Retrospective Analysis of the Outcomes in Elderly Patients with Adenocarcinoma of the Stomach and Esophagogastric Junction Following Three Different Treatments

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ABSTRACT

Objective: To compare survival outcomes and complications in elderly patients who underwent three different treatments.

Methods: The data of patients aged 70 years old or older diagnosed with adenocarcinoma of the stomach and esophagogastric junction (Siewert types II and III) between January 2005 and December 2016 were reviewed. The results of different treatments and risk factors for post-treatment morbidity and mortality were analyzed.

Results: In total, 220 elderly patients were included: 102 (46.4%) who underwent curative intended gastrectomy with radical lymphadenectomy (Curative group), 62 (28.2%) who underwent non-curative surgery or endoscopy (Non-curative group), and 56 (25.4%) who received best supportive care (BSC group). Mean ages were 76.6, 78.1, and 78.7 years old, respectively (p=0.596). Median overall survival was 32, 5, and 3 months, respectively (p<0.001). In the curative group, overall survival was associated with the pathological stage (p=0.017), but not the resection category (p=0.298). Concerning the curative and non-curative groups, severe post-treatment complications occurred in 14 (8.5%) patients (7.8%, curative group; 9.7%, non-curative group). Severe post-treatment complication was associated with age ≥80 years (p=0.023) and coronary artery disease (p<0.001); however, multivariate analysis identified coronary artery disease as an independent risk factor for severe post-treatment complication. 5 (3%) patients had in-hospital mortality, associated with age ≥80 years old (p=0.039) and coronary artery disease (p=0.005).

Conclusion: Curative and non-curative procedures can be safely performed in elderly patients. However, caution should be taken with extreme elderly patients, especially those with coronary artery disease. Best supportive care should be considered only for unfit patients.

Keywords: Stomach neoplasms; gastrectomy; aged; mortality; esophagogastric junction (Siriraj Med J 2019; 71: 457-465)

INTRODUCTION

The number of elderly cancer patients has increased worldwide during the past few decades. According to the National Cancer Institute of Thailand[1], 20% of gastric cancer patients are aged over 70 years old. Realizing that the older a patient is the more often they may experience comorbidities or poor treatment performance status could help decide the proper care for each patient.

In gastric cancer, including esophagogastric junction cancer, surgery is the main modality of treatment, and

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can be classified into curative and non-curative surgery. For patients who cannot tolerate surgery and who do not have metastatic disease, palliative and best supportive care are the preferable choices.

From a recent study in elderly gastric cancer patients over 80 years old, curative resection showed a significant better overall survival compared to supportive care.[2,3] Those who received non-surgical care mostly died from gastric cancer.[3] Cancer-specific survival was 100% in clinical stage I. which can imply that this group died from non-cancer diseases.[4] Surgery with reduced nodal dissection in stage I disease also offered no significant difference in survival compared to standard surgery.[5] Furthermore, complications in patients who underwent curative surgery were more common in older age, especially medical complications, occurring in 7.4% of patients aged 80 years old or older compared to 2.2% of patients aged 60-64 years old[6], particularly cardiac events and pulmonary complications, such as pneumonia and respiratory failure.[7] With older age, the mortality rate is significantly higher than for younger patients.[6]

This study aimed to measure the survival outcome of these elderly patients receiving curative surgery, non-curative treatment, and best supportive care. Postoperative complications and mortalities were reviewed and analyzed by statistics. The results from this study may suggest treatment guidance for elderly patients. Old age may not be a contraindication for curative surgery in surgical resectable diseases. Hopefully, elderly patients will receive the appropriate treatment concerning the stage of the disease and their performance status.

MATERIALS AND METHODS

Patient population

We retrospectively reviewed the records of a total of 220 patients aged over 70 years old with pathologically diagnosed adenocarcinoma of the stomach and Siewert–Stein types II and III adenocarcinoma of the esophagogastric junction (EGJ)[8] treated between January 2005 and December 2016 at the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. Of these patients, 102 patients who had underwent curative surgical resection, which was defined as a curative intent surgical procedure with the extent of gastric resection and lymph node dissection as per the Japanese classification and treatment guidelines for gastric carcinoma,[9,10] were assigned to the Curative group; while 62 patients who had underwent non-curative treatment, which referred to any kind of surgical or endoscopic management for relieving patients' symptoms, were assigned to the Non-curative group; and 56 patients who had underwent best supportive care alone were assigned to the BSC group. BSC was defined as any non-invasive treatments that aimed to relieve symptoms such as analgesics, antibiotics and blood transfusion, and did not involve any interventions as in the two previous groups. None of patients in the BSC group received palliative chemotherapy. Patients who received neoadjuvant chemotherapy, underwent endoscopic resection for curative intention, underwent cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy, and a transthoracic approach for surgical resection were excluded from this study.

The clinicopathological characteristics were reviewed from the patients' medical records, including the patients' age, gender, active smoking, comorbidities, such as diabetes mellitus, hypertension, cerebrovascular accident, chronic obstructive pulmonary disease, coronary artery disease, valvular heart disease, and chronic kidney disease ≥ stage IV, patient's performance status using the Eastern Cooperative Oncology Group performance status score (ECOG), body mass index, preoperative serum albumin level, American Society of Anesthesiologists physical status classification (ASA grade), preoperative tumor location, macroscopic Borrmann classification, tumor differentiation, and preoperative clinical staging using TNM staging according to the American Joint Committee on Cancer.

Outcome measurements

The primary objective of this study was to evaluate the overall survival between these three groups. Overall survival was defined as the time from the date of confirmed pathological diagnosis at our center to the date of death from any causes. We obtained the date of death from the Bureau of Registration Administration of Thailand and from family members of the patients. Postoperative complications, which were classified by the Clavien–Dindo classification system[11], in-hospital mortalities, and 30-days postoperative mortalities in curative surgery and non-curative treatment groups, were also reviewed and analyzed. This study protocol was approved by the Siriraj Institutional Review Board (Si 024/2018 EC1).

Statistical methods

All the statistical analyses were performed using SPSS statistical software version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Categorical variables were analyzed by using the chi-square test, and continuous variables were compared using the Student's t-test. Quantitative data was conducted using n%, mean ± SD, or median (min, max). Survival analysis was performed using the Kaplan–Meier method and log-rank test. Univariate

and multivariate analysis were performed using the logistic regression model. All the statistical results were considered significant when the *p*-value was less than 0.05.

RESULTS

Clinicopathological characteristics

All the patients in this study were over 70 years of age and had pathologically diagnosed adenocarcinoma of either the stomach or esophagogastric junction. Their clinicopathological characteristics were analyzed and the results are shown in Table 1. The average age of the patients was 76.6 years old in the curative group, 78.1 years old in the non-curative group, and 78.7 years old in the BSC group. There was a higher proportion of only hypertensive patients in the curative group, but no difference in the other comorbidities. A better performance status according to the ECOG score and a higher preoperative serum albumin level were found in the curative group. The majority of patients in the curative group had an ASA physical status grade 2, while the other two groups had ASA physical status grade 3. In terms of the tumor characteristics, there were similar preoperative tumor locations, macroscopic Borrmann types, and tumor differentiations among the three groups. Preoperative clinical metastasis was found to be positive in the non-curative group and BSC group more often than in the curative group. Two positive clinical metastasis in the curative group were suspected liver metastasis according to preoperative computed tomography but were found to be negative during operation.

In the curative group, there were 51 distal gastrectomy, 46 total gastrectomy including extended gastrectomy, 3 proximal gastrectomy, and 2 partial gastrectomy. All the patients underwent standard lymph node dissection according to the Japanese classification of gastric carcinoma.[9]

In the non-curative group, the choice of treatments was according to the clinical symptoms of the patients, such as bleeding or obstruction. There were a total of 40 operative surgical procedures and 22 endoscopic treatments. For the surgical procedures, there were 15 gastric resections (9 distal gastrectomy, 5 total gastrectomy, and 1 partial gastrectomy), 10 feeding jejunostomy, 6 surgical bypass with gastrojejunostomy, and 2 simple sutures for perforated gastric cancer. The remaining 7 patient cases involved 6 laparoscopies and 1 laparotomy, in which metastasis was found so the curative surgical operations were terminated and changed to non-curative intention instead. For the endoscopic treatments, there were 10 stent placements, 8 nasojejunal tube insertions, 2 endoscopic treatments for bleeding control, 1 nasogastric tube insertion, and 1 percutaneous endoscopic gastrostomy by push technique.

Therapeutic outcomes

Overall survival analysis was conducted using Kaplan–Meier survival curves. Comparing all the treatment groups, there was a significant better overall survival in the curative group ($p < 0.001$) and the 5-year OS survival was 22.5%. The median survival times were 32 months (95%CI 10.7-53.3), 5 months (95%CI 3.2-6.8), and 3 months (95%CI 2.2-3.8) after diagnosis for the curative group, non-curative group, and BSC group, respectively (Fig 1). Although the non-curative group was treated for palliative intention, they also had a significantly better overall survival compared with best supportive care alone ($p = 0.020$). For all three types of treatment, no statistically significant difference in overall survival ($p = 0.079$) was found for the extremely old patients, classified as 80 years old or over, compared to the younger patients, although the median survival time was better in the younger group (5 months vs. 12 months). In addition, pathological staging after curative surgery showed significantly better survival for the earlier stage than more advanced stage of the disease ($p = 0.02$) as the median survival times were 82, 34, 26, and 24 months for stages I, II, III, and IV, respectively (Fig 2). There were five patients who had underwent macroscopically curative resection but had a positive peritoneal cytology, so they were considered as being in stage IV of the disease. However for the final resection category, either R0 or R1 resection, there was no statistical difference in overall survival ($p = 0.298$).

Postoperative and treatment complications from the curative group and non-curative group were detected and classified by Clavien–Dindo classification[11] for both surgical-related and non-surgical-related complications. The surgical-related complications were gastroparesis (16.5%), superficial surgical site infection (7.3%), pancreatic fistula (3.7%), intraabdominal collection (3%), bleeding (2.4%), anastomotic leakage (1.8%), and intestinal obstruction (0.6%). The non-surgical-related. complications were renal (15.9%); acute kidney injury and volume overload, respiratory (11.6%); atelectasis and pneumonia, cardiovascular (5.5%); myocardial infarction, cardiac arrhythmia and heart failure, and infection (4.3%); urinary tract infection, catheter-related blood stream infection and septicemia, and neurologic complications (3%); ischemic stroke and delirium Severe complication was defined as Clavien–Dindo grade 3b or higher. There were 14 (8.5%) patients with severe complications from these two groups. The postoperative mortality rate was 3%. The clinical details are shown in

TABLE 1. Clinicopathological characteristics.

Variables	Curative n = 102	Non-curative n = 62	BSC n = 56	*P*-value
Age, (years)	76.63 ± 4.93	78.05 ± 5.92	78.73 ± 5.39	0.596
Gender				0.075
Male	64 (62.7)	29 (46.8)	27 (48.2)	
Female	38 (37.3)	33 (53.2)	29 (51.8)	
Active smoking	6 (5.9)	6 (9.7)	5 (8.9)	0.628
Comorbidities				
DM	24 (23.5)	16 (25.8)	16 (28.6)	0.783
HT	70 (68.6)	24 (38.7)	27 (48.2)	<0.001
CVA	12 (11.8)	2 (3.2)	6 (10.7)	0.162
COPD	6 (5.9)	3 (4.8)	2 (3.6)	0.814
CAD	11 (10.8)	7 (11.3)	3 (5.4)	0.464
VHD	6 (5.9)	1 (1.6)	0 (0)	0.093
CKD (≥ stage 4)	9 (8.8)	3 (4.8)	7 (12.5)	0.333
ECOG				<0.001
0-2	98 (96.1)	49 (79)	35 (62.5)	
3-4	4 (3.9)	13 (21)	21 (37.5)	
Body mass index (kg/m^2)				0.872
<18.5	23 (22.5)	16 (25.8)	8 (14.3)	
18.5-24.9	54 (52.9)	31 (50.0)	16 (28.6)	
25-29.9	17 (16.7)	7 (11.3)	2 (3.6)	
≥30	5 (4.9)	2 (3.2)	1 (1.8)	
Unknown	3 (2.9)	6 (9.7)	29 (51.8)	
Albumin (g/dL)	3.61 ± 0.47	3.23 ± 0.65	2.94 ± 0.67	<0.001
ASA grade				0.344
I	1 (1)	1 (1.6)	1 (1.8)	
II	62 (60.8)	27 (43.5)	27 (48.2)	
III	38 (37.3)	33 (53.2)	28 (50)	
IV	1 (1)	0 (0)	0 (0)	
V	0 (0)	1 (1.6)	0 (0)	
Preoperative				0.828
Tumor differentiation				
Well	9 (8.8)	6 (9.7)	4 (7.1)	
Moderately	32 (31.4)	16 (25.8)	20 (35.7)	
Poorly	52 (51.0)	37 (59.7)	31 (55.4)	
Unknown	9 (8.8)	3 (4.8)	1 (1.8)	
Preoperative				0.204
Tumor location				
EGJ	17 (16.7)	15 (24.2)	17 (30.4)	
Upper 1/3	7 (6.9)	2 (3.2)	6 (10.7)	
Middle 1/3	15 (14.7)	10 (16.1)	10 (17.9)	
Lower 1/3	57 (55.9)	30 (48.4)	19 (33.9)	
Diffuse	3 (2.9)	4 (6.5)	4 (7.1)	
Anastomosis	2 (2.0)	0 (0)	0 (0)	
Borrmann classification				0.039
I	11 (10.8)	6 (9.7)	10 (17.9)	
II	35 (34.3)	25 (40.3)	15 (26.8)	
III	43 (42.2)	18 (29.0)	15 (26.8)	
IV	11 (10.8)	11 (17.7)	16 (28.6)	
Unknown	2 (2.0)	2 (3.2)	0 (0)	
Clinical T staging				<0.001
cT1	10 (9.8)	2 (3.2)	0 (0)	
cT2	58 (56.9)	18 (29.0)	22 (39.3)	
cT3	26 (25.5)	26 (41.9)	17 (30.4)	
cT4	7 (6.9)	14 (22.6)	10 (17.9)	
Unknown	1 (1)	2 (3.2)	7 (12.5)	
Clinical N staging				<0.001
Negative	79 (77.5)	32 (51.6)	20 (35.7)	
Positive	21 (20.6)	25 (40.3)	24 (42.9)	
Unknown	2 (2.0)	5 (8.1)	12 (21.4)	
Clinical M staging				<0.001
Negative	99 (97.1)	33 (53.2)	11 (19.6)	
Positive	2 (2.0)	23 (37.1)	38 (67.9)	
Unknown	1 (1.0)	6 (9.7)	7 (12.5)	

Abbreviations: DM = Diabetes mellitus; HT = Hypertension; CVA = Cerebrovascular accident; COPD = Chronic obstructive pulmonary disease; CAD = Coronary artery disease; VHD = Valvular heart disease; CKD = Chronic kidney disease; ECOG = Eastern Cooperative Oncology Group performance status score; ASA = American Society of Anesthesiologists physical status score.

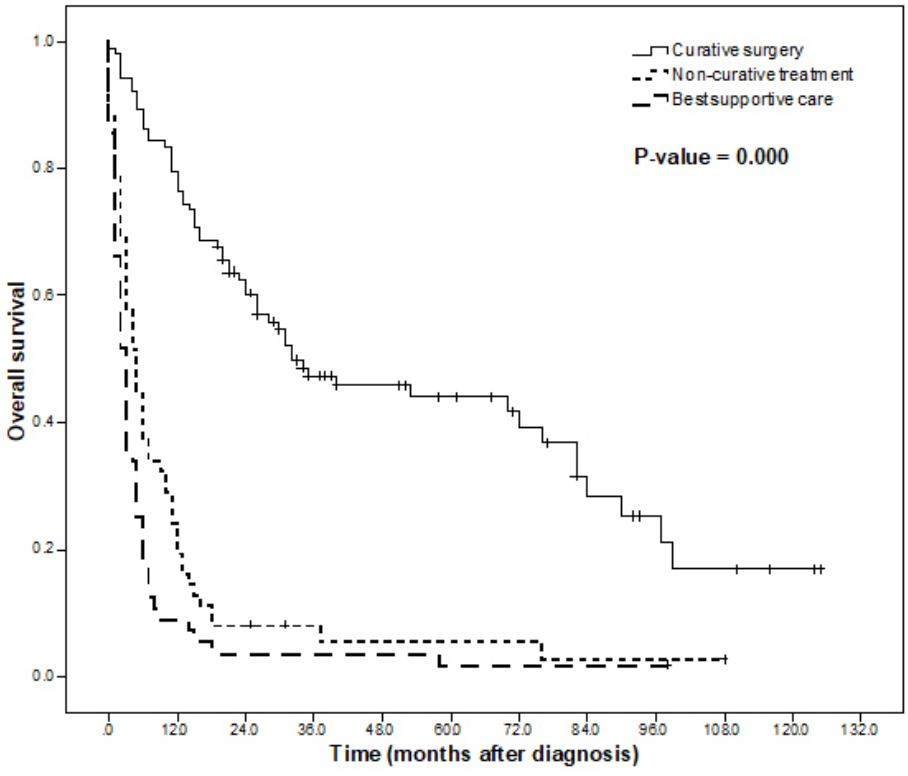

Fig 1. Kaplan-Meier overall survival curves of the curative surgery, non-curative treatment and best supportive care groups.

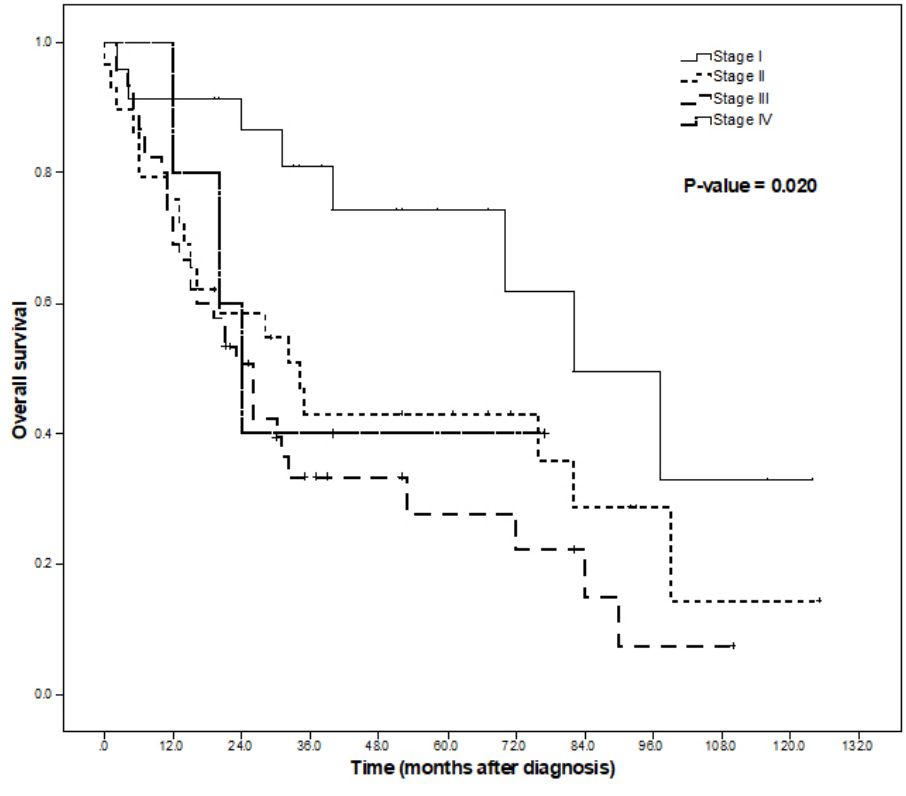

Fig 2. Kaplan-Meier overall survival curves of the different pathological stages in the curative surgery group.

Table 2. The risk factors for severe complications in these two groups were extremely old age over 80 years old and the presence of coronary artery disease according to the univariate analysis (Table 3). Multivariate analysis showed that only the presence of coronary artery disease (OR 7.65, 95%CI 2.2-26.6; $p = 0.001$) was an independent risk factor. In the subgroup analysis of curative surgery group, severe complications were found to be significantly higher in distal gastrectomy than in total gastrectomy (11.8% vs. 4.3%; $p = 0.033$). We found that there was a similar proportion of coronary artery disease patients in both types of surgery, but a higher proportion of

TABLE 2. Clinical details of the fourteen patients with severe complications.

No	Age	Procedure	Complications		Grade (IIIb–V)	Management	Result
			Surgical related	Non-surgical related			
Curative surgery							
1	71	Distal gastrectomy with wedge liver resection	Gastroparesis	Myocardial infarction, acute kidney injury, volume overload	IIIb	Nasojejunal tube placement, medical treatment	Improved
2	80	Distal gastrectomy	Intestinal obstruction	None	IIIb	Segmental jejunal resection	Improved
3	81	Distal gastrectomy	Gastroparesis	None	IIIb	Diagnostic EGD, intravenous prokinetics, parenteral nutrition	Improved
4	80	Distal gastrectomy	Gastroparesis	None	IIIb	Nasojejunal tube placement	Improved
5	74	Robotic-assisted laparoscopic distal gastrectomy	Gastroparesis	None	IIIb	Nasogastric tube placement under fluoroscopy	Improved
6	79	Robotic-assisted laparoscopic total gastrectomy	Accidentally clipped hepatic artery proper	Pneumonia, myocardial infarction, acute kidney injury, volume overload	IVb	Repair hepatic artery, hemodialysis, mechanical ventilation, blood transfusion, medical treatment	Improved
7	85	Extended gastrectomy	Anastomotic leakage, intraabdominal collection	Pneumonia, cardiac arrhythmia, catheter-related blood stream infection	V	Abdominal toilet with feeding jejunostomy, mechanical ventilation, tracheostomy, intravenous antibiotics	Death from severe sepsis on day 49
8	92	Distal gastrectomy	Bleeding from anterior pancreaticoduodenal artery and anterior surface of pancreas	Cardiac arrhythmia, acute kidney injury, liver failure, coagulopathy	V	Reexplore laparotomy to stop bleeding, massive blood transfusion, medical treatment	Death from severe meta bolic acidosis on day 2

Abbreviation: EGD = Esophagogastroduodenoscopy

TABLE 2. Clinical details of the fourteen patients with severe complications.

No	Age	Procedure	Complications		Grade (IIIb–V)	Management	Result
			Surgical related	Non-surgical related			
Non-curative treatment							
1	76	Simple suture with omental graft with feeding jejunostomy	Superficial surgical site infection	Atelectasis, volume overload, delirium, septic shock	IVa	Mechanical ventilation, medical treatment, intravenous antibiotics, wound dressing	Improved
2	75	Simple suture with omental graft	None	Pneumonia, cardiac arrhythmia, volume overload, catheter-related blood stream infection	IVa	Mechanical ventilation, tracheostomy, medical treatment, intravenous antibiotics	Improved
3	86	Palliative distal gastrectomy	None	Pneumonia, acute kidney injury, volume overload	IVb	Mechanical ventilation, hemodialysis, intravenous antibiotics	Improved
4	92	Laparoscopic feeding jejunostomy	Bowel ileus	Septicemia	V	Intravenous prokinetics, intravenous antibiotics	Death from septicemia on day 24
5	71	Diagnostic laparoscopy	None	Myocardial infarction, congestive heart failure, volume overload	V	Mechanical ventilation, medical treatment	Death from myocardial infarction on day 19
6	83	Diagnostic laparoscopy with feeding jejunostomy	None	Pneumonia, volume overload, ischemic stroke	V	Intravenous antibiotics, oxygen supplement	Death from respiratory failure on day 24

Abbreviation: EGD = Esophagogastroduodenoscopy

TABLE 3. Factors affecting severe postoperative complications.

Variables	Univariate		Multivariate	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age ≥ 80	3.667 (1.19-11.22)	0.023	3.173 (0.98-10.28)	0.054
Sex	1.344 (0.45-4.02)	0.597		
ASA ≥ 3	1.744 (0.58-5.27)	0.325		
Comorbidities				
DM	1.267 (0.37-4.28)	0.704		
HT	1.964 (0.59-6.55)	0.272		
CAD	8.625 (2.57-28.98)	<0.001	7.652 (2.20-26.60)	0.001
CKD (≥ stage 4)	2.333 (0.46-11.89)	0.308		
ECOG ≥ 3	1.500 (0.31-7.35)	0.617		
Albumin < 3	0.378 (0.05-3.07)	0.363		

Abbreviations: ASA = American Society of Anesthesiologists physical status score; DM = Diabetes mellitus; HT = Hypertension; CAD = Coronary artery disease; CKD = Chronic kidney disease; ECOG = Eastern Cooperative Oncology Group performance status score.

extremely old aged patients over 80 years underwent distal gastrectomy surgery (66.6% vs. 50%). In contrast, there was no statistically significant difference in the severe complications in the subgroup analysis of the various treatment options for the Non-curative group ($p = 0.137$). There were five in-hospital mortalities and four 30-days-postoperative mortalities, which are also shown in Table 2. The significant risk factors for in-hospital mortalities were extremely old age over 80 years old (OR 10.36, 95%CI 1.1-95.3; $p = 0.039$) and the presence of coronary artery disease (OR 14.30, 95%CI 2.2-92.5; $p = 0.005$). For the 30-days-postoperative mortalities, the only significant risk factor was the presence of coronary artery disease (OR 9.00, 95%CI 1.2-68.3; $p = 0.034$). The mean hospital length of stay from the curative and non-curative groups was 12 days. The risk factors for prolonged hospitalization were an extremely old age over 80 years old, the presence of hypertension, the presence of coronary artery disease, and patients who had severe complications according to the univariate analysis, but severe complications was the only independent risk factor (OR 22.84, 95%CI 4.9-107.4; $p < 0.001$) identified from the multivariate analysis.

DISCUSSION

Life expectancy has been increasing globally, paralleling the advancement in holistic medical care. The extent of comorbidities and decline of functional status increase with age, and these also affect morbidity and mortality in cancer patients. A better understanding of frailty in an oncology population may assist in identifying older adults who are candidates for palliative therapy as well as those patients who may benefit from standard treatment.[12] In 2006, Gretschel et al.[13] Reported the higher mortality rate of curative surgery for gastric cancer in a more elderly age group. With the improvement of surgical techniques and postoperative care over time, recent studies have revealed a significant better survival outcome in curative surgical resection regardless of older age,[2] with no significance differences in postoperative morbidity and mortality.[5,14]

In the present study, curative surgery showed significantly better overall survival compared to non-curative treatment and best supportive care despite the more advanced age. This result corresponded to a previous study by Choo et al.[2] The better survival outcomes might be from unavoidable selection bias in choosing curative surgery for patients who tend to have a better performance status, relatively higher nutritional status, and the absence of clinical metastasis at the time of the treatment decision. Only four patients in our curative surgery group had a poor performance status, and none of them had severe postoperative complications. A previous study at our center showed that positive microscopic

residual tumor after standard gastrectomy seemed to have a downward tendency for the survival outcome[15] and this was relevant to the results from the present study. For the remaining patients beyond this curative group, they were treated as having incurable gastric cancer based on physicians and patients' reasons. Hsu et al.[16] found that palliative gastrectomy still offered a better median survival time than the non-resection procedure. In serious symptomatic patients, stent placement for obstruction has been shown to be clinically effective[17], and endoscopic hemostasis for bleeding associated gastric cancer achieved an initial successful for 83% of patients.[18] These evidences support our various options for non-curative treatment, which depended on the clinical symptoms and yielded a significantly better survival result compared to best supportive care alone.

Due to the lack of complete follow-up data and the recurrence rate from our retrospective study design, disease-specific survival could not be clearly interpreted. As the mortality rate in our study was relatively low, the risk factors for postoperative mortality could not be analyzed. Hopefully, further research and progression in treatment would provide better survival outcomes and less morbidities.

Severe complications in our series occurred in 7.8% of patients in our curative surgery group and 9.7% in the non-curative treatment group (p = 0.77). The only predictive risk factor for severe complications was the presence of coronary artery disease, which differed from the previous study, which reported a low serum albumin level and male sex as risk factors[19] From all the severe complication cases in the non-curative group, there was none from endoscopic management. This might be from it being a less invasiveness and quicker procedure.

CONCLUSION

Elderly gastric cancer patients are still candidates for curative surgical resection in spite of their more advanced age and comorbidities. Surgery offers a better survival outcome than best supportive care alone. The possibility of severe postoperative complications should be considered, especially in coronary artery disease patients.

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