement of the non-target tumor feeding arteries was also observed, along with atrophy of the target arteries and a decrease in tumor dyeing on CAIC (*Figures 3,4*). These results not only corroborated the report of Kruk-Bachonko *et al.* that enhancement of the GC lesion would weaken if chemotherapy was effective (1), but also acted as evidence for the effectiveness of neoadjuvant CAIC. Unfortunately, only 1-year postoperative follow-up was available, and thus, the long-term effects require further evaluation.

This preliminary pilot study showed promising efficacy and good tolerance of CAIC in NAC treatment of locally advanced GC. Future studies with a larger sample sizes and long-term outcomes are needed for a final conclusion.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-304/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-304/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-304/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the independent Institutional Review Board of the Second Affiliated Hospital of Zhejiang University School of Medicine (No.2021-1051). Written informed consent was obtained from each patient.

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