Evaluation of the role of palliative gastrectomy in management of patients with advanced gastric cancer

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Received: 24 February 2021
Revised: 6 March 2021
Accepted: 11 March 2021
Published: 12 October 2021

The Egyptian Journal of Surgery 2021, 40:695–702

Background and objectives
Gastric cancer is responsible for more than 10% of cancer-related deaths worldwide and remains the second most common cause of cancer-related death. Surgical resection is considered the most effective treatment for early gastric cancer, but its value remains debatable for patients with advanced disease. Adjuvant therapy is still considered the main line of management of these patients. Some studies had reported that palliative gastrectomy may have a beneficial effect for survival and quality of life in patients with advanced disease. On the contrary, many studies had reported that palliative gastrectomy was associated with significant morbidity and poor quality of life. Our study aims to evaluate the value of palliative gastrectomy with systemic chemotherapy in comparison with systemic chemotherapy alone in the management of cases of advanced gastric cancer.

Patients and methods
Between May 2015 and May 2020, patients with advanced gastric cancer (T4N1-3 M0, T1-4N3M0, and any T or N with M1) were prospectively included in this study. Enrolled patients were assigned either to have palliative gastrectomy followed by systemic chemotherapy or to have systemic chemotherapy alone. The patients were followed up regularly after treatment. Postoperative parameters, disease-specific mortality, mean survival, and Kaplan–Meier survival analysis were used to assess the outcomes.

Results
A total of 35 patients completed the study, including 20 patients in the surgery group and 15 in the systemic chemotherapy group. Partial gastrectomy was done in nine cases, and total gastrectomy was done in 11 cases. Seven (35%) patients had postoperative complications, and two (10%) cases of postoperative mortality were recorded. The mean survival length of patients of the surgery group was 11.3±1.6 months, which was significantly longer than that of the patients who received systemic chemotherapy alone (7.3±1.1 months). Kaplan–Meier survival analysis showed that the overall survival probability estimate in the surgery group was 32.8% at 1 year and 12.4% at 2 years, compared with 15.9% at 1 year and 0% at 2 years in the chemotherapy group, with difference being statistically significant.

Conclusion
Palliative gastrectomy can be done in patients with advanced gastric cancer with acceptable morbidity and mortality rates. It may provide a survival benefit in select cases of advanced gastric cancer when combined with systemic chemotherapy.

Keywords:
adjuvant chemotherapy, advanced gastric cancer, palliative gastrectomy

Egyptian J Surgery 40:695–702

1110-1121

Introduction

Gastric cancer accounts for more than 10% of cancer-related deaths worldwide and is the second most frequent cause of cancer death after lung cancer [1,2]. New treatment modalities involving radical D2 gastrectomy combined with adjuvant therapy had improved the long-term outcomes for early diagnosed gastric cancer, but advanced cases still have poor outcome [3,4].

Surgical resection is considered to be the best treatment for early gastric cancer, but it remains debatable for patients with advanced disease, and adjuvant therapy is considered the main line of management of these patients. The National Comprehensive Cancer Network (NCCN) guidelines suggest that gastric resections should be reserved only for palliation of symptoms (e.g. obstruction or uncontrollable bleeding) in patients with incurable disease [5]. On the contrary, the Japanese Gastric Cancer Association

(JGCA) guidelines suggest that patients with gastric cancer with metastases but without major symptoms may be treated with gastrectomy [6].

In theory, palliative gastrectomy could enable better oral food intake and treat obstruction and bleeding, thus improving the quality of life [7,8]. Some studies reported that palliative gastrectomy may also have a survival benefit [8–12].

Palliative gastrectomy is usually technically difficult with locally advanced tumors. In addition, poor patients' preoperative general condition may adversely affect surgical outcomes, resulting in higher postoperative morbidity and mortality [13–15]. Studies had reported that palliative gastrectomy was associated with significant morbidity, longer hospital stay, and poor quality of life [16,17], thus recommending gastrectomy only for cases with serious complications, such as tumor bleeding or perforation [18,19].

Our study aims to evaluate the value of palliative gastrectomy with adjuvant therapy in comparison with adjuvant therapy alone in the management of cases of advanced gastric cancer.

Patients and methods

Study design

Our study was conducted in General Surgery and Clinical Oncology Departments at Ain Shams University hospitals, Cairo, Egypt, between May 2015 and May 2020.

It was a prospective comparative study which included patients with advanced gastric cancer (defined as T4N1-3 M0, T1-4N3M0, and any T or N with an M1 tumor category according to the tumor, node, metastasis classification 7th edition) [20]. The exclusion criteria were (a) patients who received neoadjuvant chemotherapy or radiotherapy and (b) patients with concomitant severe comorbidities who might not tolerate general anesthesia. All included patients were required to sign an informed consent. IRB approval was obtained before the start of the study.

Included patients were assigned to either gastrectomy with chemotherapy group (group A) or systemic chemotherapy alone group (group B). Patients were assigned to surgery group based on the following indications: (a) patients with tumor-related complications (e.g. bleeding, obstruction, or perforation) and (b) patients who had chosen to undergo surgery to reduce tumor burden after careful discussion of management options. Patients were assigned to systemic chemotherapy group if they do not have any emergency complications and/or refused to undergo surgery.

Preoperative workup

All patients had to undergo upper gastrointestinal endoscopy and biopsy with histopathological examination of specimens, contrast-enhanced computed tomography scans of the abdomen and pelvis, complete laboratory investigations (including complete blood picture, liver and kidney function tests, fasting and postprandial blood sugar, and tumor markers), and chest radiograph in addition to any other necessary investigations. All tumors were diagnosed as adenocarcinomas by histopathological assessment of biopsy specimens.

Surgical procedures

The patients included in the study underwent either total gastrectomy (for tumors of the body or fundus) or distal gastrectomy (for distal stomach tumors) together with lymph node dissection. A small gastric remnant was left in cases of distal gastrectomy, and a Billroth II type reconstruction was done. In cases of total gastrectomy, a Roux-en-Y end-to-side esophagojejunal reconstruction was done. Multivisceral resection was attempted in cases which required that. Patients in which resection could not be done were excluded from the study.

Figures 1–3 show preoperative, operative, and postoperative pictures of select patients in the surgery group.

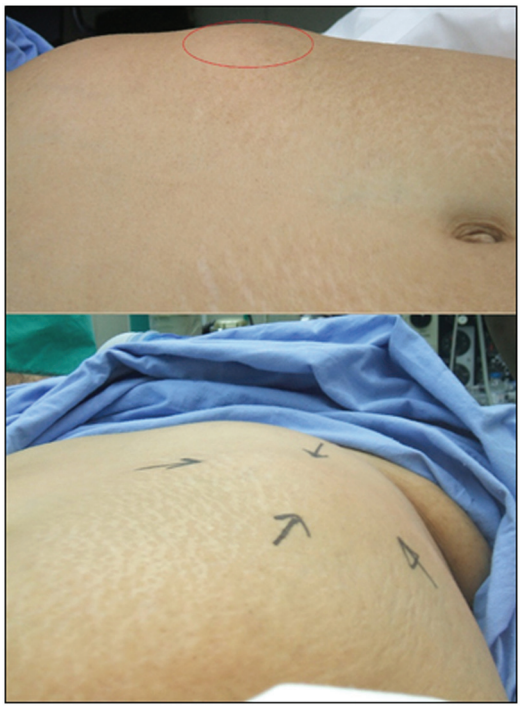
Postoperative care

Postoperatively, the nasojejunal tube was removed when fluid drainage was less than 100 ml/24 h. Overall, 200–300 ml of clear fluids per 24 h was given on the following days. Between the sixth and eighth postoperative days, a gastrografin study was performed to detect any anastomotic leakage. The patients were then given a gradually increasing oral diet. Patients were followed up for presence of postoperative complications, operation-related mortality (within 30 days), and operation-related readmissions. Patients without any morbidity or mortality after the first month were sent to the oncology department for adjuvant therapy.

Systemic chemotherapy

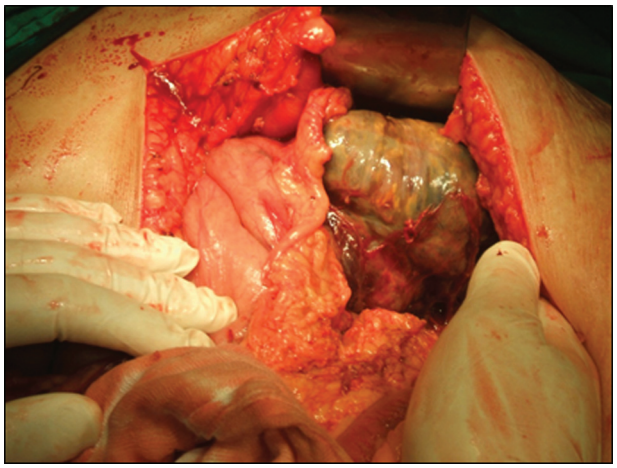
A combination of epirubicin 50 mg/m^2 intravenous, cisplatin 60 mg/m^2 intravenous, and oral capecitabine 625 mg/m^{2}twice daily was given for 21 days, and the whole regimen was repeated every 21 days, and reassessment was done after three cycles. Responders

Figure 1



A picture showing a large tumor visible by inspection at the left upper quadrant of the abdomen.

Figure 2



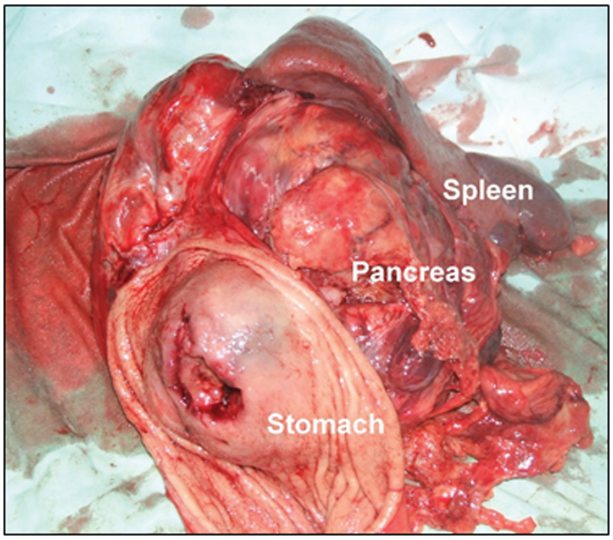
An intraoperative picture of a tumor invading the spleen and tail of pancreas.

continued for a total of six cycles, whereas nonresponders discontinued treatment. The same regimen was used for patients undergoing surgery, 1 month after operation.

Follow-up

Patients of both groups had regular follow-up visits for at least 12 months (monthly for the first 6 months and every 3 months for the next 6 months and twice a year thereafter). The routine examination during follow-up included a physical examination, blood chemistry tests,

Figure 3



Postoperative picture of resected specimen including the stomach, spleen, tail of pancreas, and omentum.

chest radiograph, abdominal ultrasound. Pelvi-abdominal computed tomography, bone scan, and endoscopy were done for selected patients when indicated, with documentation of any operation or tumor-related morbidity and mortality.

Statistical analysis

The disease was staged according to the tumor, node, metastasis classification. The following variables were evaluated: age, sex, tumor site, tumor size, histological type (differentiated or undifferentiated), lymph node metastasis, depth of invasion [T2 (muscularis propria and subserosa)], T3 (serosa penetrated), or T4 (adjacent organs)], peritoneal dissemination [P0 with CY1 (positive lavage cytology), P1 (few metastases near the stomach), P2 (few distant metastases), or P3 (many distant metastases)], distant metastasis (absence or presence), its site, and operative method (partial or total).

Data were analyzed using the SPSS statistical software program, version 21, for Windows (SPSS Inc., Chicago, Illinois, USA). The survival rate and parameters from collected data were compared between the two groups. χ^2 test, independent t test, and Kaplan–Meier survival analysis were used. A P value less than 0.05 was considered significant.

Results

A total of 39 patients were enrolled in our study, comprising 15 in the systemic chemotherapy group and 24 in the surgery group. Overall, four patients in the surgery group were excluded from the study (two were found to have nonresectable tumors and two were

lost to follow-up), so the final number of included patients for analysis was 35.

Overall, 19 (54.3%) patients were males and 16 (45.7%) were females. The mean age of the patients was 53.6 ±16.5 years (range, 33–69 years).

Table 1 shows the preintervention characteristics of the patients and their disease.

These characteristics were compared between both surgery and systemic chemotherapy groups using χ^2 test and independent t test, and no significant difference was found between both groups.

Surgery was performed owing to emergency indications in nine cases and for elective indication in 11 cases. The indication of surgery was bleeding tumor in five cases, obstruction and vomiting in four cases, and for reducing tumor burden, the remaining 11 cases.

Partial gastrectomy was done in nine cases, and total gastrectomy was done in 11 cases. Overall, two cases with tumor invading the spleen and tail of pancreas necessitated performing splenectomy and distal pancreatectomy in addition to the gastrectomy. No intraoperative mortalities or major intraoperative complications were recorded in our study. Operative data and indications for operation are shown Table 2 and Figs 4 and 5.

The mean length of hospital stay was 7.8±8.2 days (range, 5–19 days). During the follow-up period, seven (35%) patients had surgery-related postoperative complications (three cases of anastomotic leakage, two cases of subphrenic abscess, and two cases of postoperative bleeding). One patient had to be re-explored owing to hemorrhage after operation, but bleeding was controlled and the patient had recovered well after that. Two (10%) cases of operation-related mortality were recorded in the first month after surgery (one owing to generalized sepsis after anastomotic leakage and the other owing to severe pneumonia) (Fig. 6).

Patients of both groups (surgery group patients 1 month after the operation) had systemic chemotherapy according to same protocol and were followed up by the same schedule.

The mean follow-up period length in our study was 12.1±8.2 months (range, 7–22 months). The mean survival duration in the patients of the surgery group

Table 1 Characteristics of the study population

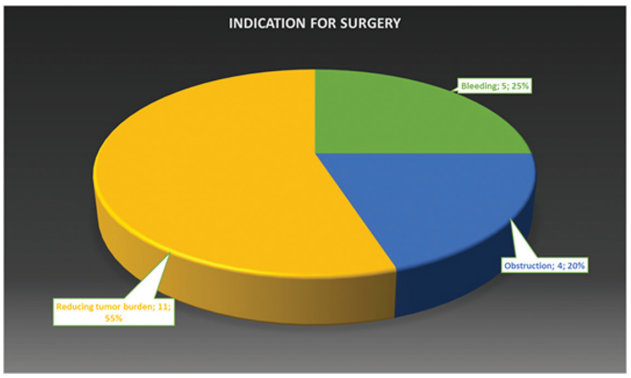
Variables	Surgery: group A	Systemic chemotherapy: group B
Number	20	15
Age	52.7±13.3	55.8±13.4
Sex		
Male	11	8
Female	9	7
Tumor site		
Fundus/body	11	9
Distal stomach	9	6
Tumor size (cm)		
<5	6	5
5–10	12	7
>10	2	3
Histological type		
Well differentiated	8	4
Ill differentiated	12	11
Preintervention TNM stage		
T-stage		
T1	0	0
T2	4	1
T3	12	9
T4	4	5
N-stage		
N0	0	0
N1	7	5
N2	9	7
N3	4	3
M-stage		
M0	6	3
M1	14	12
Depth of invasion		
T2 (MO, SS)	5	NA
T3 (serosa)	14	
T4 (adjacent organ)	1	
Peritoneal dissemination		
P0	11	NA
P1	6	
P2	3	
P3	0	
Site of metastasis		
Peritoneal	9	NA
Liver	4	6
Lung	6	5
Ovary	1	2
Other	0	2

TNM, tumor, node, metastasis.

Table 2 Operative data in the surgery group

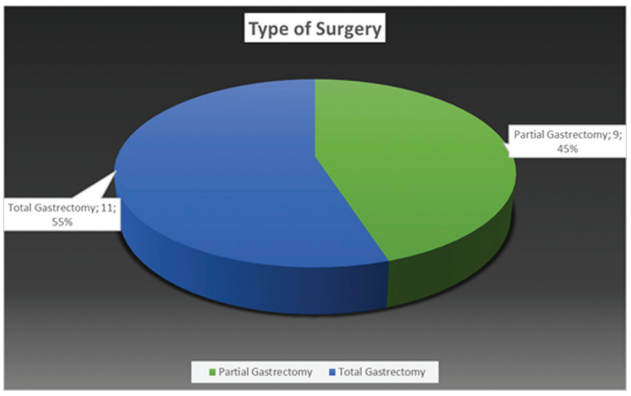
Items	Mean±SD	Minimum	Maximum
Operative time			
Partial gastrectomy	158.2±31.3	93	204
Total gastrectomy	198.2±47.7	131	246
Intraoperative blood loss			
Partial gastrectomy	300±150	100	500
Total gastrectomy	550±250	150	850

Figure 4



Indications for operation in the surgery group.

Figure 5



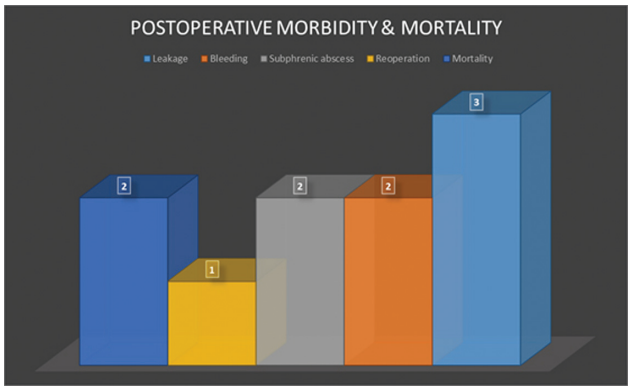
Types for operation in the surgery group.

was 11.3±1.6 months. This was found to be significantly longer than that of the patients who received systemic chemotherapy alone (7.3±1.1 months). Kaplan–Meier survival analysis showed that the overall survival probability estimate in the surgery group was 32.8% at 1 year and 12.4% at 2 years, compared with 15.9% at 1 year and 0% at 2 years in the systemic chemotherapy group. There was a statistically significant difference in survival between patients treated with palliative gastrectomy followed by systemic chemotherapy and those treated with systemic chemotherapy alone (Fig. 7).

Discussion

Gastric cancer is not very common in Egypt as in most other countries; hence, the disease is often overlooked and the presentation is advanced at the time of diagnosis, leading to poor patient survival rates. Based on the published literature, the average survival for patients with stage IV gastric cancer is ~16 weeks, with only 25% of patients surviving 34 weeks or longer [21].

Figure 6



Postoperative morbidity and mortality in the study.

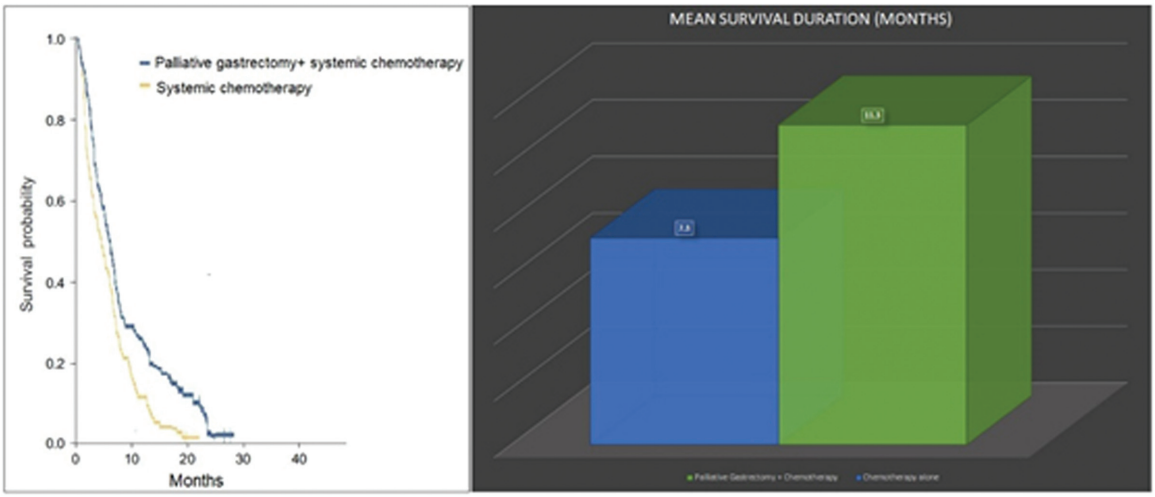
Radical surgical resection had always been considered the main line of treatment for gastric cancer, but for patients with advanced or metastatic disease, the benefit of surgical resection is unclear.

The role of palliative gastrectomy in patients with advanced gastric cancer is a matter of controversy. Palliative gastrectomy had been proposed as an option for management of patients with advanced gastric cancer. The rationale is that the primary tumor may cause complications (obstruction, perforation, or bleeding), and resection is the treatment for these complications. Moreover, resection may be associated with improvement of function and quality of life by removing bulky symptomatic tumors. It is also suggested that removing a significant proportion of the tumor load may enhance the response to systemic chemotherapy and have an immunologic benefit [22,23]. Because of that, some studies reported the presence of benefits for palliative gastrectomy for advanced gastric cancer [7,11,24]. On the contrary, many studies argued that resection in these patients is associated with higher incidences of postoperative morbidity and mortality, prolonged hospital stay, and poor quality of life [16,17,25].

Our study aimed to evaluate the value of palliative gastrectomy with adjuvant therapy in comparison with adjuvant therapy alone in the management of cases of advanced gastric cancer at our university hospitals.

In our study, 24 patients were operated upon for advanced gastric cancer; two of them were found to have nonresectable tumors and were excluded from the study, in addition to another two patients who were lost to follow-up. Moreover, two cases with tumors invading the spleen and tail of pancreas necessitated

Figure 7



Kaplan–Meier survival probability curve and mean survival plot in the study.

performing splenectomy and distal pancreatectomy in addition to the gastrectomy. We tried not to do multiorgan resection in our study to decrease the operative morbidity as possible. Some authors had identified that resectability rate is inversely proportional to the number of tumor sites spread (100% resectability rate with one site and 11% with four sites) [10]. This delineates the importance of accurate preoperative staging in planning a proper management strategy for every patient.

In our study, the operative data (operative time and intraoperative blood loss), as well as postoperative data (hospital stay period) and postoperative complications and mortality rates were generally higher than those reported in the literature. A recently published randomized trial by Fujitani and colleagues about palliative gastrectomy with chemotherapy versus chemotherapy alone reported a median duration of surgery of 180 min (140–210 min), with a median blood loss of 200 ml (100–398 ml) among patients assigned to gastrectomy plus chemotherapy. They had postoperative complications in 16% of the 87 patients who underwent gastrectomy. No patient in their study underwent reoperation. Operation-related death occurred in one (1%) patient in their study [26]. Their results are better than ours because their study took place in large referral centers in Japan and Korea that have better experience and expertise in dealing with patients with gastric cancer.

Our operative and postoperative data suggest the technical difficulty of palliative gastrectomy. Many authors had reported high postoperative complication rates following palliative gastrectomy (10–38%). They attributed that to technical difficulties and poor preoperative nutritional status [11,14,27–30]. Minimizing postoperative complications is important for reducing morbidity and mortality and improving the survival outcomes in patients undergoing palliative gastrectomy, as systemic chemotherapy should be given as early as possible.

Our study had shown a significant survival benefit in patients undergoing palliative gastrectomy followed by systemic chemotherapy in comparison with those having chemotherapy alone (mean survival of 11.3±1.6 vs. 7.3 ±1.1 months, and Kaplan–Meier survival probability estimate of 32.8% at 1 year and 12.4% at 2 years, compared with 16.1% at 1 year and 0% at 2 years).

Kunisaki *et al.* [28] found that for patients undergoing palliative gastrectomy, the 1-, 3-, and 5-year disease-specific survival rates were 37.7, 16.7, and 5.0%, respectively, with a median survival time of 9 months. In their study, Samarasam *et al.* [10] found that there was a significant survival advantage of palliative gastrectomy versus nonresectional operation (24 vs. 12 months). Chang *et al.* [31] reported that palliative gastrectomy carried a significant survival benefit in patients receiving chemotherapy who had metastasis to one organ compared with nonresection group (14 vs. 9.7 months). In their study, Saidi *et al.* [24] reported that the overall survival of patients who were treated with surgery plus adjuvant treatment was far better than for those who did not have resection (the mean survival among patients who underwent palliative gastrectomy was 14.4 months in comparison with 5.9 months for those treated without gastrectomy).

A meta-analysis of 'clinical significance of palliative gastrectomy on the survival of patients with incurable advanced gastric cancer' including 14 different studies was published by Sun and colleagues. Their results showed that palliative gastrectomy may improve survival in patients with incurable advanced gastric cancer. They found that that the weighted average of median survival time in patients undergoing palliative gastrectomy was longer than those without resection (14.96 months compared with 7.07 months). They concluded that palliative gastrectomy improved the long-term survival in patients with advanced gastric cancer. Their analysis also suggested that combined palliative gastrectomy with hepatectomy may be beneficial for patients with liver metastasis [18].

A randomized controlled trial had been conducted in Japan and Korea between 2008 and 2013 to determine the value of gastrectomy performed in patients with advanced gastric cancer. It included 175 patients randomly assigned to either chemotherapy alone or gastrectomy plus chemotherapy. They published their results, and it was somewhat different from the previously mentioned data. In this study, gastrectomy plus chemotherapy did not provide a survival advantage compared with chemotherapy alone in the treatment of advanced gastric cancer with a single noncurable factor (overall survival at 2 years was 31.7% for patients assigned to chemotherapy alone compared with 25.1% for those assigned to gastrectomy plus chemotherapy). The median overall survival was 16.6 months for patients assigned to chemotherapy alone and 14.3 months for those assigned to gastrectomy plus chemotherapy. In their analysis of the results, they found that gastrectomy plus chemotherapy was associated with significantly worse overall survival in patients with upper-third tumors, because the median number of chemotherapy cycles was reduced after gastrectomy to half of that for chemotherapy alone. This may be the reason that result of surgery was found inferior to chemotherapy alone in their study [26].

Combining our results and literature data into account, it is evident that palliative gastrectomy may have a survival benefit in certain patients with advanced gastric cancer, but not all of them. In clinical practice, the benefits of gastrectomy must be balanced with its risks and costs before the decision of treatment is taken [2,17,18,26,29,32].

Our study has its limitations. First, the sample size is not large enough, restricting the statistical power to support conclusions. Second, patients were not randomized but rather selected for each treatment group. Third, the patient population was heterogeneous, with some having only locally advanced disease, whereas others having metastatic disease, and the sample size did not allow for analyzing the effect of treatment on every category separately. Finally, assessment of quality of life was not done, which is an important consideration for patients with a limited lifespan when choosing the optimum treatment strategy.

Conclusion

Palliative gastrectomy may be done in patients with advanced gastric cancer with acceptable perioperative morbidity and mortality rates. It may provide a survival benefit in select cases of advanced gastric cancer when combined with systemic chemotherapy. More research is needed to accurately identify patient population who may benefit from the operation as a treatment choice.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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