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Palliative care for advanced gastric cancer

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Abstract

Introduction—Proactive palliative care can effectively relieve symptoms early and effectively as well as improve quality of life of patients with gastric adenocarcinoma (GAC).

Areas covered—The review summarizes palliative care for GAC. GAC caused specific symptoms, such as malignant gastric outlet obstruction (GOO), bleeding, weight loss, and/or ascites, therefore these symptoms must be addressed specifically.

Expert Opinion—Palliative care should start early to control general symptoms, thus may improve patient's condition to make the patient eligible for anti-cancer treatment. As some stage IV GAC patients can now live longer, palliative interventions become more important. A multimodality interdisciplinary approach is strongly encouraged.

Keywords

Gastric adenocarcinoma; palliative care; palliative gastrectomy; malignant gastric outlet obstruction; palliative radiotherapy

1. Introduction

Gastric adenocarcinoma (GAC) is estimated to be the fifth most frequently diagnosed cancer in the world (1,033,701 cases), and the third leading cause of cancer deaths (782,685 deaths) [1]. Prognosis of GAC remains dismal. In United State, 35% of patients with GAC are diagnosed in stage IV since early detection strategy is not feasible. [2]. The median overall survival (OS) remains around 9–10 months [3]. Even when GAC is localized, patients treated with preoperative chemotherapy followed by surgery results in a low 5-year OS rate of 38% [4]. Thus, most patients with GAC end up requiring palliative care.

World Health Organization (WHO) has defined palliative care for cancer as “Palliative care is an approach that improves the quality of life of patients and their families facing the problem, through the prevention and relief of suffering by means of early identification and

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impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual” (<https://www.who.int/cancer/palliative/definition/en/>). Several reports indicate that palliative care relieves symptoms and improves quality of life in patients with advanced cancer [5–7]. Palliative care should be offered not only towards the end of life, but should start early. Scarpi et al. showed that early intervention of systematic palliative care improves quality of life for patients with GAC [8]. Merchant et al. showed that palliative care, whenever it is performed, reduced the need for more intensive treatment towards the end of life of these patients [9]. Occasionally, early management of symptoms can improve well-being of patients enough so that they can even tolerate anti-cancer therapy.

Common initial symptoms of GAC are early satiety, nausea, vomiting, fatigue (anemia), pain, and weight loss. Anemia occurs due to chronic or active bleeding from GAC. An analysis of patients being treated in the second line setting showed that most prominent symptoms included fatigue, pain, and loss of appetite [10]. Moreover, it showed that, when systematic therapy was active, it improved the quality of life, especially emotional functioning, pain, loss of appetite, nausea, and vomiting [10]. Even after the third line therapy, systemic therapy could improve Eastern Cooperative Oncology Group (ECOG) performance status (PS) [11]. Large primary GAC can cause malignant gastric outlet obstruction (GOO) or severe bleeding. To manage GOO or bleeding, multidisciplinary tools, such as endoscopy, surgery, and/or radiotherapy, are needed.

2. Specific symptom in Gastric cancer

2.1 Gastric outlet obstruction (GOO)

Malignant GOO is not an uncommon circumstance in patients with GAC (particularly those arising in the lower half of the stomach). GOO causes symptoms of nausea, vomiting, and abdominal pain, resulting in malnutrition and dehydration. Thus, GOO can reduce patient’s quality of life rather dramatically. The GOO scoring system (GOOSS) score (0 = no oral intake, 1 = liquid diet, 2 = soft solid diet, 3 = low residue or normal diet) is used to assess the oral intake and patient status. Endoscopic examination can assess the degree and location of stenosis and able to inform if endoscopic interventions (such as a stent placement) can be implemented. Treatment for GOO aims to reduce nausea and vomiting and to enable resumption of oral intake. Surgical and endoscopic approaches are commonly used [12]. But clearly an endoscopic approach is preferred. Radiation therapy or chemotherapy can also be useful to relieve GOO, but the benefit is not prompt [13]. Thus, radiation or chemotherapy are not suitable for GOO with severe stenosis.

Surgical approach for GOO is gastrectomy or gastrojejunostomy (GJ). The endoscopic approach is to place a self-expandable metal stent (SEMS). GJ and SEMS have strengths and limitations (Table 1) [14–19]. Strength of GJ is the higher success rate for allowing patient to eat regular meals for a longer period of time, and less re-intervention as opposed to SEMS [20–23]. However, a longer hospital stay and high rate of morbidity after GJ are the notable limitations. Recently, less invasive technique has been developed, such as laparoscopic gastrojejunostomy (Lap-GJ) or endoscopic ultrasound-guided gastrojejunostomy (EUS-GJ), reducing the hospital stay and morbidity compared with open GJ [24–27]. On the other hand, endoscopic placement of SEMS is associated with early resumption of oral intake and

often no hospital stay, but the risks remain [28]. Approach to overcome GOO should be carefully selected based on factors like tumor location, stage of cancer, and remaining therapeutic option to treat the cancer. We always recommend a multimodality interdisciplinary approach to reach the best decisions.

2.2 Bleeding

Bleeding is common a symptom in patients with GAC, especially if the cancer is ulcerated. Acute and severe bleeding can be a lethal event, therefore, a prompt assessment of all potential options should be considered at once. Consultation with other disciplines (surgery, interventional radiology, gastroenterology, and radiation oncology) can be very beneficial for making a balanced decision.

Endoscopic intervention is recommended as the first assessment as well as the first line management. Endoscopic intervention, such a metallic hemoclips, ethanol, epinephrine, and coagulation methods (laser photocoagulation, argon plasma coagulation), can reduce or stop bleeding [29]. The success rate of hemostasis was reported as high (31–100%), but re-bleeding rate was also high (41–80%)[29]. The second approach for uncontrolled bleeding is transcatheter arterial embolization (TAE). Clinical success rate of TAE was reported as 40–65% [30–32]. Palliative gastrectomy can be recommended for highly symptomatic and uncontrolled cases. However, surgical mortality can be high if a patient is malnourished and has a bulky cancer [33]. Radiation therapy can effectively control bleeding, but the benefit is not instant. The favorable response rate to radiation therapy was reported to be 69% to 91% [34–40]. Proton pump inhibitors (PPIs) are considered beneficial but may not directly reduce or stop the bleeding. Their effect may be to reduce inflammation by reduced the acid level. A Korean randomized study showed that PPI did not significantly reduce the incidence of tumor bleeding [41].

2.3 Ascites

Japanese retrospective study showed that approximately 10 % of patients who underwent gastrectomy developed peritoneal recurrence [42,43]. In Stage IV patients, 37.2 % experienced peritoneal metastases over time [43]. Although, one approach to treat ascites is restriction of sodium intake and use of diuretics. However, such measures have only limited value.

Recently, novel cell-free and concentrated ascites reinfusion therapy (KM-CART) has been developed in Japan [44]. KM-CART use an external pressure system, not an internal pressure system, with a membrane cleaning function, allowing to filtering malignant cells (cell rich ascites) and then to reinfuse cell-free ascites[44]. Re-injection of ascites can cause disseminate intravascular coagulation because ascites contains inflammatory cells and cytokine. KM-CART can remove all cell components, such as red blood cells, bacteria, and cancer cells, therefore KM-CART is considered safe. One suggestion is that the concentrated ascites that is rich in protein, can preserve these elements and protect the immune system, however, this is only conjectural [45]. A report of KM-CART treatment in more than 300 patients has claimed good safety and efficacy of procedure [46]. KM-CART significantly improved performance status, including dietary intake, urine volume, body weight, and

abdominal circumference [46]. Yamaguchi et al. reported the experiences of KM-CART in combination with chemotherapy [47]. In limited circumstances, KM-CART might provide palliative care for GAC patients with malignant ascites. Further investigation is warranted and we do not recommend this approach outside of clinical trials.

3. Palliative treatment

3.1 Palliative gastrectomy

Symptoms due to advanced GAC, such as bleeding, obstruction, or perforation, require palliative resection. For controlling bleeding, endoscopic approach and arterial embolization are preferred, but gastrectomy becomes essential in some circumstances. For managing obstruction, gastrectomy is preferred rather than the bypass surgery. For perforation, gastrectomy is needed, but morbidity after surgery is high.

Whether palliative gastrectomy can improve prognosis of Stage IV GAC patients is debated in some circles. Several retrospective studies have demonstrated that patients after palliative gastrectomy tended to have better survival than patients treated without palliative gastrectomy [48]. Contrary, the REGATTA study, a phase 3 randomized controlled trial, showed that palliative gastrectomy before chemotherapy had no survival benefit for Stage IV GAC patients [49]. Importantly, the patients who underwent total gastrectomy were less able to tolerate chemotherapy. The decision to offer a palliative gastrectomy should be made thoughtfully and with consultations with other colleagues.

3–2. Bypass

GJ is effective for GOO due to distal GAC. One type of bypass procedure, stomach-partitioning GJ, enabled 88% patients to eat regular meals 2 weeks after surgery [20]. GJ has been considered superior in several aspects compared to SEMS. First, one report showed that patients who underwent GJ were able to take a regular meal at 2 weeks compared to patients who had SEMS; 12 of 16 patients in the GJ group were eating by mouth compared to only 1 of 9 patients in the SEMS group [21]. Second, GJ was significantly reduced the risk of re-intervention compared to SEMS [22,23]. Third, several reports showed that GJ was significantly associated with a longer overall survival [21–23]. However, longer hospital stays and high morbidity after surgery are the disadvantages. Therefore, GJ is suitable for patients who have good performance status and possibility of a long survival.

Recently, less intrusive methods, such as Lap-GJ and EUS-GJ, have been used. Previous studies comparing open-GJ and Lap-GJ showed that Lap-GJ was associated with less intraoperative blood loss, less postoperative delayed gastric emptying, and less postoperative hospital stays [24–26]. EUS-GJ was less invasive than Lap-GJ [27]. EUS-GJ consists of creation of a fistulous tract between the stomach and the jejunum by using EUS and placement of lumen-apposing fully covered self-expanding metal stent through the fistulous tract. EUS-GJ was shown to be feasible and less morbid compared with Lap-GJ [50]. Cost for EUS-GJ is lower than laparoscopic GJ [50] EUS-GJ seems optimal for the patients who might not tolerate a surgical intervention.

Bypass procedure for obstruction caused by esophagogastric junction cancer should be considered highly invasive. For esophageal cancer, Baba et al. presented esophageal bypass surgery using a Y-shaped gastric tube followed by the retrograde insertion of a decompression tube [51]. However, it seem to be effective for only select esophagogastric junction cancer patients, whose tumor is limited in esophagogastric junction and not invading stomach.

3–3. Palliative radiotherapy

Palliative radiotherapy is one option for controlling localized symptom, such as bleeding, obstruction, and pain. Radiotherapy is less invasive than other treatments. However, response to radiotherapy can take time, therefore surgery, endoscopic, or interventional radiology treatment are suitable in an urgent situation. The most common dose was 30Gy in 10 fractions. It remains controversial whether increasing the RT dose is better or not more effective [13].

The favorable response rate for bleeding appears high; 69% to 91% [34–40]. Kondoh et al. reported that 73% patients achieved hemostasis at a median interval of 2 days. The median hemoglobin level was significantly increased after 30 days from baseline; before 6.0 g/dl but after 9.0 g/dl [38]. However, re-bleeding rate was 25–53% [34–40,52]. Median time to re-bleeding was 3.85 – 50.0 weeks [34–40,52].

For obstruction, Kim et al. reported a response rate of 81% and obstruction was controlled for a median duration of 6.2 months [35]. Hiramoto et al. reported that a response rate of 80% and obstruction was controlled for a median duration of 104 days [52]. However, radiation only is not suitable for severe stenosis.

3–4. Stent

The SEMS is an effective method to overcome (sometimes only temporarily) GOO and allows a faster resumption of oral intake, almost no hospital stays, and lower cost compared to GJ [15–17]. However, SEMS is associated with high rate of re-obstruction and need for re-intervention [53]. One report showed that the median time to stent dysfunction was 67.5 days [54]. There are two type SEMSs: covered stent and uncovered stent. Uncovered stent is shown to be associated with increasing risk dysfunction due to tumor ingrowth compared with covered stent [55]. On the other hand, covered stent is associated with a high risk of migration (Table 2) [55–60]. Importantly, taking chemotherapy was shown to be risk factor for stent migration, but covered ones prevent tumor in-growth [54,55]. Therefore, when treatment is planned, un-covered stent might be recommended. A study of stent for colon cancer suggested that history of treatment both before and after stenting was a risk factor for perforation [61,62]. Perforation and severe bleeding are directly related to mortality; however, it is not frequent. A lot of caution should be exercised when recommending a stent [53].

The incidence of gastroesophageal junction adenocarcinoma has been rising worldwide [63]. Therefore, stenting for cardia obstruction is getting more common. However, stenting for cardia obstruction has several issues, such as high rate of migration, reflux symptoms and hiccup, compared with stenting for distal of stomach. Park et al found that the rate of stent

migration for cancer of the gastric cardia was 24% and concluded that stenting for esophagogastric junction strictures was independent risk factor for migration [64]. Approximately, half of the patients were found to suffer from significant reflux symptoms after stenting for esophageal cancer [65]. Stent with anti-reflux valve were anticipated to reduce reflux symptom, but recent data showed no benefit [66,67]. Hiccups is a rare complication and sometimes it is relieved only after stent removal [65].

4. Conclusion

In conclusion, palliative care should start early to control general symptoms, which might improve quality of life and additionally increase the chance for the patient to receive cancer therapy. GACs cause specific symptoms, such as GOO, bleeding, or ascites, therefore need to individualize the interventional approach. As patients, fortunately, living longer, the need for palliative care is getting more important.

5. Expert opinion

Palliative care should be started early. A multidisciplinary team discussion can help to decide on an optimal timing and approach.

Palliative care and anti-cancer treatment are closely related. Palliative care not only improves PS and reduces symptoms, but also enables anti-cancer treatment in some patients. Combination of palliative care and anti-cancer treatment could improve the quality of life of patients, as well as their prognosis.

As chemotherapy, molecular targeting drugs, and immunotherapy have produced longer survival in some GAC patients making palliative care even more important [11,68–72]. Recently, metastatic GAC that respond to systemic therapy might lead to even gastrectomy, the so called conversion surgery [73]. A Korean multi-institutional analysis showed that gastrectomy after chemotherapy improved survival [74]. Especially, patients who underwent R0 conversion surgery had favorable prognosis than patients who underwent R1–2 [74–76]. Therefore, conversion surgery is one option for patients who have dramatic response to systemic therapy [77]. Early intervention with palliative care can allow more patients to preserve their PS.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes

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Article highlights

- Early intervention to palliate symptoms can improve GAC patients' quality of life, which, in turn, can allow patients to tolerate anti-cancer therapies.
- To address malignant gastric outlet obstruction, an endoscopic approach is preferred over the surgical approach. When successful, symptoms improve right away and in some for considerable length of time.
- Acute and severe bleeding can be a life threatening event, therefore, a multidisciplinary evaluation and discussion followed by appropriate intervention is recommended.
- A novel cell-free and concentrated ascites reinfusion therapy (KM-CART) has been developed for ascites management. However, more research is needed to understand its true impact on reducing morbidity from ascites.
- Palliative gastrectomy is avoided in symptomatic patients with stage IV GAC, therefore, other means of palliation should be considered (radiation therapy, etc.).

Table 1: Summary of study comparing stenting and gastrojejunostomy for management of malignant gastric outlet obstruction

Year Authors	Treatment	n	Clinical success	Days to eat	Hospital Stay (days)	Re-intervention	Survival (median)
2007 Jeumink et al [14]	Bypass	42	59%	10 (mean)	18(mean)	6.4%	88 days
	Stent	53	73%	3.6 (mean)	6 (mean)	13.9%	70 days
2010 Jeumink et al [15]	Bypass	18	72 (median)	8 (median)	15	11.1%	78 days
	Stent	21	50 (median)	5 (median)	7	33.3%	56 days
2012 Chandrasegaram et al [16]	Bypass	19	37%	9 (median)	25	N/A	134 days
	Stent	26	73%	2 (median)	11	11.5%	70 days
2012 Roy [17]	Bypass	75	100%	10.7 (mean)	10.7 (mean)	6.7%	132 days
	Stent	29	100%	1.5 (mean)	1.5 (mean)	13.8%	118 days
2013 Khashab [18]	Bypass	270	91%	N/A	13	8.7%	N/A
	Stent	120	87%	N/A	10.1	27.3%	N/A
2013 No et al [19]	Bypass	41	95.1%	5 (median)	18	5.5%	293 days
	Stent	72	87.5%	2 (median)	16	43.0%	189 days

Summary of study comparing covered and uncovered stent for management of malignant gastric outlet obstruction

Table 2:

Year Authors	Type of stent	n	Migration	Restenosis	Reintervention	Median period of stent patency
2010 Kim et al [56]	Uncovered	40	8.3%	44.4%	N/A	13 weeks
	Covered	40	32.3%	3.25	N/A	14 weeks
2014 Lim et al [57]	Uncovered	61	0%	21.3%	21.3%	92 day
	Covered	59	13.6%	6.8%	22%	95 days
2014 Maetani et al. [58]	Uncovered	31	3.2%	19.3%	N/A	88 days
	Covered	31	6.4%	0%	N/A	68 days
2015 Lee et al. [59]	Uncovered	37	5.4%	37.8%	37.8%	N/A
	Covered	42	9.5%	7.1%	14.3%	N/A
2017 Hori et al [55,60]	Uncovered	126	0.79%	11.9% (ingrowth)	N/A	63 days
	Covered	126	8.73%	0.79% (ingrowth)	N/A	86 days