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ORIGINAL ARTICLE

Gastrectomy for Metastatic Gastric Cancer: a 15-year Experience from a Developing Country

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Abstract

The role of surgery in the management of metastatic gastric cancer (MGC) remains unclear. The aim of this study was to investigate the surgical and oncologic outcomes of gastrectomy in patients with MGC. The study included prospectively collected data of patients with MGC operated at four medical centers in Yerevan, Armenia, between 2000 and 2014. Armenian National Center of Oncology Registry and hospital records were used to obtain survival data. Factors associated with performing gastrectomy in patients with MGC were analyzed by using the logistic regression model. The Kaplan-Meier method was applied for survival analysis, and the Cox regression model with backward selection was used for multivariate analysis. A total number of 733 patients were operated for gastric cancer including 112 (15.3%) with MGC. Of those, 70 underwent gastrectomy, while 42 had exploratory laparotomy or bypass. Morbidity and mortality were similar after gastrectomy and exploratory laparotomy/bypass (18.6 vs 21.4%, $p = 0.71$ and 2.9 vs 7.1% $p = 0.36$, respectively). Female gender, involvement of N1 and/or N2 lymph node stations, and differentiated adenocarcinoma were associated with opting for gastrectomy. Gastrectomy with synchronous resection of distant metastases resulted in postoperative outcomes similar to those following gastrectomy without synchronous organ resection. Median follow-up was 6 months. Eighteen (16.1%) patients received chemotherapy. Median survival following gastrectomy and exploratory laparotomy/bypass were 7 and 4 months ($p = 0.015$), respectively. The use of chemotherapy following gastrectomy significantly improved survival compared with gastrectomy only (14 vs 6 months, $p = 0.01$). In the multivariable analysis, chemotherapy and nodal stage correlated with survival after gastrectomy. Gastrectomy for MGC is associated with satisfactory surgical outcomes and can be combined with synchronous resection of distant metastases in selected patients. Gastrectomy results in longer survival compared with exploratory laparotomy/bypass, especially when followed by chemotherapy.

Keywords Gastric cancer · Metastases · Gastrectomy · Laparotomy · Chemotherapy

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Background

Gastric cancer is the fourth most common cancer and the second leading cause of cancer-related death worldwide [1, 2]. According to the literature, 40% of patients with gastric cancer are diagnosed with metastases [3]. The management of metastatic gastric cancer (MGC) is challenging. Although surgical resection is the cornerstone in the multimodal treatment of gastric cancer, its role in MGC remains controversial [4, 5]. The opponents of gastrectomy for MGC underscore its high morbidity and mortality [6, 7], as patients' poor performance status, local and distant disease spread, and surgery-related trauma were shown to prolong postoperative hospital stay leading to a cost increase and unclear therapeutic benefits [8, 9]. Thus, several authors suggest performing gastrectomy only for complications of MGC, such as uncontrollable bleeding, stenosis, and perforation [10, 11]. Yet some reports found benefits in gastrectomy for MGC [12–14]. According to Nazli et al.,[7] gastrectomy results in better quality of life and prolongs survival. These findings are explained by the fact that upfront gastrectomy precludes the development of the aforementioned complications of gastric cancer. At the same time, positive outcomes of these procedures largely depend on patient selection [7, 15].

In this study, factors associated with opting for gastrectomy in MGC and its short- and long-term outcomes were examined.

Methods

Patients

Consecutive patients with MGC operated from 2000 to 2014 in four medical centers (National Center of Oncology after V.A. Fanarjyan, 2000–2003; "Izmirlyan" MC, 2003–2004; "Kanaker-Zeytun" MC, 2004–2009; and "ArtMed" MC, 2009–2014) in Yerevan, Armenia, were included in this study. The study has been approved by the institutional data protection officers in these institutions.

Indications for gastrectomy were satisfactory performance status and resectable primary tumor. Preoperative endoscopy and biopsy were carried out to identify and histologically verify the presence of cancer. Abdominal ultrasound examination and computed tomography were utilized to assess the extent of the disease. Of note, none of the patients received neoadjuvant chemotherapy. All operations were performed in the elective setting by one surgeon (AMS). Following laparotomy and intraoperative revision, the final decision on the extent of surgery was made. The latter included one of the following options: (a) exploratory laparotomy only (tumor debulking/lymph node sampling), (b) laparotomy and bypass, and (c) gastrectomy. Gastrectomy with synchronous metastasectomy was performed when possible. Postoperative management protocol was similar throughout the study period. Adjuvant chemotherapy was initiated in these patients over the last few years. All patients underwent repeat examinations including the measurement of tumor markers (CEA, Ca 19–9), abdominal ultrasound and chest X-ray, or abdominal and chest computed tomography 3, 6, 12 months after surgery. Thereafter, patients had checkups every 6 months within the next 4 years.

Definitions and Data Collection

The classification from the 7th edition of the Union for International Cancer Control was used for TNM staging of gastric cancer [16]. The evaluation of lymph node stations surrounding stomach was carried out according to the criteria set by the Japanese Research Society for the Study of Gastric Cancer [17].

Perioperative data were prospectively registered in the database, while the long-term oncologic data were obtained from hospital records or from the Armenian National Center of Oncology Registry. Surgical outcomes were examined in patients undergoing gastrectomy (cases) and exploratory laparotomy or laparotomy + bypass (controls). Furthermore, factors associated with performing gastrectomy for MGC were investigated. Given the heterogeneity of patient cohort, those diagnosed with tumors other than gastric adenocarcinoma were excluded from survival analysis.

Postoperative mortality included all cases of death that occurred within 30 days of surgery. Overall survival was estimated from the date of surgery until the date of death from any cause or the date of the last checkup. Survival data were censored at the last follow-up.

Statistics

Data were presented in frequencies and expressed as numbers (percentages). The chi-square test or Fisher's exact test were applied to compare frequencies. Logistic regression analysis was used to determine prognostic factors associated with utilization of gastrectomy for MGC. Two-tailed $p < 0.05$ was considered statistically significant.

Survival was estimated by the Kaplan-Meier method. The log-rank test was used to compare survival between the groups. Two-tailed $p < 0.05$ was considered statistically significant. To identify predictors for survival in patients with MGC, variables significant at $p < 0.05$ were included in the multivariable Cox regression model with backward selection, and two-tailed $p < 0.05$ was considered statistically significant. Statistical analyses were performed using the SPSS software (SPSS Inc., version 22 for Windows, IBM, Chicago, IL).

Results

Perioperative Outcomes

A total number of 733 patients had undergone surgery for gastric cancer between 2000 and 2014. Of those, 112 (15.3%) were diagnosed with MGC. Exploratory laparotomy or laparotomy and bypass were performed in 42 (37.5%) patients, while gastrectomy was carried out in 70 (62.5%) patients. The latter included subtotal and total gastrectomy in 29 (41.4%) and 41 (58.6%) patients, respectively.

Most of the patients ($n = 60$, 53.6%) were diagnosed with peritoneal carcinomatosis. Some of those had also other organ metastasis ($n = 9$). In those without peritoneal carcinomatosis ($n = 52$, 46.4%), both single-organ and multi-organ distant metastases were found. The most common locations were liver ($n = 31$), the left adrenal gland ($n = 6$), pancreas ($n = 5$), greater omentum ($n = 4$), ovaries ($n = 4$), spleen ($n = 3$), and umbilicus ($n = 3$). Lymph node metastases were found in 108 (96.4%) cases including 56 patients with the involvement of N1/N2 lymph node stations and 52 patients with the involvement of N3/N4 lymph node stations.

Patient demographics and preoperative data are presented in Table 1. Female gender positively correlated with performing gastrectomy (45.7 vs 26.2%, $p = 0.04$), while age ≥ 65 years was associated with opting for exploratory laparotomy or laparotomy and bypass ($p = 0.003$). Another predictor of gastrectomy was a disease history of less than 3 months ($p = 0.013$). Among patients with T4 stage gastric cancer, a greater proportion underwent gastrectomy than laparotomy/bypass (58.6 vs 35.7%, $p = 0.019$). In contrast, the latter was more often performed in patients with N3 stage MGC (97.6 vs 77.1%, $p = 0.005$). All patients subjected to laparotomy/bypass were diagnosed with tumors-sized ≥ 6 cm (100 vs 81.4%, $p = 0.002$). Factors such as tumor histology other than adenocarcinoma, metastases in the distant lymph node stations, and peritoneal carcinomatosis were associated with opting for laparotomy/bypass. In multivariable regression analysis, female gender, metastases in N1 and/or N2 lymph node stations, and tumor histology of adenocarcinoma were associated with opting for gastrectomy.

Table 1 Demographics and clinicopathological data of patients with metastatic gastric cancer submitted to surgery

Variable		All patients ($n = 112$)	Laparotomy/ bypass ($n = 42$)	Gastrectomy ($n = 70$)
Gender*	Male	69 (61.6%)	31(73.8%)	38 (54.3%)
	Female	43 (38.4%)	11 (26.2%)	32 (45.7%)
Age, years*	< 64	63 (56.3%)	16 (38.1%)	47 (67.1%)
	≥ 65	49 (43.7%)	26 (61.9%)	23 (32.9%)
Comorbidities	Cardiovascular	37 (33.0%)	9 (21.4%)	28 (40.0%)
	Other	21 (18.8%)	7 (16.7%)	14 (20.0%)
Disease history, months*	< 3	10 (8.9%)	0 (0%)	10 (14.3%)
	≥ 3	102 (91.1%)	42 (100%)	60 (85.7%)
ASA[+] score	I/II	14 (12.5%)	14 (33.3%)	0 (0%)
	III	94 (83.9%)	28 (66.7%)	66 (94.3%)
	IV	4 (3.6%)	0 (0%)	4(5.7%)
T stage*	T1/T2/T3	56 (50%)	27 (64.3%)	29 (41.4%)
	T4	56 (50%)	15 (35.7%)	41 (58.6%)
N stage*	N0	4 (3.6%)	0 (0%)	4 (5.8%)
	N1/N2	13 (11.6%)	1 (2.4%)	12 (17.1%)
	N3	95 (84.8%)	41 (97.6%)	54 (77.1%)
Tumor size*	< 6 cm	13 (11.6%)	0 (0%)	13 (18.6%)
	≥ 6 cm	99 (88.4%)	42 (100%)	57 (81.4%)
Tumor involvement of adjacent organs	No	42 (37.5%)	12 (28.6%)	30 (42.9%)
	Yes	70 (62.5%)	30 (71.4%)	40 (57.1%)
Histology*	Adenocarcinoma	73 (65.2%)	12 (28.6%)	61 (87.1%)
	Other	39 (34.8%)	30 (71.4%)	9 (12.9%)
Metastases in lymph node stations*	N1/N2	56 (50%)	7 (16.7%)	49 (70%)
	N3/N4	52 (46.4%)	35 (83.3%)	17 (24.3%)
Peritoneal carcinomatosis *		60 (53.6%)	35 (83.3%)	25 (35.7%)

*Statistically significant difference found between the groups; [¶] Erythrocyte sedimentation rate; [+] American Society of Anesthesiologists

Postoperative complications and mortality occurred in 22 (19.6%) and 5 (4.5%) patients, respectively. No significant differences were found between gastrectomy and laparotomy/bypass groups in terms of these parameters (Table 2).

A total number of 57 and 55 procedures were performed for MGC in 2000–2007 (early period) and 2008–2014 (late period), respectively. The proportion of gastrectomies performed for MGC had markedly increased over time—from 24 (42.1%) in 2000–2007 to 46 (83.6%) in 2008–2014 ($p = 0.001$). The extent of lymph node dissection also increased in the late period resulting in ≥ 15 lymph nodes being removed in 63% of patients compared with 50% of those in 2000–2007. Morbidity decreased from 24.6% in the early period to 14.5% in the late period, although without statistical significance ($p = 0.18$).

Adjuvant chemotherapy was initiated in 18 (16.1%) patients with MGC including 17 after gastrectomy ($p = 0.002$). Of note, chemotherapy was administrated only in patients operated in the period from 2008 to 2014.

Subgroup Analysis of Patients Undergoing Gastrectomy

The subgroup analysis demonstrated higher morbidity following total gastrectomy compared with subtotal gastrectomy (26.8 vs 6.9%, $p = 0.035$). At the same time, 25 (35.7%) patients referred to gastrectomy underwent synchronous resection of distant metastases. These included liver resection ($n = 9$), ovarectomy ($n = 4$), and resection of 2 and more organs ($n = 12$). Morbidity and mortality rates of gastrectomy with synchronous metastasectomy were similar to those of standard gastrectomy for MGC—20 vs 17.8% ($p = 1.0$) and 0 vs 4.4% ($p = 0.53$), respectively.

Survival

Median and mean follow-up periods were 6 and 10.5 months, respectively. Given postoperative mortality in 2 cases, only 71 patients were eligible for survival analysis.

Median survival following surgery for MGC was 6 (2–53) months. Gastrectomy and laparotomy/bypass resulted in median survival of 7 vs 4 months ($p = 0.015$, log-rank), respectively (Fig. 1). After laparotomy/bypass, only one patient had survived for more than 8 months, while gastrectomy was associated with 1-, 2-, and 3-year survival rates of 29.3%, 11.2%, and 9%, respectively. Median survival after gastrectomy with and without subsequent chemotherapy was 14 (3.8–24.2) and 6 (4.6–7.4) months ($p = 0.01$, log-rank), respectively (Fig. 2), while 1- and 3-year survival rates in these patients were 57.1 vs 20.5% and 22.2 vs 2.3%, respectively.

Patients undergoing gastrectomy with synchronous metastasectomy had similar survival compared to those without metastasectomy—6 (4–7.9) vs 7 (5.5–8.5) months ($p = 0.41$, log-rank).

In the univariable analysis, N3 stage, metastases in N3/N4 lymph node stations and no chemotherapy were associated with poor prognosis after gastrectomy for MGC (Table 3). In the multivariable Cox model, nodal stage and chemotherapy were the independent predictors of survival.

Discussion

In this study, gastrectomy was associated with better prognosis compared with exploratory laparotomy/bypass in patients with MGC. While only one patient with laparotomy/bypass survived for more than 8 months, the 3-year survival following gastrectomy was 9%. In contrast with these findings,

Table 2 Morbidity, its types and mortality following surgery for metastatic gastric cancer

Variable	All patients ($n = 112$)	Laparotomy/bypass ($n = 42$)	Gastrectomy ($n = 70$)
Morbidity	22 (19.7%)	9 (21.5%)	13 (18.6%)
Bile leakage	2 (1.8%)	0 (0%)	2 (2.9%)
Ileus	2 (1.8%)	0 (0%)	2 (2.9%)
Colonic fistula	1 (0.9%)	0 (0%)	1 (1.4%)
Bleeding	2 (1.8%)	1 (2.4%)	1 (1.4%)
Peritonitis	1 (0.9%)	0 (0%)	1 (1.4%)
Wound infection	2 (1.8%)	0 (0%)	2 (2.9%)
Liver/kidney failure	1 (0.9%)	0 (0%)	1 (1.4%)
Pulmonary complications	1 (0.9%)	1 (2.4%)	0 (0%)
Cardio-pulmonary failure	4 (3.6%)	3 (7.1%)	1 (1.4%)
Anastomosis insufficiency	3 (2.7%)	2 (4.8%)	1 (1.4%)
Anastomosis stricture	3 (2.7%)	2 (4.8%)	1 (1.4%)
Mortality	5 (4.5%)	3 (7.1%)	2 (2.9%)

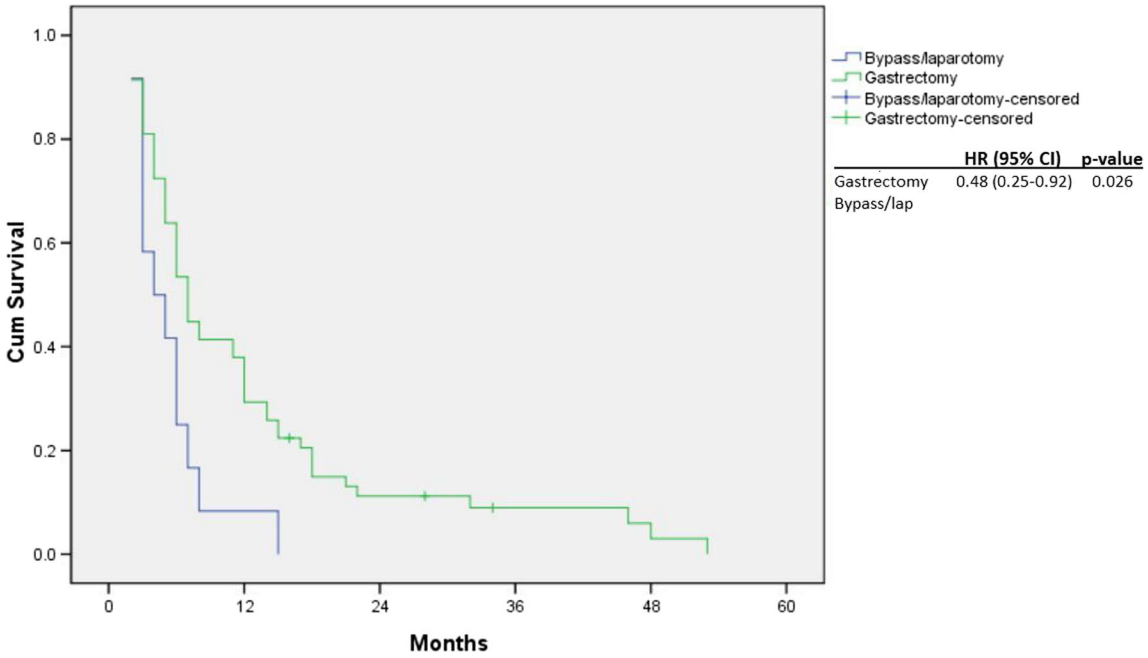

Fig. 1 Survival in patients with metastatic gastric cancer following gastrectomy and exploratory laparotomy/bypass

current literature does not clearly define the role of gastrectomy in the treatment of MGC, as the former is still mostly applied for its complications, such as uncontrollable bleeding, stenosis, and perforation [8, 9, 18, 19]. Nazli et al.[7] suggest that palliative gastrectomy results in better prognosis for metastatic and locally advanced gastric cancer. These findings were also confirmed by Cai et al. [20] who reported superior 1- and 2-year survival following palliative gastrectomy vs no gastrectomy (48.1 and 23.1% vs 13.5 and 0%, respectively,). Several studies underscore the importance of patient selection for gastrectomy considering the risk factors such as patient age and performance status [6, 12–14, 21–24]. Based on our experience, we believe that patient age itself is not a contraindication for gastrectomy, if the performance status is satisfactory.

Tumor resectability is presumed to be determined by several factors including the extent of tumor invasion and cancer stage [7, 20]. Four criteria precluding resection for gastric

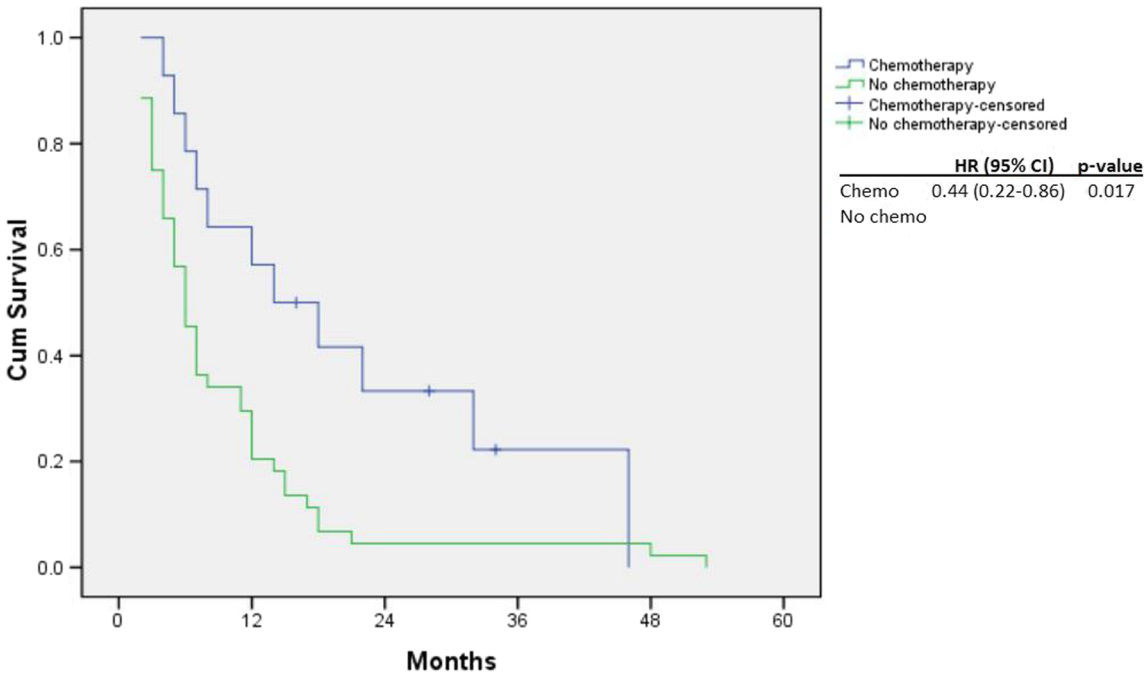

Fig. 2 Survival following gastrectomy for metastatic gastric cancer with or without subsequent chemotherapy

Table 3 Univariable and multivariable analysis of prognostic factors for survival after gastrectomy for metastatic gastric cancer

Variable		Univariable analysis		Multivariable analysis	
		Median survival	*P* value	HR (95% CI)	*P* value
Gender	Male	11 (7.4–14.6)	0.42		
	Female	5 (3.8–6.2)			
Age, years	< 64	6 (4.0–8.0)	0.84		
	≥ 65	7 (5.5–8.4)			
Length of the disease, months	< 3	6 (2.1–7.8)	0.09		
	≥ 3	7.1 (1.9–12.5)			
T stage	T1/T2/T3	7 (4.6–9.4)	0.78		
	T4	6 (2.4–9.6)			
N stage	N1/N2	13 (3.2–20.9)	0.01	3.5 (1.7–6.4)	0.02
	N3	7 (4.8–7.5)			
Tumor size	< 5 cm	12 (6.5–17.5)	0.07		
	≥ 5 cm	7 (5.7–8.3)			
Tumor involvement of adjacent organs	No	7 (4.6–9.4)	0.78		
	Yes	6 (2.4–9.6)			
Metastases in lymph node stations	N1/N2	7 (3.8–10.5)	0.03	1.6 (0.4–2.9)	0.42
	N3/N4	5 (2.5–7.6)			
Metastases	Liver/other	7 (5.5–9.6)	0.45		
	Peritoneal carcinomatosis	6 (4.2–7.2)			
Gastrectomy	Total	7 (2.2–11.8)	0. 52		
	Subtotal	7 (5.1–8.9)			
Lymph node yield	< 15	6 (4.4–6.9)	0.17		
	≥ 15	8 (3.8–11.7)			
Morbidity	No	7 (5.0–8.9)	0.17		
	Yes	6 (4.4–7.6)			
Years	before 2007	7 (5.5–7.4)	0.45		
	2008–2014	8 (3.1–12.3)			
Chemotherapy	Yes	14 (3.8–24.2)	0.01	2.4 (1.2–4.9)	0.011
	No	6 (4.6–7.4)			

cancer have been distinguished: unresectable tumor, distant metastases, peritoneal carcinomatosis, and distant lymph node metastases [25]. At the same time, oligometastatic gastric cancer was shown to be associated with better prognosis compared with multi-metastatic gastric cancer (10.5 vs 6.7 months), while the increase in the number of metastatic sites decreased the possibility of resection [15]. Thus, patient selection is the key in the management of these patients. Current study suggests that female gender, metastases in N1/N2 lymph node stations and histology of adenocarcinoma are positive predictors for gastrectomy in the setting of MGC.

Some studies suggest increased morbidity and mortality after gastrectomy for MGC to be a result of poor performance status, low serum protein, albumin, and hemoglobin levels [6, 7]. Postoperative complication rate of 57.1% has been reported in these patients [26]. Unlike these findings, current study suggests a trend towards higher morbidity and mortality following exploratory laparotomy/bypass compared with gastrectomy (21.4 vs 18.6% and 7.1 vs 2.9%, respectively). Although these results may be affected by selection bias, i.e., considering more suitable cases for gastrectomy, they are still in line with several studies reporting no association between the extent of resection and postoperative complications [13, 25, 27]. Interestingly, we observed a decrease in postoperative morbidity in the period from 2000–2007 to 2008–2014 despite an increase in the extent of surgery and lymphadenectomy. Thus, surgical outcomes in these patients seem to be primarily dependent on surgeon experience. Most importantly, wider application of gastrectomy for MGC from 2008 onwards resulted in significantly increased survival.

Gastrectomy with synchronous resection of distant metastases was found to provide surgical and survival outcomes comparable with those of standard gastrectomy for MGC, thus metastasectomy seems to be of limited oncological value in these patients.

This study suggests that chemotherapy significantly improves survival following gastrectomy for MGC resulting in 3-year survival of 22.2%. Furthermore, chemotherapy and

nodal stage were identified as prognostic factors for patients with MGC undergoing gastrectomy. According to Saidi et al.,[9] the median survival of these patients is 5.9 months, when subjected to palliative chemotherapy only, and 16.3 months when subjected to gastrectomy and subsequent chemotherapy. These findings have been confirmed by the reports highlighting the positive role of chemotherapy following palliative resections in patients with MGC [21, 28, 29]. In this study, chemotherapy was applied in only 16.1% of patients and in 24.3% of those undergoing gastrectomy. Such low numbers can be attributed to several factors. First and foremost, Armenia is a developing country with decentralized medical system, where complete implementation of chemotherapy in the management of patients with gastric cancer has been achieved only within the last decade. Second, in the setting of limited medical insurance and no government-provided health care, burden of treatment costs relies entirely on patients and their families, which significantly complicates the decision-making process precluding the use of the most suitable treatment modality in some cases. Given the results of this study, aggressive treatment with gastrectomy and subsequent chemotherapy should be encouraged in selected patients with MGC, especially in countries experiencing the abovementioned problems in the health care system.

This study has obvious weaknesses and limitations. First and foremost, this is a retrospective study with its inherent biases including clear selection bias in the gastrectomy group. Second, all procedures were done by one surgeon, and the decision on operative approach (gastrectomy or laparotomy/bypass) was left at surgeon's discretion. As a result, further management of these patients largely depended on surgeon experience, which obviously varied in the early and late periods of this study. Finally, patients with MGC referred to chemotherapy without surgery were not included in this study, while a comparative analysis with those undergoing surgery could be useful in understanding the role of gastrectomy in MGC. All in all, well-designed, multicenter studies, and prospective registries are needed to assess the results of gastrectomy in patients with MGC.

Conclusion

Our findings indicate that gastrectomy in patients with MGC is both effective and beneficial, as it is associated with prolonged survival compared with exploratory laparotomy or laparotomy and bypass. In experienced hands, gastrectomy with synchronous resection of distant metastases does not increase postoperative morbidity. These approaches are recommended in selected patients with satisfactory performance status and limited disease spread. Adjuvant chemotherapy and lower nodal stage are independently associated with better prognosis following gastrectomy for MGC.

Authors' Contributions All authors have made substantial contributions to research design, as well as have read and approved the final manuscript. Besides that, all authors have participated in the following parts of the manuscript preparation:

Data acquisition—AG, DLA, HP, SY, AC, AMK, and AMS
Data analysis—MAS and AMS
Data interpretation—MAS, AMS, AMK, DLA, SY
Manuscript drafting—MAS and AMS
Critical revision—AG, DLA, HP, SY, AMK, and AC

Availability of Data and Material The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with Ethical Standards

Competing Interests The authors declare that they have no competing interests.

Consent for Publication Not applicable.

Ethics Approval and Consent to Participate Not applicable.

Abbreviation MGC, Metastatic gastric cancer

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