Palliative Therapy for Gastric Cancer

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K. Ji, P. Yuan, Z. D. Bu, and J. F. Ji

The past decades have witnessed the constant decrease in the morbidity and mortality of gastric cancer; however, as the fifth most common malignant tumor, gastric cancer is still the third most common cause of cancer death [1]. There were about one million new cases and 723,000 deaths from gastric cancer in 2012, among which Chinese patients accounted for about 50% [1]. Due to its insidious onset and the lack of specificity of signs and symptoms, over 80% of gastric cancer cases are in an advanced stage for being diagnosed. The 5-year survival rate is low. Even in patients who have received radical resection, the risk of distal metastasis or local recurrence can still be high [1]. The vast majority of patients with gastric cancer still need palliative care after the disease progresses to a certain stage. For patients with unresectable or advanced gastric cancer, palliative care should be provided as early as possible. The principles of palliative treatment for advanced gastric cancer are to relieve pain, improve their quality of life, and prolong survival by alleviating symptoms. The palliative care for advanced gastric carcinoma can be either local therapy or systemic therapy. Cytotoxic chemotherapy has been applied as the preferred systemic treatment in patients with metastatic gastric cancer; however, it often cannot alleviate the local symptoms (e.g., nausea, pain, gastrointestinal obstruction, and bleeding) in patients with locally advanced tumors or with distant metastasis. For these patients, multidisciplinary management using local treatments including endoscopy, surgery, and radiotherapy should be used. In this chapter, we will describe the palliative care in patients with locally advanced unresectable gastric cancer or those with metastatic gastric cancer.

Local Palliative Care

Local palliative care is a therapeutic option for controlling the progression of local symptoms such as obstruction, pain, nausea, and bleeding. It includes palliative surgery, surgical bypass, endoscopic techniques, and palliative radiotherapy. Improving the overall prognosis of patients should be the major principle during the selecting of any local palliative care protocol; that is, effort should be made to lower the morbidity and mortality of patients with advanced gastric cancer and avoid long hospital stay.

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Palliative Gastrectomy

Palliative gastrectomy is feasible for advanced gastric cancer patients who had received systemic treatment. The benefits of palliative gastrectomy include alleviating symptoms including obstruction, bleeding, pain, and nausea. Retrospective studies have suggested surgery may be associated with a survival benefit [2–5]. Meanwhile, some literature also has questioned the benefits of palliative resection for patients with advanced gastric cancer (Fig. 25.1) [6, 7]. In a retrospective study, Schmidt B. et al. found that the survival was not significantly different between patients who had undergone palliative gastrectomy and those had not, although they also mentioned that there might be sample selection bias. Compared with patients who had only received bypass surgery or those without surgical intervention, patients who had undergone surgical resection might have lower disease burden, better physical status, and better prognosis [6].

In a phase III clinical randomized controlled trial (REGATTA) jointly initiated by Fujitanni K and Yang HK, the authors investigated the superiority of gastrectomy followed by chemotherapy

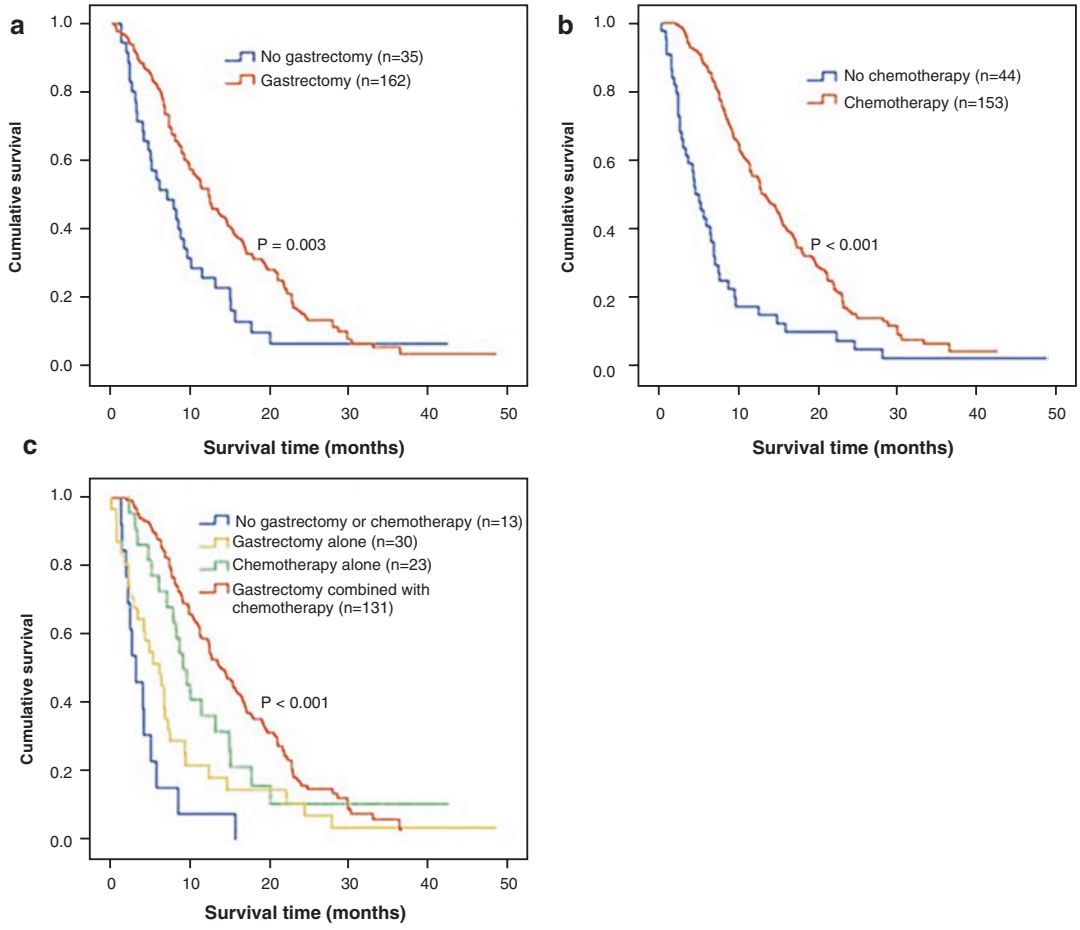

Fig. 25.1 Survival curves of patients grouped with different treatments. (**a**) Overall survival between patients undergoing non-curative gastrectomy and those without (12.4 vs. 7.1 months, $P = 0.003$). (**b**) Overall survival between patients with and without postoperative chemotherapy (MST 13.2 vs. 4.3 months, $P < 0.001$). (**c**) The comparison between patients with non-curative gastrectomy combined with postoperative chemotherapy and the other treatment groups ($P < 0.001$). *MST* median survival time [5]

versus chemotherapy alone with respect to overall survival in patients with advanced gastric cancer with a single non-curable factor [8]. A single non-curable factor was defined as hepatic metastasis (H1), peritoneal metastasis (P1) without massive ascites or intestinal obstruction, or para-aortic lymph node metastasis above the celiac axis or below the inferior mesenteric artery (lymph node N016a1/b2 of maximum diameter ≥1 cm), or both [8]. Patients were randomized into two groups: in the surgery group, patients underwent gastrectomy (D1) followed by palliative chemotherapy, without receiving D2 lymphadenectomy or multivisceral resection; in the chemotherapy alone group, only palliative chemotherapy was applied. The overall survival analysis showed that there was no significant survival benefit in patients who had received palliative gastrectomy. The 2-year survival (25.7% vs. 31.4%, HR 1.08, 95% CI 0.74–1.58, $P = 0.66$) and median overall survival (mOS) (14.3 months vs. 16.6 months, HR 1.09, 95% CI 0.78–1.52, $P = 0.70$) were even worse in the surgery group, although the difference was not statistically significant [8]. In addition, the incidences of several chemotherapy-associated adverse events (leucopenia, anorexia, nausea, and hyponatremia) significantly increased in patients assigned to surgery group; thus, gastrectomy cannot be justified for treatment of patients with these tumors [8].

Gastrojejunal Anastomosis

Gastrojejunal anastomosis (e.g., surgical bypass) is suitable for patients with unresectable advanced gastric cancer accompanied by malignant gastric outlet obstruction. Palliative gastrojejunostomy can improve food intake in these patients [9]. Minimally invasive laparoscopic gastrojejunal anastomosis is a feasible procedure for the palliative treatment of malignant gastric outlet obstruction. In a small-scale retrospective study compared the surgical outcomes of laparoscopic ($n = 10$) and open ($n = 10$) gastrojejunostomies in patients with gastric outlet obstruction secondary to advanced malignancies. It was found that there was no significant difference between groups in mean surgery time (116 vs. 116 min) ($P = 0.99$); however, the blood loss (23 vs. 142 ml; $P = 0.19$) was less, and the length of stay (8 vs. 14 days; $P = 0.14$) was shorter in the laparoscopic group, although the difference was not statistically significant due to the small sample size [10]. According to the currently available evidences, gastrojejunal anastomosis may be an alternate treatment for patients who cannot be treated by minimally invasive approaches (e.g., palliative radiotherapy and endoscopic techniques [such as ablation, stenting, or J-tube placement] with/without chemotherapy).

Endoscopic Stent Placement

Malignant intestinal obstruction is a common complication in patients with advanced gastric cancer. Its main symptoms include pain, nausea, vomiting, abdominal distention, and decreased oral intake, which can lead to dehydration and malnutrition and thus seriously affect the patients' quality of life. Compared to traditional gastroduodenal anastomosis, the self-expandable metal stents (SEMS) have become a routine clinical technique and can be used in patients with inoperable malignant intestinal obstruction due to advanced gastric cancer or other accompanying medical conditions; in particular, it can be used as a palliative treatment for elderly patients [11]. The indications of SEMS for advanced gastric cancer include the following: (a) unable to eat; (b) with poor nutritional status; (c) inoperable; and (d) with surgical risk or refuse to take a surgery. In our center, the gastric outlet obstruction scoring system (GOOSS) was used for assessing the oral intake. In 13 advanced gastric cancer patients and 1 patient with duodenal cancer accompanied by pyloric obstruction who had undergone the placement of uncovered self-expandable metal stents (Niti-STM Taewoong Medical, Korea) in our center in 2016 (Figs. 25.2 and 25.3 and Table 25.1), GOOSS scoring results (Table 25.2) showed that the oral intake was significantly improved after stent placement (Fig. 25.4). The median time to reconstruction after stent placement was 186 days, during

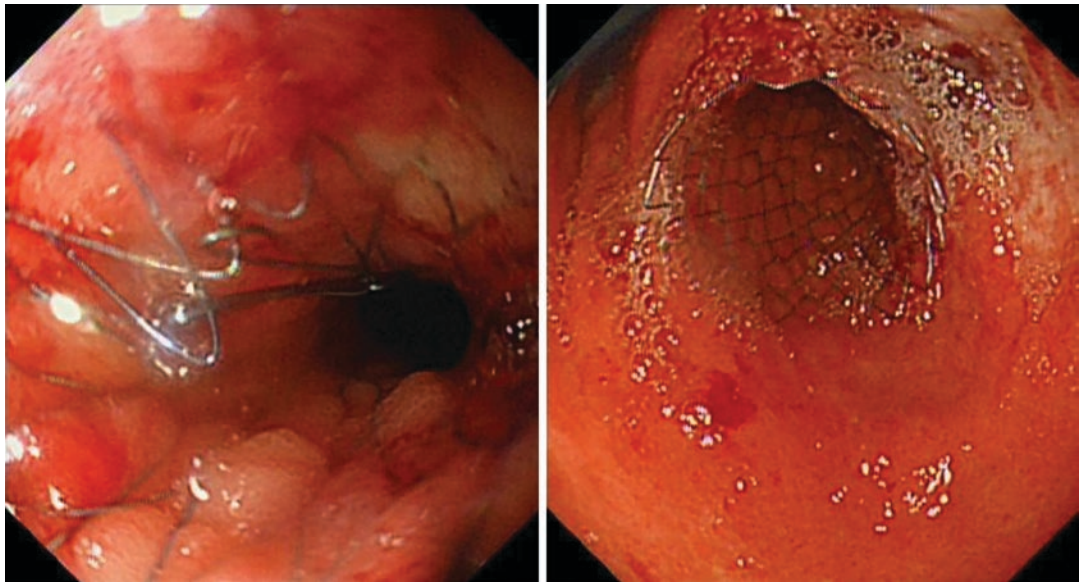

Fig. 25.2 Endoscopic view of SEMS at the site of sinuses ventriculi

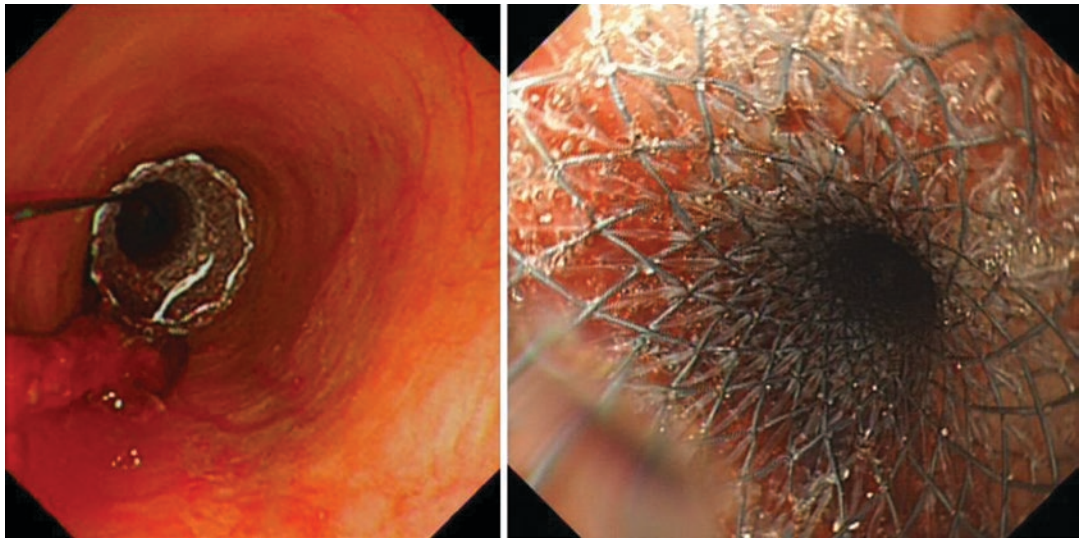

Fig. 25.3 Endoscopic view of SEMS at the site of esophagogastric junction

which three patients suffered from complications and one patient with duodenal cancer died from bleeding 3 days after stent placement at pylorus (Tables 25.3 and 25.4). Notably, all patients suffered from pain and discomfort after stent placement and thus needed the oral administration of pain medications. Although our study has shown that SEMS, as a non-surgical treatment for malignant gastric outlet obstruction, is safe and effective and can maintain the patency of the gastrointestinal tract within a certain time, it still has certain limitations. For malignant obstruction caused by other reasons, endoscope placement of a gastrojejunal feeding tube can also be applied in patients who are unable to undergo endoscopic placement of SEMS.

Table 25.1 Patient characteristics

Characteristics	No.	%
Patients	14	
Sex (M/F)	14	(100/0)
Mean ± SD age, years (range)	68.79 ± 10.47	
Causative disease		
Esophagogastric junction carcinoma	6	42.88
Recurrences of at the anastomotic site after operation for gastric carcinoma	1	7.14
Gastric antrum carcinoma with pyloric obstruction	2	14.28
Recurrences of remnant gastric cancer	1	7.14
Gastric antrum carcinoma	2	14.28
Duodenal carcinoma with pyloric obstruction	1	7.14
Gastric carcinoma with abdominal metastases	1	7.14

M male, *F* female, *SD* standard deviation

Table 25.2 Patient scores

	Before SEMS placement		After SEMS placement	
GOOSS score	No.	%	No.	%
3	0	0	4	28.5
2	0	0	9	64.3
1	5	35.7	1	7.2
0	9	64.3	0	0

Table 25.3 Results

Technical success, no./total no. (%)	14/14(100%)
Clinical success, no./total no. (%)	13/14(92.86%)
Mean procedure time, minutes	68.79 ± 10.47
Improvement in mean GOOSS score (pre → post)	0.36 → 2.21*
Median stent patency, days	186

GOOSS gastric outlet obstruction scoring system
*$P < 0.001$

Table 25.4 Stent malfunction and complications

Stent malfunction	No./Total No.	%
Occlusion	0/14	0
Migration	0/14	0
Other complications		
Stent fracture	0/14	0
Insufficient stent expansion	0/14	0
Breeding	1/14	7.14
Stent obstruction	2/14	14.28
Cholangitis	0/14	0
Pancreatitis	0/14	0
Perforation	0/14	0
Death	1/14	7.14
Cause		
Breeding	1/14	7.14

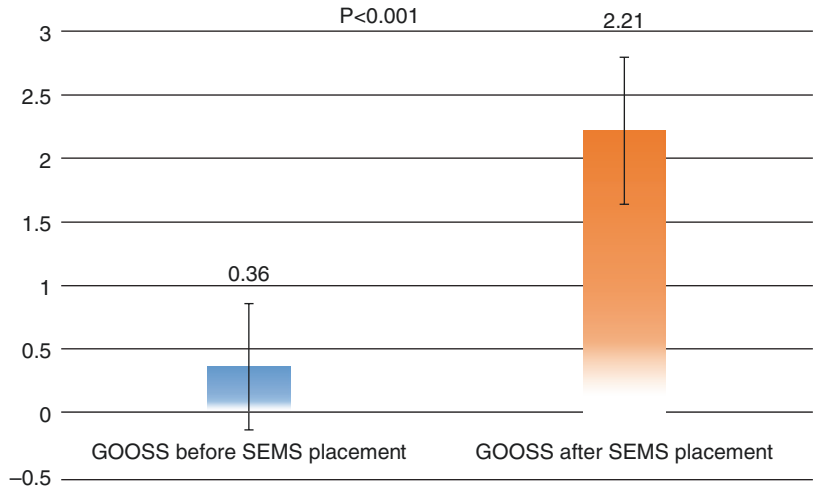

Fig. 25.4 A statistically significant improvement demonstrates in the comparison between the mean value of GOOSS before SEMS placement and after SEMS placement

Palliative Radiotherapy

As a noninvasive treatment, palliative radiotherapy can reduce tumor burden and help to control the common clinical symptoms (e.g., pain, dysphagia, and malignant obstruction) in patients with locally advanced gastric cancer or in those with distant metastasis and thus improve the patients' quality of life [12–14]. Tey J. et al. retrospectively analyzed the outcomes of 115 gastric cancer patients who had received three-dimensional (3D) conformal radiation therapy. Dose fractionation regimen ranged from 8-Gy single fraction to 40 Gy in 16 fractions. Of 115 patients with median age of 77 years, 78 (67.8%) patients had metastatic disease at the time of treatment. Index symptoms included gastric bleeding (89.6%), obstruction (14.3%), and pain (9.2%). Response rates for bleeding, obstruction, and pain were 80.6%, 52.9%, and 45.5, respectively. Median survival was significantly longer in patients who responded to radiotherapy compared with patients who did not (113.5 vs 47 days, $P < 0.001$). There was no significant difference in response rates between low (≤39 Gy) and high (>39 Gy) biologically effective dose (BED) regimens [14]. No controlled study has directly compared the effectiveness of palliative radiotherapy and endoscopic techniques in alleviating symptoms. However, compared with endoscopic techniques or palliative gastrectomy, palliative radiotherapy has relatively *extended* efficacy. Research has shown that a BED of 40 Gy in fractions is preferred for controlling bleeding, and this dose is also recommended for alleviating obstruction [15].

Endoscopic Laser Therapy

For 75–93% of patients with tumors of the esophagus or with gastric cardia cancer, endoscopic laser therapy can effectively relieve dysphagia due to obstruction [16]. Although laser photocoagulation has definite effectiveness and is suitable for large tumors and diffuse hemorrhage, it requires expensive equipment and thus cannot be widely applied [17]. As an alternative technique to laser photocoagulation, argon plasma coagulation has increasingly been applied.

Conclusions and Recommendations

1. Palliative treatment is recommended after the gastric cancer has progressed to a certain stage.
2. For local symptoms (e.g., nausea, obstruction, pain, and bleeding caused by locally advanced or locally recurrent primary tumors) that are not responsive to systemic therapy (e.g., chemotherapy), endoscopic techniques and palliative radiotherapy are recommended for multidisciplinary management.
3. According to the REGATTA study initiated by Fujitanni K and Yang HK, palliative gastrectomy is recommended for some advanced gastric cancer patients who have received systemic therapy.
4. In advanced gastric cancer patients with obstructive symptoms, endoscopic stent placement is recommended, whereas palliative surgery should not be used.
5. Compared with endoscopic techniques, palliative radiotherapy has relatively extended efficacy in controlling bleeding and obstruction. Research has shown that a BED of 40 Gy in fractions is preferred for controlling bleeding and alleviating obstruction.
6. Endoscopic laser therapy may be an alternative treatment option for alleviating dysphagia due to obstruction.

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