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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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The *WJGO* is now indexed in Science Citation Index Expanded (also known as SciSearch®), PubMed, PubMed Central, and Scopus. The 2020 edition of Journal Citation Reports® cites the 2019 impact factor (IF) for *WJGO* as 2.898; IF without journal self cites: 2.880; 5-year IF: 3.316; Ranking: 143 among 244 journals in oncology; Quartile category: Q3; Ranking: 55 among 88 journals in gastroenterology and hepatology; and Quartile category: Q3. The *WJGO*'s CiteScore for 2019 is 2.0 and Scopus CiteScore rank 2019: Gastroenterology is 86/137.

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EDITORIAL

Angiotensin-converting enzyme 2 connects COVID-19 with cancer and cancer immunotherapy

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in more than two million deaths. Underlying diseases, including cancer, are high-risk factors for severe COVID-19 outcomes. Angiotensin-converting enzyme 2 (ACE2), as a SARS-CoV-2 host cell receptor, plays a crucial role in SARS-CoV-2 invading human cells. ACE2 also has significant associations with cancer. Recent studies showed that ACE2 was inversely correlated with the activities of multiple oncogenic pathways and tumor progression phenotypes, and was positively correlated with antitumor immune response and survival prognosis in diverse cancers, suggesting a potential protective role of ACE2 in cancer progression. Positive expression of ACE2 is also correlated with programmed death-ligand 1 (PD-L1) in cancer. The positive associations of ACE2 expression with antitumor immune signatures and PD-L1 expression indicate that ACE2 expression is a positive predictor for the response to immune checkpoint inhibitors (ICIs). This was evidenced in multiple cancer cohorts treated with ICIs. Thus, ACE2 may build potential connections between COVID-19 and cancer and cancer immunotherapy. The potential connections suggest that ACE2 inhibitors may not be a good option for treating COVID-19 patients with cancer, particularly in cancer patients who are receiving immunotherapy. Furthermore, the relationships between ACE2, COVID-19, and cancer are worth confirming by more experimental and clinical data, considering that many cancer patients are at high risk for COVID-19.

Key Words: Angiotensin-converting enzyme 2; COVID-19; Cancer progression; Antitumor immune responses; Cancer immunotherapy

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Core Tip: Angiotensin-converting enzyme 2 (ACE2) is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) host cell receptor and plays a crucial role in SARS-CoV-2 invading human cells to cause coronavirus disease 2019 (COVID-19). ACE2 also plays a role in preventing tumor progression and promoting cancer immunotherapy response. Thus, the use of ACE2 inhibitors to prevent and treat COVID-19 should be carried out cautiously in cancer patients.

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INTRODUCTION

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused more than 113 million cases of coronavirus disease 2019 (COVID-19) and 2.5 million deaths as of February 25, 2021[1]. More seriously, a second wave of the COVID-19 pandemic has emerged and is expected to be more infectious and more deadly. Abundant evidence[2] has shown that many underlying diseases, including cancer, are risk factors for severe COVID-19 outcomes. Thus, specific measures to protect people with underlying diseases from SARS-CoV-2 infection or the development of severe COVID-19 are crucial for reducing COVID-19 deaths. Similar to cancer, COVID-19 may affect various human organs or tissues, including the lungs, kidneys, liver, brain, colon, stomach, and skin, in light of the fact that the SARS-CoV-2 host cell receptor angiotensin-converting enzyme 2 (ACE2) is expressed in a wide range of human tissues[3]. In fact, the essential role of ACE2 in SARS-CoV-2 invasion into human tissues is well recognized[4].

ASSOCIATION BETWEEN ACE2 AND CANCER

ACE2 also plays an important role in cancer. For example, Dai *et al*[5] showed that increased ACE2 expression was associated with a better survival prognosis in liver cancer. ACE2 exerts antitumor effects by inhibiting tumor angiogenesis[6]. Several recent studies explored the associations of ACE2 with antitumor immunity and immunotherapy response[7-9]. Yang *et al*[7] showed that the elevated expression of *ACE2* was correlated with increased antitumor immune response in uterine corpus endometrial and renal papillary cell cancers. Bao *et al*[8] revealed strong associations between *ACE2* expression and immune gene signatures in cancer. Our recent study[9] systematically explored the associations of *ACE2* expression with antitumor immune signatures, tumor progression phenotypes, oncogenic signatures, and clinical features in 13 cancer cohorts. We found that the expression levels of *ACE2* were inversely correlated with the levels of tumor proliferation, stemness, and epithelial-mesenchymal transition in diverse cancers. Moreover, *ACE2* expression levels were inversely correlated with the activities of multiple oncogenic pathways in cancer, including the cell cycle, vascular endothelial growth factor, transforming growth factor-β, Wnt, and Notch signaling. In contrast, the expression levels of *ACE2* correlated positively with diverse antitumor immune signatures in cancer, including antigen processing and presentation, T cell and B cell receptor signaling, nucleotide-binding and oligomerization domain-like receptor signaling, chemokine signaling, cytokine-cytokine receptor interaction, natural killer cell-mediated cytotoxicity, and Jak-STAT signaling. As a result, increased *ACE2* expression was associated with a favorable survival prognosis in multiple cancer cohorts, including renal clear cell carcinoma, renal papillary cell carcinoma, lung adenocarcinoma, and ovarian carcinoma[9]. Interestingly, the expression levels of *ACE2* were significantly lower in advanced than in non-advanced tumors in renal clear cell carcinoma. Overall, these data suggest a potential protective role of ACE2 in cancer development. Interestingly, positive expression of *ACE2* was significantly correlated with the gene encoding programmed death-ligand 1 (PD-L1) in cancer. As both the inflamed immune microenvironment and high PD-L1 expression are positively associated with the

response to immune checkpoint inhibitors (ICIs), *ACE2* upregulation may indicate an increased immunotherapy response in cancer. Indeed, in four cancer cohorts involving three cancer types (melanoma, renal clear cell carcinoma, and bladder cancer), the cancers with higher *ACE2* expression levels (> median) showed a higher rate of response to ICIs than the cancers with lower *ACE2* expression levels (< median).

CONCLUSION

Emerging evidence suggests potential associations between COVID-19 and cancer and cancer immunotherapy through ACE2 (Figure 1). In light of the important roles of ACE2 in preventing tumor progression and promoting cancer immunotherapy response, ACE2 inhibitors may not be a good option for treating COVID-19 patients with cancer, particularly in cancer patients who are receiving immunotherapy. The protective role of ACE2 in cancer progression and the function of ACE2 in promoting cancer immunotherapy response need to be further confirmed by more experimental and clinical data.

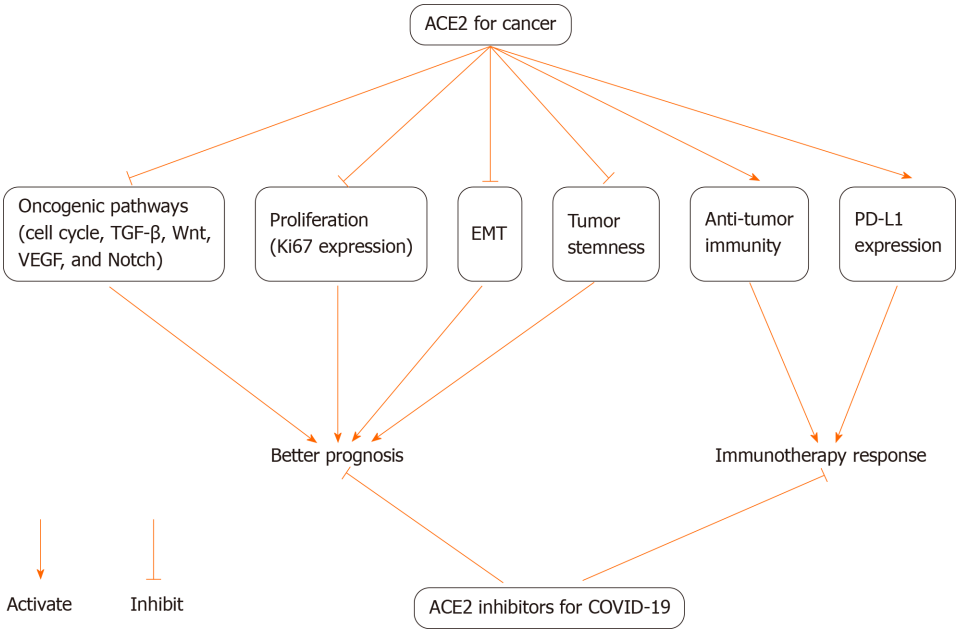

Figure 1 An illustration of the relationships between angiotensin-converting enzyme 2, coronavirus disease 2019, and cancer. ACE2: Angiotensin-converting enzyme 2; COVID-19: Coronavirus disease 2019; EMT: Epithelial-mesenchymal transition; PD-L1: Programmed death-ligand 1; TGF-β: Transforming growth factor-β; VEGF: Vascular endothelial growth factor.

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ORIGINAL ARTICLE

Retrospective Study

Low body mass index is an independent predictor of poor long-term prognosis among patients with resectable gastric cancer

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Author contributions: Tian YT performed study conception and design; Ma S, Liu H, Ma FH, Li Y, Jin P, Hu HT, Kang WZ, Li WK and Xiong JP performed acquisition of data; Ma S and Tian YT performed analysis and interpretation of data; Ma S performed drafting of the manuscript; Ma S, Liu H, Ma FH and Tian YT performed critical revision; Tian YT provided final approval.

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Abstract

BACKGROUND

The association between body mass index (BMI) and clinical outcomes remains unclear among patients with resectable gastric cancer.

AIM

To investigate the relationship between BMI and long-term survival of gastric cancer patients.

METHODS

This retrospective study included 2526 patients who underwent radical gastrectomy for gastric cancer between September 2013 and June 2018. The patients were divided into four groups: Group A (low BMI, < 18.5 kg/m^2), group B (normal BMI, 18.5-24.9 kg/m^2), group C (overweight, 25-29.9 kg/m^2), and group D (obese, ≥ 30 kg/m^2). Clinicopathological findings and survival outcomes were recorded and analyzed.

RESULTS

Preoperative weight loss was more common in the low-BMI group, while diabetes was more common in the obese group. Upper-third gastric cancer accounted for a large proportion of cases in the higher BMI groups. Major perioperative complications tended to increase with BMI. The 5-year overall survival rates were 66.4% for group A, 75.0% for group B, 77.1% for group C, and 78.6% for group D. The 5-year overall survival rate was significantly lower in group A than in group C (P = 0.008) or group D (P = 0.031). Relative to a normal BMI value, a BMI of < 18.5 kg/m^2 was associated with poor survival (hazard ratio: 1.558, 95% confidence

interval: 1.125-2.158, P = 0.008).

CONCLUSION

Low BMI, but not high BMI, independently predicted poor survival in patients with resectable gastric cancer.

Key Words: Gastric cancer; Malnutrition; Obesity; Body mass index; Survival benefit

Core Tip: The association between body mass index (BMI) and clinical outcomes remains unclear among patients with resectable gastric cancer. The findings of this study suggest that low BMI may result in unfavorable long-term outcomes among patients with resectable gastric cancer. The factor associated with poor overall survival based on multivariate analysis was low BMI, rather than high BMI.

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INTRODUCTION

Gastric cancer is the fifth most common cancer and the third leading cause of cancer-related death[1]. Gastric cancer patients often experience malnutrition, which may lead to obvious weight loss before surgery[2], particularly at advanced stages of the disease[3]. However, obesity is becoming increasingly common in both Western and Eastern countries[4,5]. Some studies have examined the association between body mass index (BMI) and the prognosis of gastric cancer[6-15], although the long-term outcomes remain unclear for patients with different BMIs.

Low preoperative BMI is associated with poor long-term outcomes among patients with gastric cancer[6,7], which may highlight the clinical importance of preoperative weight loss. However, some studies have claimed that BMI is not a risk factor for poor survival[8,9], while others have suggested that overweight/obese gastric cancer patients have a higher risk of postoperative complications and experience poorer outcomes[10,11]. Moreover, different studies have indicated that a high BMI is not associated with an increased risk of perioperative complications[12,13], and that patients with gastric cancer and a high BMI have comparable or better long-term outcomes, relative to individuals with a normal BMI[14,15]. Considering the discrepancies in these findings, this retrospective study aimed to clarify the relationship between preoperative BMI and long-term prognosis among patients with resectable gastric cancer.

MATERIALS AND METHODS

Patients and eligibility

The study included 3370 patients who were diagnosed with primary gastric cancer and underwent radical gastrectomy at the Department of Pancreatic and Gastric Surgery, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, and Peking Union Medical College between September 2013 and June 2018. The retrospective study protocol was approved by the institutional review board of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, and Peking Union Medical College.

The inclusion criteria were as follows: (1) Primary gastric adenocarcinoma; (2) A single focal tumor; (3) An available comprehensive pathological report; (4) Age 18–75 years; (5) An Eastern Cooperative Oncology Group score of 0–2; and (6) No chronic diseases involving major organs (heart, liver, or kidney). The exclusion criteria were as follows: (1) History of surgery (565 patients excluded); (2) Benign or malignant tumor

informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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history (49 patients were excluded); (3) M1 status confirmed during surgery (122 patients excluded); and (4) Incomplete clinicopathological information (108 patients excluded). Thus, the present study analyzed data from 2526 eligible patients.

Radical gastrectomy was performed for all eligible patients according to the Japanese gastric cancer treatment guidelines[16]. Surgical procedures included proximal, total, and distal gastrectomy. After surgery, specimens were reviewed by pathologists at the Department of Pancreatic and Gastric Surgery, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, and Peking Union Medical College. The pathological Tumor-node-metastasis (pTNM) stage was assessed according to the 8th edition American Joint Committee on Cancer (AJCC) TNM cancer staging guidelines[17]. Perioperative management was performed according to routine practice and did not differ between the groups. The patients' medical records were reviewed to collect data regarding clinicopathological characteristics: Sex, age, preoperative weight loss (%), preoperative BMI, diabetes, tumor location, Borrmann classification, histological type, perineural invasion, lymphovascular invasion (LVI), pTNM stage, examined lymph nodes (eLNs), metastatic lymph nodes, major complications (Clavien-Dindo classification of ≥ III), and survival.

Group division

BMI was classified as very obese (≥ 35 kg/m^2), obese (30.0-34.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and normal weight (18.5-24.9 kg/m^2) according to the World Health Organization (WHO) guidelines[18]. However, the present study only included a small number of very obese patients; therefore, the very obese and obese groups were combined. Thus, in the present study, we assigned the patients into four groups: Group A (low BMI, < 18.5 kg/m^2), group B (normal BMI, 18.5-24.9 kg/m^2), group C (overweight, 25-29.9 kg/m^2), and group D (obese, ≥ 30 kg/m^2).

Statistical analyses

Data were compared between the four groups to identify differences in postoperative outcomes (major complications) and long-term survival. Categorical variables were compared using the χ^2 test and non-normally distributed continuous variables were compared using Kruskal-Wallis one-way analysis of variance. Survival outcomes were compared using the Kaplan-Meier life table method and the log-rank test. Cox proportional hazards models were used to assess the associations between the predictor variables and outcomes. Results were considered statistically significant at P values of < 0.05. All statistical analyses were performed using IBM SPSS Statistics software (version 23 for Mac, IBM Corp.), R software (version 4.0.2 for Mac, IBM Corp.), and Prism 7 software for Mac (IBM Corp.).

RESULTS

Patients and clinicopathological characteristics

The study included 2526 patients who were treated between September 2013 and June 2018 (Table 1). All patients underwent radical gastrectomy. Significant differences in sex were observed among the four groups. The low BMI group had a greater proportion of preoperative weight loss and a lower proportion of diabetes. The proportion of upper-third gastric cancer tended to increase with increasing BMI. Significant differences in the number of eLNs were also observed among the four groups (Table 1 and Figure 1). In a paired comparison (Figure 1), more lymph nodes were harvested for group B than for group C (median: 30 *vs* 28, P = 0.021). Increasing BMI tended to be associated with an increased incidence of major complications (Table 1). There were no significant differences in the other clinicopathological characteristics among the four groups.

Long-term survival

The median follow-up period was 50.2 mo, the median survival time was not reached, and 1906 patients (75.5%) were alive at the last follow-up. Figure 2 shows the Kaplan-Meier overall survival (OS) curves according to BMI classification. The 5-year OS rates were 66.4% for group A, 75.0% for group B, 77.1% for group C, and 78.6% for group D (P = 0.039, Figure 2A). Group A had poorer 5-year OS than group C (P = 0.008) and group D (P = 0.031). When the cases were stratified according to the pTNM stage, a significant difference was observed only for pTNM stage III disease (P = 0.041, Figure 2D). The results of the paired comparisons are shown in Table 2. Among

Table 1 Patient characteristics and clinicopathological findings

	Group A (< 18.5 kg/m²)	Group B (18.5-24.9 kg/m²)	Group C (25-29.9 kg/m²)	Group D (≥ 30 kg/m²)	*P* value
Male sex, *n* (%)	73 (61.3)	1124 (77.1)	713 (85.1)	84 (75.0)	**< 0.001**
Age < 65 yr, *n* (%)	79 (66.4)	1067 (73.2)	615 (73.4)	79 (70.5)	0.384
Preoperative weight loss, *n* (%)					**< 0.001**
0% or increased	75 (63.0)	1010 (63.9)	623 (74.3)	89 (79.5)	
0-5%	7 (5.9)	127 (8.7)	88 (10.5)	10 (8.9)	
> 5%	37 (31.1)	320 (22.0)	127 (15.2)	13 (11.6)	
BMI, median (range)	17.1 (14.0-18.4)	22.5 (18.5-24.9)	26.7 (25.0-29.9)	31.2 (30.0-48.8)	**< 0.001**
Diabetes, *n* (%)	3 (2.5)	100 (6.9)	107 (12.8)	22 (19.6)	**< 0.001**
Tumor location					**0.044**
Upper	41 (34.5)	481 (33.0)	337 (40.2)	46 (41.1)	
Middle	24 (20.2)	294 (20.2)	164 (19.6)	24 (21.4)	
Lower	49 (41.2)	604 (41.5)	308 (36.8)	38 (33.9)	
Entire	5 (4.2)	78 (5.4)	29 (3.5)	4 (3.6)	
Tumor diameter ≤ 5 cm, *n* (%)	857 (71.4)	1019 (69.9)	603 (72.0)	83 (74.1)	0.642
Borrmann type, *n* (%)					0.116
EGC	26 (21.8)	298 (20.5)	181 (21.6)	30 (26.8)	
I	8 (6.7)	112 (7.7)	55 (6.6)	13 (11.6)	
II	30 (25.2)	376 (25.8)	247 (29.5)	29 (25.9)	
III	53 (44.5)	582 (39.9)	317 (37.8)	34 (30.4)	
IV	2 (1.7)	89 (6.1)	38 (4.5)	6 (5.4)	
Histological type, *n* (%)					0.931
Differentiated	31 (26.1)	351 (24.1)	201 (24.0)	25 (22.3)	
Undifferentiated	88 (73.9)	1106 (75.9)	637 (76.0)	87 (77.7)	
PNI, *n* (%)	48 (40.3)	701 (48.1)	419 (50.0)	49 (43.8)	0.177
LVI, *n* (%)	41 (34.5)	583 (40.0)	322 (38.4)	55 (49.1)	0.105
pT status, *n* (%)					0.606
1a	13 (10.9)	164 (11.3)	78 (9.3)	12 (10.7)	
1b	16 (13.4)	216 (14.8)	131 (15.6)	21 (18.8)	
2	18 (15.1)	202 (13.9)	119 (14.2)	18 (16.1)	
3	38 (31.9)	434 (29.8)	280 (33.4)	34 (30.4)	
4a	29 (24.4)	401 (27.5)	198 (23.6)	23 (20.5)	
4b	5 (4.2)	40 (2.7)	32 (3.8)	4 (3.6)	
pN status, *n* (%)					0.143
0	50 (42.0)	593 (40.7)	344 (41.1)	45 (40.2)	
1	22 (18.5)	276 (18.9)	163 (19.5)	18 (16.1)	
2	18 (15.1)	238 (16.3)	137 (16.3)	27 (24.1)	
3a	21 (17.6)	169 (11.6)	116 (13.8)	13 (11.6)	
3b	8 (6.7)	181 (12.4)	78 (9.3)	9 (8.0)	
pTNM stage, *n* (%)					0.261
IA	24 (20.2)	307 (21.1)	173 (20.6)	29 (25.9)	

IB	10 (8.4)	156 (10.7)	88 (10.5)	9 (8.0)	
IIA	17 (14.3)	185 (12.7)	99 (11.8)	15 (13.4)	
IIB	19 (16.0)	202 (13.9)	127 (15.2)	14 (12.5)	
IIIA	20 (16.8)	253 (17.4)	154 (18.4)	21 (18.8)	
IIIB	22 (18.5)	173 (11.9)	124 (14.8)	15 (13.4)	
IIIC	7 (5.9)	181 (12.4)	73 (8.7)	9 (8.0)	
eLNs, median (range)	30 (7-65)	30 (3-119)	28 (5-89)	27 (4-71)	**0.008**
mLN, median (range)	1 (0-24)	1 (0-67)	1 (0-48)	2 (0-29)	0.824
Major complications, *n* (%)	11 (9.2)	200 (13.7)	117 (14.0)	28 (25.0)	**0.004**

Statistically significant results are shown in bold font. BMI: Body mass index; EGC: Epigallocatechin; PNI: Perineural invasion; LVI: Lymphovascular invasion; eLNs: Examined lymph nodes; mLN: Metastatic lymph nodes; pTNM: Pathological tumor-node-metastasis.

Table 2 Paired log-rank test in all pathological tumor-node-metastasis stages/pathological tumor-node-metastasis stage I/pathological tumor-node-metastasis stage II/pathological tumor-node-metastasis stage III

	B	C	D
A	0.054/0.497/**0.030**/0.074	**0.008**/0.485/**0.023**/**0.006**	**0.031**/0.952/0.136/0.070
B		0.143/0.870/0.593/0.081	0.246/0.426/0.750/0.428
C			0.605/0.414/0.886/0.964

Statistically significant results are shown in bold font.

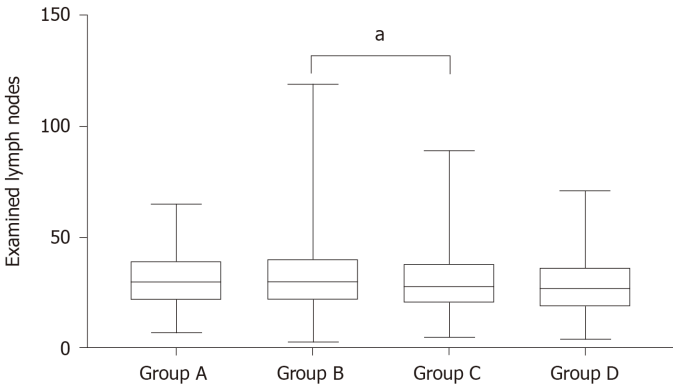


Figure 1 Examined lymph nodes in each group. $^{a}P < 0.05$.

patients with pTNM stage III disease, group A had poorer 5-year OS than group C (44.9% *vs* 59.5%, $P = 0.006$). Among patients with pTNM stage II disease, group A had poorer 5-year OS than group B (66.7% *vs* 84.8%, $P = 0.03$) and group C (66.7% *vs* 83.2%, $P = 0.023$).

The multivariate analyses (Table 3) revealed that a poor OS was independently associated with a BMI of < 18.5 kg/m^2 [*vs* BMI of 18.5-24.9 kg/m^2, hazard ratio (HR): 1.558, 95% confidence interval: 1.125-2.158, $P = 0.008$], upper-third gastric cancer or entire stomach involvement, tumor diameter > 5 cm, Borrmann type IV disease, LVI, pT3–4 status, pN+ status, and having < 30 eLNs. A high BMI (≥ 30 kg/m^2) did not independently predict a poor long-term OS (*vs* BMI of 18.5-24.9 kg/m^2, HR: 0.824, 95% confidence interval: 0.551-1.230, $P = 0.343$).

Table 3 Cox proportional hazard regression model for overall survival

	Univariate		Multivariate[1]	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Sex				
Male	Ref		Ref	
Female	0.897 (0.742-1.085)	0.263	0.970 (0.798-1.180)	0.763
Age				
< 65 yr	Ref		Ref	
≥ 65 yr	1.362 (1.162-1.598)	< 0.001	1.161 (0.985-1.367)	0.075
Preoperative weight loss				
0% or increased	Ref		Ref	
0%–5%	1.210 (0.934-1.568)	0.148	0.964 (0.740-1.256)	0.786
> 5%	1.612 (1.355-1.918)	< 0.001	1.122 (0.937-1.342)	0.210
BMI				
18.5-24.9 kg/m^2	Ref		Ref	
25-29.9 kg/m^2	0.883 (0.747-1.043)	0.143	0.885 (0.746-1.049)	0.160
≥ 30 kg/m^2	0.792 (0.533-1.177)	0.249	0.824 (0.551-1.230)	0.343
< 18.5 kg/m^2	1.368 (0.996-1.880)	0.053	1.558 (1.125-2.158)	**0.008**
Tumor location				
Lower	Ref		Ref	
Middle	1.049 (0.828-1.328)	0.692	1.098 (0.863-1.395)	0.447
Upper	1.886 (1.579-2.253)	< 0.001	1.409 (1.155-1.717)	**0.001**
Entire	3.512 (2.639-4.674)	< 0.001	1.748 (1.292-2.366)	**< 0.001**
Tumor diameter				
≤ 5 cm	Ref		Ref	
> 5 cm	2.488 (2.141-2.892)	< 0.001	1.256 (1.068-1.477)	**0.006**
Borrmann type				
EGC	Ref		Ref	
I	4.861 (3.082-7.666)	< 0.001	1.206 (0.659-2.208)	0.544
II	4.374 (2.971-6.440)	< 0.001	1.205 (0.685-2.120)	0.518
III	8.817 (6.114-12.717)	< 0.001	1.587 (0.905-2.784)	0.107
IV	14.778 (9.703-22.510)	< 0.001	1.967 (1.070-3.613)	**0.029**
Histological type				
Differentiated	Ref		Ref	
Undifferentiated	1.495 (1.237-1.806)	< 0.001	0.891 (0.724-10.96)	0.275
PNI				
No	Ref		Ref	
Yes	2.785 (2.390-3.246)	< 0.001	1.064 (0.886-1.278)	0.507
LVI				
No	Ref		Ref	
Yes	2.764 (2.355-3.243)	< 0.001	1.231 (1.039-1.457)	**0.016**
pT status				

1a	Ref		Ref	
1b	1.596 (0.778-3.274)	0.202	1.343 (0.652-2.765)	0.424
2	3.338 (1.727-6.454)	< 0.001	1.607 (0.749-3.451)	0.223
3	9.302 (5.086-17.012)	< 0.001	2.519 (1.201-5.284)	**0.014**
4a	17.766 (9.732-32.433)	< 0.001	3.898 (1.844-8.239)	**< 0.001**
4b	18.263 (9.415-35.427)	< 0.001	3.950 (1.778-8.775)	**< 0.001**
pN status				
0	Ref		Ref	
1	3.055 (2.316-4.030)	< 0.001	1.787 (1.314-2.394)	**< 0.001**
2	4.849 (3.717-6.326)	< 0.001	2.544 (1.898-3.411)	**< 0.001**
3a	9.325 (7.207-12.066)	< 0.001	4.095 (3.042-5.512)	**< 0.001**
3b	11.071 (8.540-14.352)	< 0.001	4.345 (3.182-5.932)	**< 0.001**
eLNs				
≥ 30	Ref		Ref	
16–29	1.055 (0.901-1.236)	0.505	1.282 (1.083-1.518)	**0.004**
< 16	0.944 (0.724-1.232)	0.672	1.515 (1.139-2.015)	**0.004**

[1]Adjusted for all variables shown in the table.

Statistically significant results are shown in bold font. HR: Hazard ratio; Ref: Reference (hazard ratio = 1.0); BMI: Body mass index; PNI: Perineural invasion; LVI: Lymphovascular invasion; eLNs: Examined lymph nodes; EGC: Epigallocatechin.

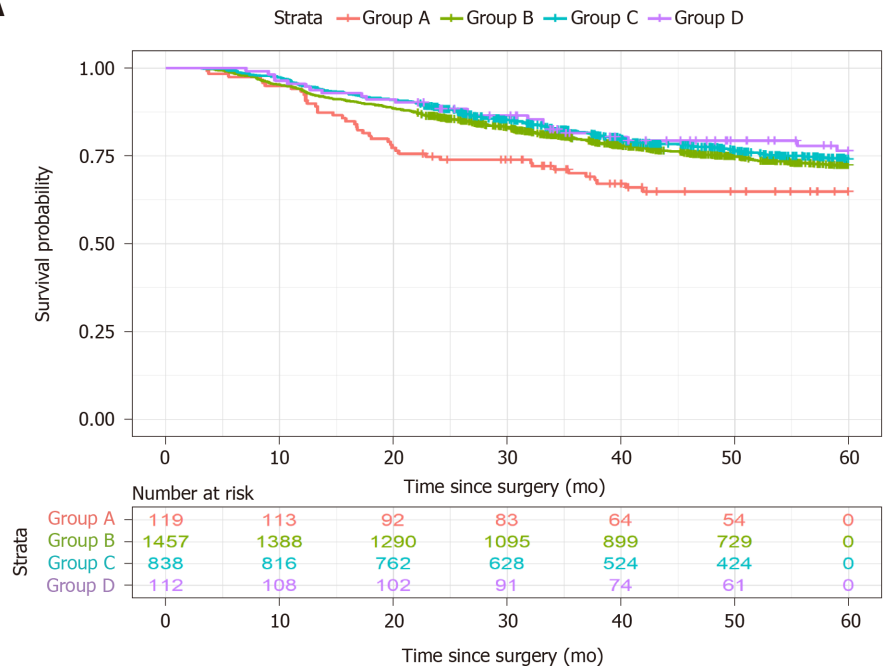
DISCUSSION

Obesity is associated with cancer mortality, and the malnutrition status of cancer patients may also be related to their long-term prognosis. However, the relationships between specific BMI groupings and cancer survival are less clear. The results of the present study suggest that low BMI independently predicted poor long-term survival, while high BMI was associated with major perioperative complications but not long-term survival.

Our group with high BMI had an increased proportion of diabetes, upper-third gastric cancer, and perioperative major complications. Similarly, a meta-analysis suggested that high BMI was associated with an increased incidence of cardiac carcinoma. In this context, obese patients are more likely to have esophagogastric junction disruption or an augmented gastroesophageal pressure gradient, which could induce reflux[19]. In addition, gastroesophageal reflux disease is strongly associated with cardiac or esophageal adenocarcinoma[20]. However, this distribution pattern was not observed in other studies[6,12].

Several studies have indicated that high BMI is associated with increased risks of major complications and perioperative mortality[9,20,21], which is consistent with our findings. Obese patients typically have poor surgical field visibility, as well as an increased possibility of oozing, which can complicate the dissection of lymph nodes and formation of an anastomosis. However, high BMI was not associated with an increased risk of perioperative complications in some medical centers[8,22-24], which could be related to high volumes and experienced surgeons reducing the risks associated with radical gastrectomy in obese patients[12]. In our study, fewer eLNs were retrieved in the higher BMI groups (groups C and D), although the only significant difference was observed between groups B and C, and these two groups had similar 5-year OS outcomes. Dhar *et al*[10] reported that a higher BMI was associated with a higher risk of local recurrence and shorter recurrence-free survival, which they attributed to the difficulty in achieving adequate lymphadenectomy in obese patients with gastric cancer. In addition, it can be challenging to determine the actual number of lymph node dissections in obese patients, considering the difficulty involved in isolating lymph nodes within the abundant intra-abdominal fat. Nevertheless, as indicated above, it is possible that experienced surgeons in high-volume centers might be able to perform appropriate radical lymphadenectomy and achieve favorable oncological outcomes even for obese patients. In our study, the median number of eLNs was similar for groups B and C, and the difference might be attributable to the

A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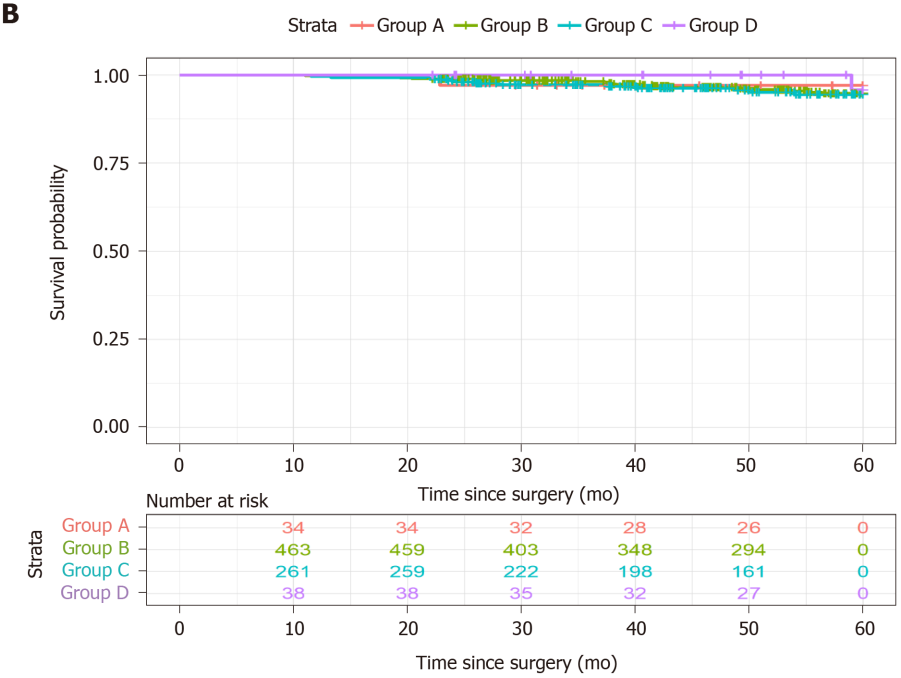
Survival probability
1.00
0.75
0.50
0.25
0.00
0 10 20 30 40 50 60
Time since surgery (mo)
Number at risk
Strata
Group A 119 113 92 83 64 54 0
Group B 1457 1388 1290 1095 899 729 0
Group C 838 816 762 628 524 424 0
Group D 112 108 102 91 74 61 0
0 10 20 30 40 50 60
Time since surgery (mo)

B


Strata Group A Group B Group C Group D
Survival probability
1.00
0.75
0.50
0.25
0.00
0 10 20 30 40 50 60
Time since surgery (mo)
Number at risk
Strata
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Group B 463 459 403 348 294 0
Group C 261 259 222 198 161 0
Group D 38 38 35 32 27 0
0 10 20 30 40 50 60
Time since surgery (mo)

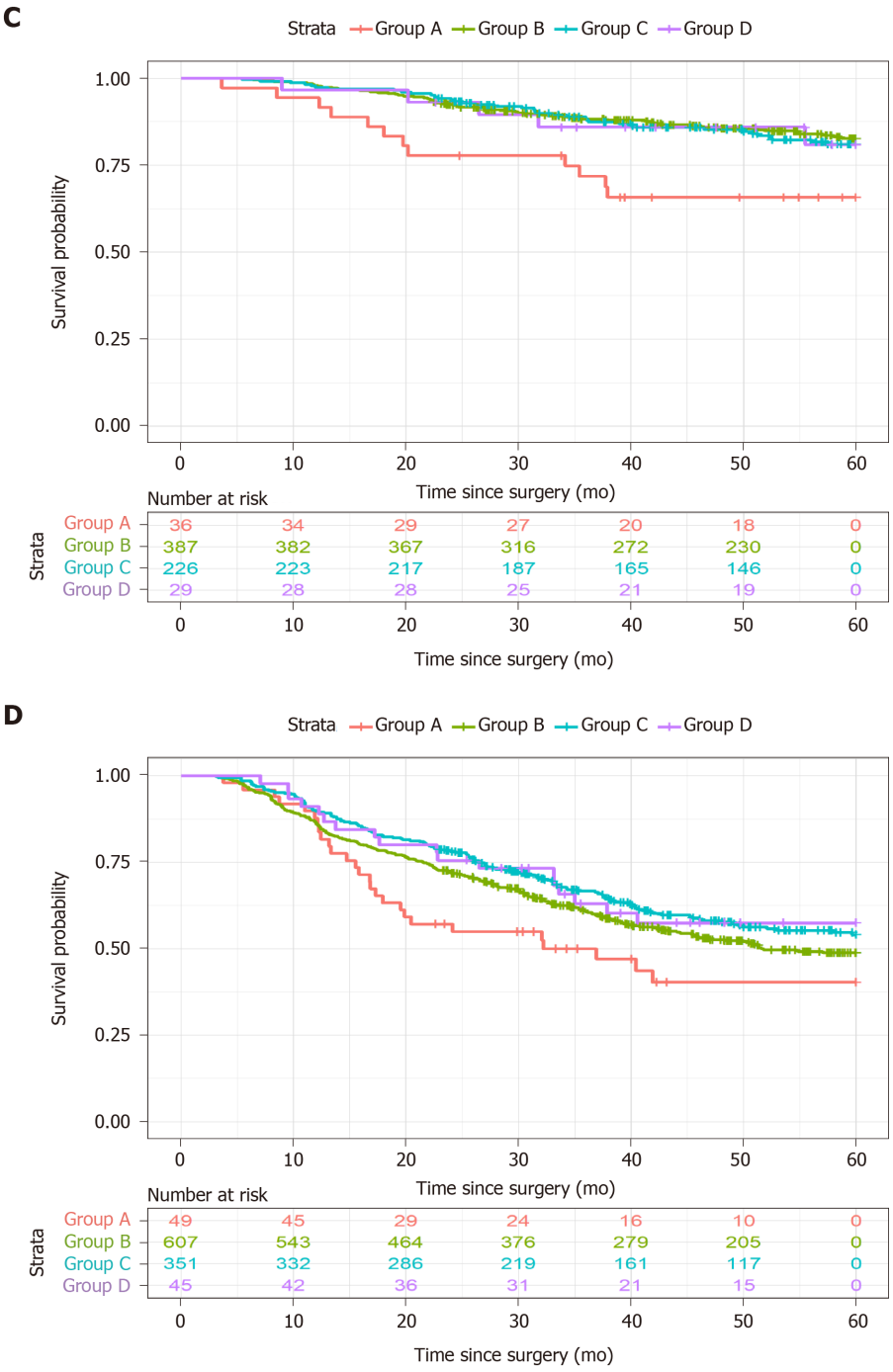

Figure 2 Kaplan-Meier curves for overall survival according to body mass index. A: Kaplan-Meier curves for overall survival are shown for all pathological tumor-node-metastasis (pTNM) stages (log-rank *P* = 0.039); B: Kaplan-Meier curves for overall survival are shown for pTNM stage I disease (log-rank *P* = 0.767); C: Kaplan-Meier curves for overall survival are shown for pTNM stage II disease (log-rank *P* = 0.117); D: Kaplan-Meier curves for overall survival are shown for pTNM stage III disease (log-rank *P* = 0.041).

difference in the range, rather than a difference in the median value. Nevertheless, we observed that an inadequate number of eLNs (< 30) was an independent predictor of poor long-term outcomes, which is consistent with the increasing number of studies[25-27] that suggest that a higher number of retrieved LNs is associated with improved long-term outcomes. The 8th edition of the AJCC TNM cancer staging guidelines[17] recommend that a minimum of 16 LNs, but preferably ≥ 30 LNs, be assessed during gastric cancer surgery. In addition, Deng *et al*[28,29] demonstrated that an insufficient number of eLNs may be a risk factor for postoperative recurrence in patients with LN-negative gastric cancer. We emphasize the importance of standard radical gastrectomy procedures and a sufficient number of eLNs for obese patients to achieve favorable short-term and oncological outcomes. Less experienced surgeons should perform D2 lymphadenectomy for obese patients with gastric cancer until they

have sufficient experience.

In our study, low BMI (< 18.5 kg/m^2) was an independent predictor of poor 5-year OS, although comparable 5-year OS rates were observed between the low and normal BMI groups. Patients with advanced gastric cancer are more likely to experience preoperative weight loss and malnutrition, which is associated with decreased survival. Moreover, gastrectomy leads to postoperative weight loss[15], and it is possible that overweight/obese patients would reach a more appropriate body weight after surgery, which could improve their long-term prognosis. Our multivariate analysis revealed that high BMI was not associated with poor survival, and a similar result was observed in a retrospective study of 427 Japanese patients with gastric cancer by Wada *et al*[7]. In the present study, stratified analyses revealed a difference in the 5-year OS rates when we compared the low-BMI and overweight groups of patients with pTNM stage II–III disease. Nevertheless, the 5-year OS rates were comparable between the four BMI-based groups of patients with pTNM stage I gastric cancer. The discrepancies between the results of the overall and stratified analyses may be related to the limited numbers of patients in groups A and D, which might have biased the stratified analysis.

Previous studies have supported different conclusions regarding the association between BMI and long-term prognosis[6-15]. Our results suggest that patients with obese and normal BMI have comparable 5-year OS rates, while conflicting results have been reported[11,13]. We speculate that these differences might be related to the specific group divisions, as only two BMI-based groups (cut-off: 25 kg/m^2) were used in the studies by Lianos *et al*[11] and Shimada *et al*[13], who concluded that high BMI independently predicted a poor prognosis. Three BMI-based groups (< 18.5 kg/m^2, 18.5-24.9 kg/m^2, and ≥ 25 kg/m^2) were used in a Chinese and a Japanese study[7,9], which revealed that low BMI, rather than high BMI, was associated with poor survival, similar to our findings. The main difference between these studies was that a BMI of < 25 kg/m^2 was analyzed either as a single group or by separating into two groups (< 18.5 kg/m^2 and 18.5-24.9 kg/m^2). Furthermore, Shimada *et al*[13] reported average BMI values of 26.4 ± 2 kg/m^2 in the obese group and 22 ± 2.2 kg/m^2 in the normal-BMI group, which are clearly different from the values in our study. The differences in average BMI values might explain the conflicting conclusions. Nevertheless, there has been a recent shift toward the general opinion that high BMI does not affect long-term outcomes among gastric cancer patients, particularly those who are treated in high-volume medical centers[12].

The present study has several limitations. First, we did not analyze data regarding adjuvant chemotherapy use, which might have influenced the patients' outcomes. Second, the surgical approach was not considered in this study, although surgical procedures can influence postoperative nutritional status and long-term outcomes, especially after total or near-total gastrectomy[30-32]. Third, the stratified analysis might have been biased based on the small numbers of patients in groups A and D.

CONCLUSION

A low BMI (< 18.5 kg/m^2) was an independent risk factor for poor long-term survival after radical gastrectomy for gastric cancer. However, a high BMI was not a risk factor for poor survival in this setting.

ARTICLE HIGHLIGHTS

Research background

Some studies showed that high body mass index (BMI) was related to unfavorable prognosis of gastric cancer, while other literature revealed low preoperative BMI was related to unfavorable prognosis of gastric cancer. To our knowledge, there are still discrepancies in the relationship between BMI and prognosis of gastric cancer.

Research motivation

Considering the controversy mentioned above, our study aimed to clarify the relationship between preoperative BMI and long-term prognosis among patients with resectable gastric cancer.

Research objectives

The aim of this study was to clarify the relationship between BMI and long-term prognosis of resectable gastric cancer patients. Clinicopathological characteristics and survival were analyzed in our study. Then, multivariate analysis was used to identify risk factors. Our findings suggest that low BMI may result in unfavorable long-term outcomes among patients with resectable gastric cancer. The factor associated with poor overall survival based on multivariate analysis was low BMI, rather than high BMI.

Research methods

This is a retrospective study. 2526 patients who had undergone radical gastrectomy for gastric cancer at the Cancer Hospital of the Chinese Academy of Medical Sciences were eligible and finally included in the study. Medical records were reviewed with regard to sex, age, preoperative weight loss (%), preoperative BMI, diabetes, tumor location, Borrmann classification, histological type, perineural invasion, lymphovascular invasion, pathological tumor-node-metastasis stage, examined lymph nodes, metastatic lymph nodes, major complications (Clavien-Dindo classification of ≥ III), and follow-up data. Cumulative survival rates were obtained using the Kaplan–Meier method and compared using the log-rank test to evaluate statistically significant differences. Cox proportional hazards regression analysis was used to evaluate risk factors for poor overall survival.

Research results

Preoperative weight loss was more common in the low-BMI group, while diabetes was more common in the obese group. Upper-third gastric cancer accounted for a large proportion of cases in the higher BMI groups. Major perioperative complications tended to increase with BMI. The 5-year overall survival rates were lower in the low BMI group. Relative to a normal BMI value, low BMI was associated with poor survival.

Research conclusions

Low BMI resectable gastric cancer patients have an unfavorable long-term outcome. Low BMI is an independent predictor of poor long-term prognosis. Disputed conclusions in previous literature regarding the relationship between BMI and long-term prognosis for resectable gastric cancer may be attributed to different cut-off values for BMI group division.

Research perspectives

Low BMI independently predicted poor survival among patients with resectable gastric cancer. Thus, additional treatment strategies should be undertaken in the management of gastric cancer patients with a low preoperative BMI.

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ORIGINAL ARTICLE

Retrospective Study

Efficacy and safety of grasping forceps-assisted endoscopic resection for gastric neoplasms: A multi-centre retrospective study

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Abstract

BACKGROUND

Endoscopic submucosal dissection (ESD) is widely accepted for early gastric cancer (EGC) without lymph node metastasis, although ESD is challenging, even for small lesions, in the greater curvature (GC) of the upper (U) and middle (M) thirds of the stomach. Grasping forceps-assisted endoscopic resection (GF-ER) is a type of endoscopic mucosal resection that is performed *via* a double-channel endoscope.

AIM

To investigate the safety and efficacy of GF-ER *vs* ESD in the GC of the stomach's U and M regions.

METHODS

We retrospectively reviewed the medical records of 506 patients who underwent ER of 522 EGC lesions in the stomach's U and M regions in three institutions between January 2016 and May 2020. Nine lesions from eight patients who underwent GF-ER for EGC (the GF-ER group) were compared to 63 lesions from 63 patients who underwent ESD (the ESD group). We also performed a subgroup analysis of small lesions (≤ 10 mm) in 6 patients (7 lesions) from the GF-ER group and 20 patients (20 lesions) from the ESD group.

RESULTS

There were no statistically significant differences between the GF-ER and ESD

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groups in the *en bloc* resection rates (100% *vs* 100%) and the R0 resection rates (100% *vs* 98.4%). The median procedure time in the GF-ER group was shorter than that in the ESD group (4.0 min *vs* 55.0 min, $P < 0.01$). There were no adverse events in the GF-ER group, although five perforations (8.0%) and 1 case of postoperative bleeding (1.6%) were observed in the ESD group. When we only considered lesions that were ≤ 10 mm, the median procedure time in the GF-ER group was still shorter than that in the ESD group (4.0 min *vs* 35.0 min, $P < 0.01$). There were no adverse events in the GF-ER group, although 1 case of perforation (1.6%) were observed in the ESD group.

CONCLUSION

These findings suggest that GF-ER may be an effective therapeutic option for small lesions in the GC of the stomach's U and M regions.

Key Words: Gastric cancer; Endoscopic resection; Endoscopic submucosal dissection; Endoscopic mucosal resection; Grasping forceps-assisted endoscopic resection

Core Tip: Endoscopic submucosal dissection (ESD) is widely accepted for early gastric cancer (EGC), although ESD is challenging, even for small lesions, in the greater curvature of the upper and middle thirds of the stomach. The major discoveries and findings in this study are; we found that grasping forceps-assisted endoscopic resection achieved *en bloc* and R0 resections with significantly shorter procedure times (*vs* ESD), without any adverse events. Although ESD is considered the first-line treatment for EGC, it is not always necessary to treat lesions in all areas using ESD, and endoscopic mucosal resection is a feasible option if *en bloc* resection is considered possible, as it can be performed easily and quickly.

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INTRODUCTION

Endoscopic submucosal dissection (ESD) was developed in Japan during the 1990s and is now widely used to treat early gastric cancer (EGC), as it allows *en bloc* resection of large lesions and ulcers and facilitates an accurate pathological diagnosis[1-3]. However, relative to in other regions, ESD is considered a technically challenging procedure in the upper (U) and middle (M) thirds of the stomach, especially in the greater curvature (GC). This is because intraoperative bleeding is more common in the U and M areas, which can prolong the procedural time. Furthermore, ESD in these regions is associated with increased rates of adverse events, such as perforation[4-6]. Endoscopic mucosal resection (EMR) is considered a technically simpler procedure, relative to ESD, and EMR requires less time, although it may not provide complete resection of large lesions. Despite the challenges associated with ESD, and the simplicity of EMR, almost all endoscopic resections (ERs) for gastric cancer in Japan are performed *via* ESD.

Grasping forceps-assisted ER (GF-ER) is an EMR procedure that uses an assistant device, which is similar to a cap or ligation device for EMR[7-10]. At the centres that were involved in this study, GF-ER was performed for lesions that fulfilled the following criteria: (1) The EGC was located in the U or M region of the stomach; (2) Small (diameter: ≤ 10 mm) or pedunculated lesions; and (3) The endoscopist judged *en bloc* resection feasible. Although GF-ER is a conventionally practiced technique, only a few studies have described the outcomes of GF-ER for EGC. Furthermore, since ESD has become established, no new studies have compared the therapeutic outcomes of GF-ER and ESD in the challenging U and M stomach regions. Thus, this study aimed to

investigate the safety and efficacy of GF-ER and ESD in the GC of the stomach's U and M regions.

MATERIALS AND METHODS

Study design and ethical approval

This multi-centre, retrospective, observational cohort study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the institutional review board of Nihon University Surugadai Hospital. Written informed consent was obtained from the patients before the ESD and GF-ER procedures. We collected and retrospectively reviewed data from the patients' medical records.

Patients

Figure 1 shows the study flowchart. A total of 506 patients underwent ER for 522 EGC lesions between January 2016 and May 2020 at three institutions (Nihon University Surugadai Hospital, Nihon University Itabashi Hospital, and Yuri-Kumiai General Hospital). Patients were excluded if they had previously undergone gastric surgery or if they had undergone ER for lesions in the lower (L) stomach region, lesser curvature, anterior side wall, or posterior side wall. Thus, we ultimately compared the safety and efficacy outcomes for 9 lesions from 8 patients who underwent GF-ER for EGC in the GC of the stomach's U and M regions (the GF-ER group) and 63 lesions from 63 patients who underwent ESD (the ESD group). We also performed a subgroup analysis of patients with small lesions (diameter: ≤ 10 mm), which included 7 lesions from 6 patients in the GF-ER group and 20 lesions from 20 patients in the ESD group.

Endoscopic procedures

All GF-ER and ESD procedures were performed at the three institutions. All patients were hospitalised on the day before the GF-ER or ESD procedure and maintained a restricted diet for 2 d after the procedure. Patients were discharged at 1 wk after the procedure if they did not experience any adverse events, although discharge was delayed for patients who developed perforations or bleeding. All patients were sedated using midazolam or propofol and pentazocine. High-frequency currents produced by ERBE-ICC200 or VIO300D electrosurgical generator units (ERBE Elektromedzin, GmbH, Tübingen, Germany) were used in the Endocut mode (effect 2), at 50 W for the forced coagulation mode, and at 50 W for mucosal resection or submucosal dissection during the GF-ER and ESD procedures. Haemostasis was achieved using the soft coagulation mode at 80 W. The GF-ER procedures were performed using the GIF-Q260J endoscope and the ESD procedures were performed using the GIF2TQ260M endoscope (Olympus, Tokyo, Japan). The ESD procedures were performed using the IT Knife2 (Olympus, Tokyo, Japan), Clutch Cutter (Fujifilm Medical, Tokyo, Japan), Dual Knife (Olympus, Tokyo, Japan), or Splash M-knife (HOYA Corp., Pentax, Tokyo, Japan) based on the endoscopist's preference. A short hood (D-201 – 13404 Olympus, Tokyo, Japan) was used on the endoscope tip.

The ESD procedure was started by using an argon plasma coagulation or needle knife to mark around the lesion. The surrounding submucosa was then injected with a saline solution and, once the area was sufficiently elevated, a complete circumferential incision was made approximately 5 mm outside the marking. The submucosa was then dissected to complete the *en bloc* resection. During ESD, the dental floss method could be used for traction assistance, based on the endoscopist's preference[11].

The GF-ER procedure was started by creating a mark around the lesion in the same manner as for the ESD procedure. After the marking, a saline solution was injected locally into the submucosa around the lesion to achieve sufficient elevation (Figure 2A). Next, the snare and grasping forceps were deployed from the double-channel scope (Figure 2B). The grasping forceps were used to firmly grasp the elevated mucosa (Figure 2C) and the snare was then placed around the grasped mucosa (Figure 2D). After ensuring that the entire lesion was inside the snare, the resection was performed (Figure 2E). Finally, we checked the mucosal defect for any residual tumour (Figure 2F).

Specimens resected during ESD and GF-ER were pinned, preserved in formalin, and cut into 2–3 mm sections. Histological diagnoses were performed by pathologists at the hospitals. Pathological diagnoses were made by gastrointestinal pathologists according to the Japanese Gastric Cancer Classification and the Japanese gastric cancer treatment guidelines[12,13].

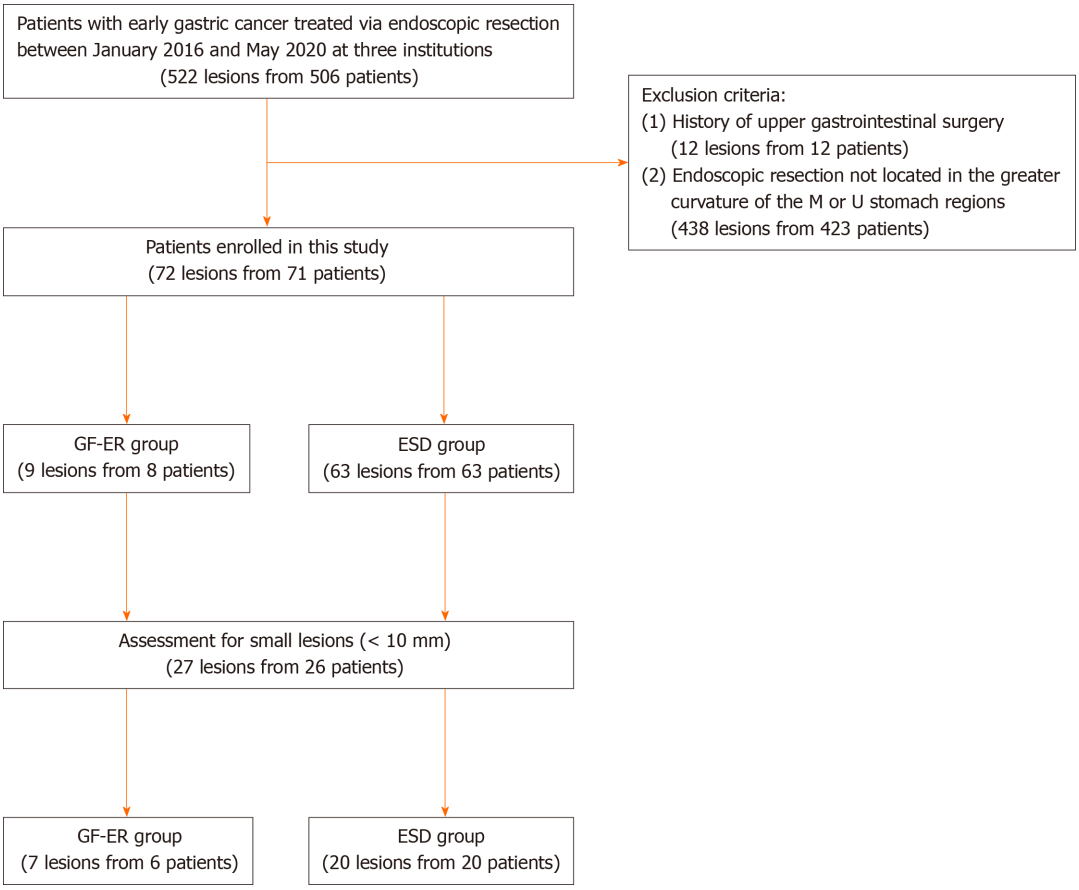

Figure 1 Study flowchart. ESD: Endoscopic submucosal dissection; GF-ER: Grasping forceps-assisted endoscopic resection; M: Middle; U: Upper.

Outcomes and definitions

The primary outcome was the procedural time and the secondary outcomes were the rates of *en bloc* resection, R0 resection, and adverse events (such as postoperative bleeding and perforations). Tumour location was defined according to the Japanese classification of gastric carcinoma based on the affected gastric region (U, M, or L) and gastric surface (lesser curvature, GC, anterior wall, or posterior wall)[12]. The GF-ER or ESD procedural times were defined as the times from the first submucosal injection to the resection of the lesion. *En bloc* resection was defined as a resection made without having to resort to a piecemeal resection. R0 resection was defined as *en bloc* resection that achieved negative horizontal and vertical tumour margins. Perforations were defined as intraoperative exposures of the mesenteric fat or free air, as confirmed by diagnostic imaging based on a post-procedural complaint of abdominal pain. Delayed bleeding was defined as an endoscopic or surgical haemostatic procedure performed for subjective symptoms, such as anaemia, haematemesis, or melena.

Statistical analysis

Continuous variables were reported as median (interquartile range) and compared using the Mann-Whitney *U* test. The Fisher test was used to compare categorical variables. A P value of < 0.05 was considered statistically significant. All statistical analyses were performed using EZR software (version 1.27; Saitama Medical Centre, Jichi Medical University, Japan)[14].

RESULTS

Baseline characteristics

Table 1 shows the baseline characteristics of the 8 patients and 9 lesions from the GF-ER group and the 63 patients and 63 lesions from the ESD group. Tumour size was significantly smaller in the GF-ER group than in the ESD group (7.0 mm *vs* 16.0 mm, $P < 0.01$). There were no significant differences between the two groups in terms of

Table 1 Comparison of baseline clinicopathologic characteristics between grasping forceps assisted endoscopic resection and endoscopic submucosal dissection groups

	GF-ER	ESD	*P* value
Age, yr			
Median (IQR)	68.0 (54-80)	75.0 (66-82)	0.28
Sex, *n* (%)			
Male	6 (75.0)	45 (71.4)	1
Female	2 (25.0)	18 (28.6)	
Morphology, *n* (%)			
Flat or depressed	5 (55.6)	46 (73.0)	0.43
Elevated	4 (44.4)	17 (27.0)	
Ulceration, *n* (%)			
Presence	0 (0)	4 (6.3)	1
Absence	9 (100)	59 (93.7)	
Tumor size, mm			
Median (IQR)	7 (4-11)	16 (9-22)	< 0.01
Tumor depth, *n* (%)			
Mucosa	6 (66.7)	49 (77.8)	0.43
Submucosa	3 (33.3)	14 (22.2)	
Histology, *n* (%)			
Differentiated	9 (100)	49 (77.8)	0.31
Undifferentiated	0 (0)	14 (22.2)	

P values were calculated using Fisher's exact test for categorical data and Mann-Whitney U test for continuous data. GF-ER: Grasping forceps assisted endoscopic resection; ESD: Endoscopic submucosal dissection; IQR: Interquartile range.

tumour morphology, depth, or histology. Table 2 shows the baseline characteristics of the patients with small lesions (diameter: ≤ 10 mm) according to their procedure. There was no significant difference in tumour size between the GF-ER and ESD groups in this subgroup.

Clinical outcomes

The therapeutic outcomes of the GF-ER and ESD groups are compared in Table 3. The median procedure time was significantly shorter for the GF-ER group than for the ESD group [4.0 min (range: 3.0-5.0 min) *vs* 55.0 min (range: 30-105 min), $P < 0.01$]. There were no statistically significant differences between the GF-ER and ESD groups in the *en bloc* resection rates (100% *vs* 100%) and the R0 resection rates (100% *vs* 98.4%). In the ESD group, 5 patients (8.0%) experienced perforations and 1 patient (1.6%) experienced postoperative bleeding. No adverse events were encountered in the GF-ER group. The therapeutic outcomes for small lesions (≤ 10 mm) are shown in Table 4. In this subgroup analysis, all patients in both groups had *en bloc* and R0 resections. However, the median procedure time was significantly shorter in the GF-ER group than in the ESD group [4.0 min (range: 3.5-4.0 min) *vs* 35.0 min (range: 25-75 min), $P < 0.001$]. One patient (5.0%) in the ESD group experienced perforation.

DISCUSSION

This study evaluated the efficacy and safety of GF-ER and ESD for EGC in the GC of the stomach's U and M regions. Lesions in these regions are considered relatively challenging to treat, although we found that GF-ER achieved *en bloc* and R0 resections with significantly shorter procedure times (*vs* ESD), without any adverse events. Similar results were observed in a subgroup analysis comparing GF-ER and ESD for

Table 2 Comparison of baseline clinicopathologic characteristics between grasping forceps assisted endoscopic resection and endoscopic submucosal dissection groups for small lesions (defined as ≤ 10 mm in diameter)

	GF-ER	ESD	*P* value
Age, yr			
Median (IQR)	67.5 (54-80)	75.5 (66-79)	0.39
Sex, *n*			
Male	4 (66.7)	16 (80.0)	0.60
Female	2 (33.3)	4 (20.0)	
Morphology, *n* (%)			
Flat or depressed	4 (57.1)	16 (80.0)	0.33
Elevated	3 (42.9)	4 (20.0)	
Ulceration, *n* (%)			
Presence	0 (0)	1 (5.0)	1.0
Absence	7 (100)	19 (95.0)	
Tumor size, mm			
Median (IQR)	6.0 (4-8)	6.5 (5-9)	0.45
Tumor depth, *n* (%)			
Mucosa	4 (57.1)	18 (90.0)	0.09
Submucosa	3 (42.9)	2 (10.0)	
Histology, *n* (%)			
Differentiated	7 (100)	17 (85.0)	1.0
Undifferentiated	0 (0)	3 (15.0)	

P values were calculated using Fisher's exact test for categorical data and Mann-Whitney U test for continuous data. GF-ER: Grasping forceps assisted endoscopic resection; ESD: Endoscopic submucosal dissection; IQR: Interquartile range.

Table 3 Comparison of treatment outcomes between grasping forceps assisted endoscopic resection and endoscopic submucosal dissection groups

	GF-ER	ESD	*P* value
Procedure time, min			
Median (IQR)	4.0 (3.0-5.0)	55.0 (30-105)	< 0.01
En bloc resection, *n* (%)	9 (100)	63 (100)	1.0
R0 resection, *n* (%)	9 (100)	62 (98.4)	1.0
Curative resection, *n* (%)	9 (100)	55 (87.3)	0.54
Perforation, *n* (%)	0 (0)	5 (8.0)	1.0
Delayed bleeding, *n* (%)	0 (0)	1 (1.6)	1.0

P values were calculated using Fisher's exact test for categorical data and Mann-Whitney *U* test for continuous data. GF-ER: Grasping forceps assisted endoscopic resection; ESD: Endoscopic submucosal dissection; IQR: Interquartile range.

lesions with diameters of ≤ 10 mm.

Many studies have compared EMR and ESD for EGC, and the results have indicated that ESD is superior to EMR in terms of the *en bloc* resection rate, while EMR is considered a shorter and safer procedure[15-17]. However, most reports included EMR for large lesions and were not limited to small lesions or lesions where *en bloc* was judged feasible. Furthermore, the reports often used data regarding EMR outcomes that were collected before ESD was developed, and focused on relatively stable

Table 4 Comparison of treatment outcomes for small lesions (defined as ≤ 10 mm in diameter) between grasping forceps assisted endoscopic resection and endoscopic submucosal dissection groups

	GF-ER	ESD	*P* value
Procedure time, min			
Median (IQR)	4.0 (3.0-5.0)	35.0 (25-75)	< 0.01
En bloc resection, *n* (%)	7 (100)	20 (100)	1.0
R0 resection, *n* (%)	7 (100)	20 (100)	1.0
Curative resection, *n* (%)	7 (100)	19 (95.0)	1.0
Perforation, *n* (%)	0 (0)	1 (5.0)	1.0
Delayed bleeding, *n* (%)	0 (0)	0 (0)	1.0

P values were calculated using Fisher's exact test for categorical data and Mann-Whitney U test for continuous data. GF-ER: Grasping forceps assisted endoscopic resection; ESD: Endoscopic submucosal dissection; IQR: Interquartile range.

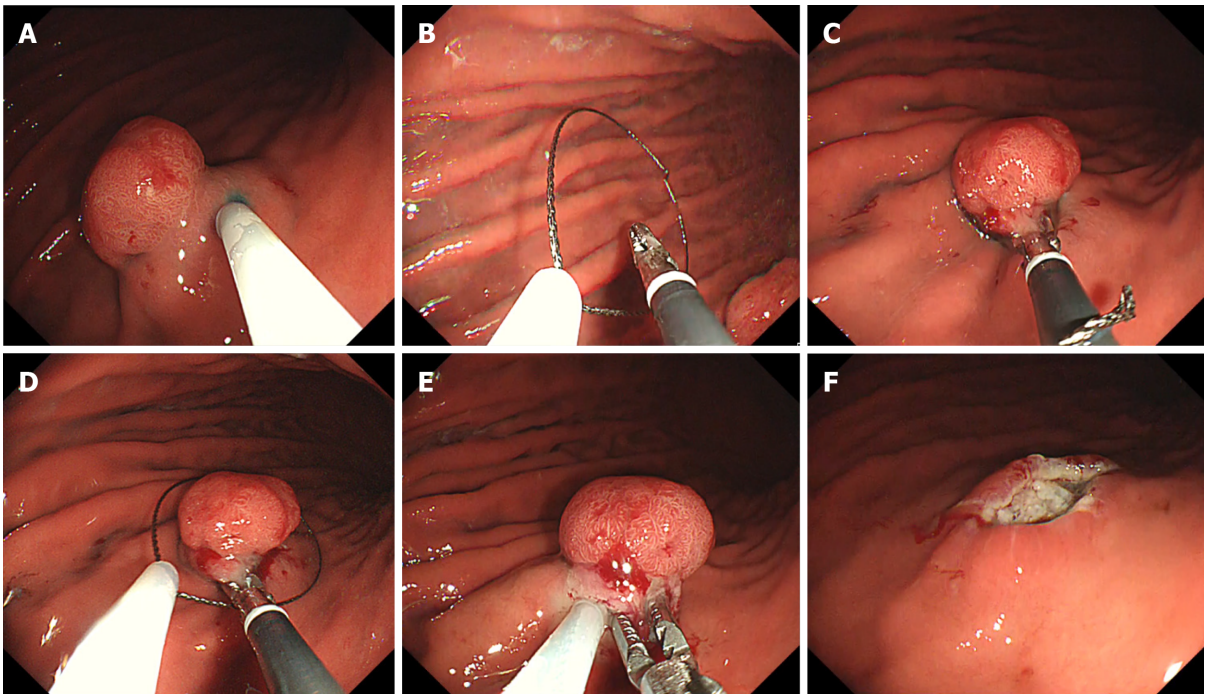

Figure 2 The grasping forceps-assisted endoscopic resection procedure. A: Normal saline solution was injected into the submucosa around the lesion; B: A snare and grasping snare were both deployed through one of the scope's two channels; C: The grasping snare was used to firmly grasp the elevated mucosa; D: The snare encircled the grasped mucosa; E: We ensured that the entire lesion was inside the snare, and then the resection was performed; F: After the resection, the mucosal defect was checked for residual tumour.

procedures. In contrast, we compared the outcomes of ESD and GF-ER during the same period to avoid issues that might be related to improvements in endoscopic procedures over time. Our facilities also only perform GF-ER for small lesions where *en bloc* resection is considered feasible, which sets our findings apart from those of previous reports.

As an established endoscopic procedure, GF-ER provides advantages over other EMR methods, as it facilitates more extensive resection by using grasping forceps to pick up the lesion. Another advantage is that, because there is no aspiration step in the cap, the endoscopist can confirm that the entire lesion is within the snare before resecting it. Thus, *en bloc* resection is considered easier to perform and an assistant technique is unnecessary.

Some favourable results have been reported for GF-ER, which indicate that is has a short procedure time and *en bloc* resection rates of up to 82.4%-100%[18-20]. This technique can be applied in situations that would be considered particularly challenging for conventional EMR or ESD, such as in the absence of the lifting sign

after the submucosal injection[18] and a large pedunculated polyp[19]. In this setting, the GF-ER might improve the procedure by directly grasping the gastrointestinal tumour, and previous reports have described areas or lesions that were considered difficult to treat using ESD. However, we are not aware of any reports directly comparing the treatment outcomes of GF-ER and ESD for gastric cancer, and we believe ours is the first report to evaluate the efficacy and safety of GF-ER and ESD for EGC. Figure 3 shows the locations of the 9 EGC lesions that were treated using GF-ER, and, despite their small size, these lesions were located in areas where ESD treatment would be considered very difficult.

Our findings suggest that GF-ER could be a useful therapeutic option in this setting, especially for small lesions located in the GC of the stomach's U and M regions. The advantage of this technique is that it is simpler and faster to use, relative to ESD, and reducing the procedure time reduces the burden on the patient and the endoscopist. In addition, GF-ER provided comparable treatment outcomes. Furthermore, GF-ER is likely cost-effective, as the snares used in EMR are cheaper than the knives used in ESD. However, the disadvantage of GF-ER is that it requires a double-channel endoscope (GIF-2TQ260M; Olympus, Tokyo, Japan), which is not commonly available, especially in Western countries. Nevertheless, it may be possible to perform this procedure *via* an additional accessory channel on the outside of the scope[21-23].

This study had some limitations. First, it was a retrospective study with a small sample size. Second, the operative method was not randomly assigned but was selected at the discretion of the endoscopist, which raises the possibility of selection bias. However, we exclusively performed GF-ER for lesions where *en bloc* resection was considered feasible *via* EMR. These lesions would have required a longer procedural time if ESD had selected.

CONCLUSION

In conclusion, this study revealed that GF-ER should be considered as an option for lesions in the GC of the stomach's U and M regions, where ESD is considered a long, technically challenging, and potentially risky procedure. Although ESD is considered the first-line treatment for EGC, it is not always necessary to treat lesions in all areas using ESD, and EMR is a feasible option if *en bloc* resection is considered possible, as it can be performed easily and quickly. However, the indications for GF-ER limit the generalization of our findings, and a large prospective study is needed to validate our findings.

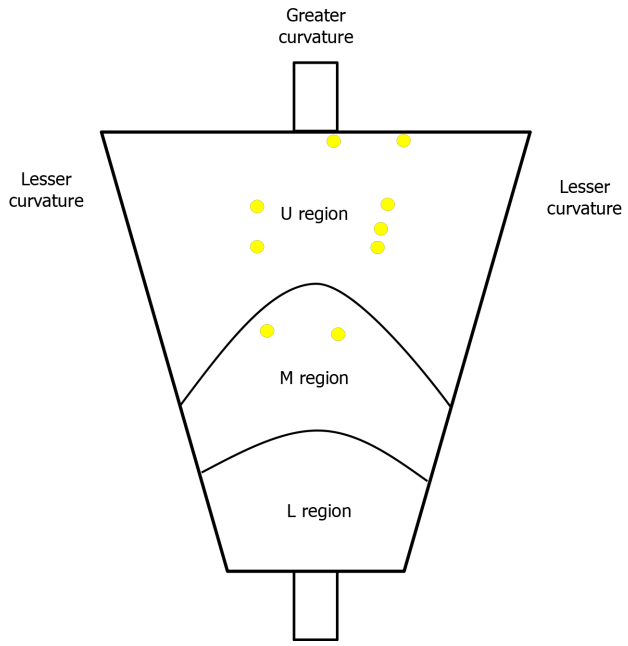

Figure 3 Location mapping for the 9 cases of early gastric cancer treated using grasping forceps-assisted endoscopic resection. The yellow circles show the locations of the lesions that were treated using grasping forceps-assisted endoscopic resection. L: Lower; M: Middle; U: Upper.

ARTICLE HIGHLIGHTS

Research background

Endoscopic submucosal dissection (ESD) is widely accepted for early gastric cancer (EGC), although ESD is challenging, even for small lesions, in the greater curvature (GC) of the upper (U) and middle (M) thirds of the stomach.

Research motivation

Since ESD has become established, no new studies have compared the therapeutic outcomes of grasping forceps-assisted endoscopic resection (GF-ER) and ESD in the challenging U and M stomach regions.

Research objectives

To investigate the safety and efficacy of GF-ER and ESD in the GC of the stomach's U and M regions.

Research methods

We retrospectively reviewed the medical records of 506 patients who underwent ER of 522 EGC lesions in the stomach's U and M regions in three institutions between January 2016 and May 2020.

Research results

En bloc resection was achieved in all patients from the GF-ER and ESD groups. The median procedure time in the GF-ER group was shorter than that in the ESD group (4.0 min *vs* 55.0 min, $P < 0.01$). There were no adverse events in the GF-ER group, although five perforations (8.0%) and 1 case of postoperative bleeding (1.6%) were observed in the ESD group. When we only considered lesions that were ≤ 10 mm, the median procedure time in the GF-ER group was still shorter than that in the ESD group (4.0 min *vs* 35.0 min, $P < 0.01$).

Research conclusions

GF-ER should be considered as an option for lesions in the GC of the stomach's U and M regions, where ESD is considered a long, technically challenging, and potentially risky procedure.

Research perspectives

A large prospective study is needed to validate our findings.

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ORIGINAL ARTICLE

Retrospective Study

Should we resect colorectal cancer in patients over the age of 85?

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Author contributions: Flynn DE designed the study, performed the research and wrote the manuscript; Mao D designed the study methodology and helped perform the research; Yerkovich S helped with data collection, statistical analysis and manuscript review; Franz R, Iswariah H, Hughes A, Shaw I and Tam D helped with data collection, clinical advice, data analysis and manuscript review; Chandrasegaram M helped with design methodology and conceptualisation, study supervision, manuscript editing and finalisation.

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Abstract

BACKGROUND

The prevalence of colorectal cancer in the elderly is rising, with increasing numbers of older patients undergoing surgery. However, there is a paucity of information on the surgical outcomes and operative techniques used in this population.

AIM

To evaluate the post-operative outcomes for patients ≥ 85 years old following colorectal cancer resection as well as evaluating the outcomes of laparoscopic resection of colorectal cancer in patients over 85.

METHODS

Patients who underwent colorectal cancer resection at our institution between January 2010 and December 2018 were included. The study was divided into two parts. For part one, patients were divided into two groups based on age: Those age ≥ 85 years old (n = 48) and those aged 75-84 years old (n = 136). Short term surgical outcomes and clinicopathological features were compared using appropriate parametric and non-parametric testing. For part two, patient's over 85 years old were divided into two groups based upon operative technique: Laparoscopic (n = 37) *vs* open (n = 11) colorectal resection. Short-term post-operative outcomes of each approach were assessed.

RESULTS

The median length of stay between patients over 85 and those aged 75-85 was

eight days, with no statistically significant difference between the groups (P = 0.29). No significant difference was identified between the older and younger groups with regards to severity of complications (P = 0.93), American Society of Anaesthesiologists grading (P = 0.43) or 30-d mortality (2% *vs* 2%, P = 0.96). Patients over 85 who underwent laparoscopic colorectal resection were compared to those who underwent an open resection. The median length of stay between the groups was similar (8 *vs* 9 d respectively) with no significant difference in length of stay (P = 0.18). There was no significant difference in 30-d mortality rates (0% *vs* 9%, P = 0.063) or severity of complication grades (P = 0.46) between the laparoscopic and open surgical groups.

CONCLUSION

No significant short term surgical differences were identified in patients ≥ 85 years old when compared to those 75-85 years old. There is no difference in short term surgical outcomes between laparoscopic or open colorectal resections in patients over 85.

Key Words: Aged; Colorectal neoplasms; General surgery; Open abdomen techniques; Laparoscopy; Colorectal surgery

Core Tip: This is a retrospective study to assess the outcomes of patients over 85 undergoing colorectal cancer resection. Patients over the age of 85 who underwent surgery were found to have equitable short term surgical outcomes when compared to those aged 75-85 years old. There was no difference in length of stay, severity of complications or mortality rates between the two groups. Patients over 85 were also analyzed based upon outcomes following open or laparoscopic surgery. There were no significant differences between length of stay, complication rates or mortality rates between the two techniques. Surgical intervention for colorectal cancer should not be based upon age alone.

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INTRODUCTION

The elderly population is increasing worldwide. In Australia, people over the age of 65 makes up 15% of the population while those aged over 85 make up 2.1% of the population. Colorectal cancer is a leading cause of morbidity and mortality in the western world with incidence rates steadily increasing in the elderly.

Historically, there was an adopted view amongst clinicians that the peri-operative risks were too high for those at the extremes of age, with older patients being offered less aggressive and palliative oncological treatments[1]. However, evidence is starting to favour surgical intervention for colorectal cancer in select patients at the extremes of age[2]. Previous studies have investigated the outcomes of colorectal resection in different age ranges (over 75's, over 80's *ect*.) and demonstrated favourable results, however there is a paucity of information on the role of colorectal cancer resection specifically in those over 85 (commonly referred to as "the oldest old")[3].

The question of laparoscopic surgery *vs* open surgery in the elderly population has also been explored with several randomised control trials demonstrating favourable outcomes in 'elderly patients'[4,5]. Once again, many of these studies focus on patients in the 6th and 7th decade of life, with a scarcity of studies investigating laparoscopic outcomes in those over 85[6,7].

In order to compare the short-term outcomes from surgery, post-operative complications must be assessed and compared. In previous studies, there has been a

because the analysis used anonymous clinical data that was obtained after each patient agreed to treatment by written consent.

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lack of consistency in grading complications. Terms such as 'mild', 'moderate' and 'severe' have been inconsistently used and compared, leading to bias. The Clavien-Dindo classification of post-operative complications has been shown to provide a reproducible and objective classification of post-surgical outcomes. The classification is based upon the severity and required treatment for each complication grade and is graded from grade I-V with Grade V being mortality, the gravest of complications. The classifications have been widely used to standardise outcomes in a variety of surgical subspecialties[8-10].

The aim of this study is two-fold: To investigate the short-term outcomes of patients over the age of 85 undergoing colorectal cancer resection and the use of laparoscopic colorectal cancer resection in those over the age of 85.

MATERIALS AND METHODS

Study design and data source

A single institution, retrospective study of patients undergoing colorectal cancer surgery at The Prince Charles Hospital.

Patients were divided in two age groups in order to assess the short-term outcomes of patients over 85. The comparison group was chosen to be those between 75-84 years of age. The demographic features, comorbidities, surgical characteristics, short-term outcomes and complications were compared between the two groups.

For the second aim of the study, patients over the age of 85 who underwent laparoscopic colorectal surgery were compared to those who underwent open surgery.

Patient charts were individually reviewed and data extracted by trained medical personnel. Data was obtained from previous admissions, current admissions as well as correspondence letters, follow up documentation and outpatient/readmission notes.

Inclusion criteria included those who underwent surgical resection of biopsy proven colorectal cancer at The Prince Charles Hospital between January 2010 and December 2018. Patients were excluded if they had endoscopic resection of the malignant lesion without surgical intervention.

Demographic and comorbidity characteristics

Basic demographic data including age, gender, date of birth, height, weight, body mass index and American Society of Anaesthesiologists (ASA) grade was documented. Specific pre-operative conditions were grouped into comorbid groups and documented for each patient: Cardiovascular (ischemic heart disease, previous coronary artery bypass grafting, previous percutaneous coronary intervention, pacemaker insertion, defibrillator insertion, previous valve repair, heart failure, cardiomyopathy, hypertension, pulmonary hypertension and atrial fibrillation), respiratory [asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, cystic fibrosis and obstructive sleep apnoea], metabolic (type I diabetes, type II diabetes and hyperlipidaemia), autoimmune (rheumatoid arthritis, psoriasis, polymyalgia rheumatica, and systemic lupus erythematosus) and renal disease.

Surgical and pathological features

Surgical data included the operation performed, urgency of surgery, operative approach, and length of stay. Pathological data included tumour histopathology, histological grade and TNM stage of disease.

Short term post-operative outcomes

Short term outcomes reviewed included complications, 30-d mortality and length of stay. Complications were Graded from I to V according to the Clavien-Dindo Classification of surgical complications (Supplementary Table 1). Post-operative complications were defined as those that arose up to 14 d post-operatively.

Statistical analysis

Differences in demographic features, comorbidities and surgical/pathological features between the two complication groups were assessed using *t*-tests, chi squared test and Fisher's exact tests as appropriate. Statistically significant results were defined as those with P value ≤ 0.05. Data was analyzed with Stata v14 software (StataCorp). Statistical analysis and review was undertaken by a biomedical statistician.

Ethics

Ethics approval for this database was granted by the Prince Charles Hospital Human Research Ethics Committee (Reference: HREC/17/QPCH/295). A waiver of consent was approved to allow access to confidential patient information without consent. Patients were not anonymized prior to data collection. However, patient names and certain other identifying data was not recorded in the database to help guard against confidentiality breaches. Patient data was accessed between January 2018 and June 2019.

RESULTS

Patient demographics

From January 2010 to December 2018, five hundred and thirty-three patients underwent colorectal cancer resection at our institution. No patients were excluded from the study. One hundred and thirty-six patients were aged between 75-85 years old at the time of surgery. Forty-eight patients were aged 85 or above at the time of surgery. These two groups were compared with the demographic features of each group outlined in Table 1.

The distribution of ASA grading was similar between the two groups, with no significant difference in distribution or prevalence. Hypertension was the most common cardiac comorbidity in both groups (75-85 age group, 63% *vs* 85+ age group, 71%, $P = 0.38$) with coronary artery bypass grafting being more prevalent within the 75-85 years old group (15% *vs* 11%, $P = 0.025$). There was also a significantly higher proportion of women in the over 85 group (69% *vs* 51%, $P = 0.043$). There was no significant difference between the two groups with regards to distribution of other cardiac comorbidities.

Asthma (15% *vs* 8 %, $P = 0.33$), COPD (16% *vs* 8%, $P = 0.23$) and obstructive sleep apnoea (7% *vs* 0%, $P = 0.066$) in both groups were not statistically different. There was no significant difference in metabolic or autoimmune comorbidities between the two groups. Those in the 85+ group had a higher incidence of renal disease (pre-operative eGFR less than 60) compared to those in the 75-85 years old group (25% *vs* 46%, $P = 0.007$).

Surgical and pathological characteristics

The majority of colorectal cancer resections in both age groups were urgent procedures that occurred within 30 d of diagnosis (75-85 age group, 74% *vs* 85+ age group, 79%, $P = 0.35$). Laparoscopic procedures were more common in both groups (67% *vs* 77%, $P = 0.50$) when compared to open procedures. Both age groups demonstrated a high number of right sided colon cancers (61% *vs* 73%, $P = 0.24$), with no significant difference in cancer locations between the two groups. In keeping with tumour location, the most common surgical procedure in both groups was a right hemicolectomy (59% *vs* 71%, $P = 0.49$). The surgical and pathological features of each group are outlined in Table 2.

For the majority of cases in both groups, histopathological analysis identified adenocarcinoma of no special type (86% *vs* 79%, $P = 0.46$) with a low histological grade of cancer (72% *vs* 72%, $P = 1.0$). There was no significant difference between groups with regards to stage of disease at time of surgery. In both groups, the most common stage of cancer progression at time of surgery was Stage IIa (29% *vs* 23%, $P = 0.57$).

Complications

Patients within both groups experienced a variety of complications which are outlined in Table 3. The most common complication in both groups was a prolonged ileus (75-85 age group, 17% *vs* 85+ age group, 11%). There was a particularly high number of patients in the 75-85 years old group with cardiac arrhythmias (13% *vs* 5%) when compared to the older group. However, there was a higher percentage of abdominopelvic collections (2% *vs* 8%) and incidences of respiratory failure (3% *vs* 8%) in the over 85's group.

Short term outcomes

The median length of stay in the 75-85 years age group and the 85+ year age group was the same at 8 d (Table 4). There was a non-statistically significant increase in the proportion of patients who stayed longer than 14 d in the 85+ year age (29% *vs* 38%, $P = 0.29$). However, the 30-d mortality was the same between both groups (2% *vs* 2%, $P =$

Table 1 Demographic and comorbidity data on patients from 75-85 years old and those ≥ 85 years old

Feature	Number of 75-85 years old patients (% of 75-85 years old patients)	Number of ≥ 85 years old patients (% of ≥ 85 years old patients)	Total	*P* value
Patients	136	48	184	
Gender				
Male	66 (49)	15 (31)	81	0.043
Female	70 (51)	33 (69)	103	
Median BMI	26	25		
Range	15-40	16-40		
< 20	2 (1)	2 (4)	4	0.14
20-24.9	44 (32)	24 (50)	67	
25-29.9	50 (37)	16 (33)	65	
30-39.9	31 (23)	5 (10)	36	
> 40	9 (7)	1 (2)	10	
ASA				
Grade I	4 (3)	1 (2)	5	0.43
Grade II	29 (21)	8 (17)	37	
Grade III	84 (62)	29 (60)	113	
Grade IV	19 (14)	9 (19)	28	
Grade V	0 (0)	1 (2)	1	
Cardiac				
Ischaemic heart disease	34 (25)	16 (34)	50	0.27
Coronary artery bypass graft	20 (15)	5 (11)	25	0.025
Percutaneous coronary intervention	9 (7)	4 (9)	13	0.75
Pacemaker insertion	4 (3)	0 (0)	4	0.57
Cardiac valve replacement	6 (4)	3 (6)	9	0.61
Heart failure (all types)	8 (6)	3 (6)	11	1.0
Cardiomyopathy	6 (4)	3 (6)	9	0.61
AICD insertion	1 (1)	1 (2)	2	0.44
Hypertension	85 (63)	34 (71)	119	0.38
Pulmonary hypertension	3 (2)	0 (0)	3	0.57
Atrial fibrillation	28 (21)	12 (25)	40	0.55
Respiratory				
Asthma	21 (15)	4 (8)	25	0.33
COPD	22 (16)	4 (8)	26	0.23
Bronchiectasis	0 (0)	2 (4)	2	0.017
Cystic fibrosis	0 (0)	0 (0)	0	-
Obstructive sleep apnoea	10 (7)	0 (0)	10	0.066
Metabolic				
Type I Diabetes	0 (0)	0 (0)	0	-
Type II Diabetes	27 (20)	11 (23)	38	0.68
Hyperlipidaemia	52 (38)	21 (44)	73	0.61

Previous cancer	31 (23)	10 (21)	11	0.78
Autoimmune				
Rheumatoid arthritis	1 (1)	1 (2)	2	0.44
Psoraisis	5 (4)	1 (2)	6	0.59
Polymyalgia rheumatica	1 (1)	2 (4)	3	0.11
SLEII	1 (1)	0 (0)	1	0.55
Pre-operative renal function				
eGFR > 90	46 (34)	12 (25)	58	0.007
eGFR 60-89	63 (46)	15 (31)	78	
eGFR 45-59	18 (13)	15 (31)	33	
eGFR 30-44	9 (7)	5 (11)	14	
eGFR 15-29	0 (0)	1 (2)	1	
eGFR < 15	0 (0)	0 (0)	0	
Current smoker (within 12 mo)	7 (5)	1 (2)	8	0.68

BMI: Body mass index; ASA: American Society of Anaesthesiologists Physical Status Classifications; COPD: Chronic obstructive pulmonary disease; AICD: Automated implantable cardiac defibrillator; eGFR: Estimated glomerular filtration rate; SLE: Systemic lupus erythematosus.

0.96). There was also a very similar distribution of post-operative complications between both groups. Thirty seven percent of patients in the 75-85 years old group had no complications which is similar to the thirty-five percent in the over 85's group.

There was a similar incidence of high-grade complications (Clavien-Dindo grade > III) between the two groups (22% *vs* 16%) however this difference was not statistically significant (P = 0.93).

Open vs laparoscopic surgery in the over 85 group

Patients over the age of 85 were analyzed as to which surgical approach was used (Table 5). Forty-eight patients over the age of 85 underwent surgical resection. Eleven patients had an open procedure (23%) while thirty-seven had a laparoscopic procedure (77%).

The median length of stay between the open and laparoscopic groups was similar at 9 and 8 d respectively. The percentage of patients whose stay was over 14 d was higher in the open technique group (open group, 55% *vs* laparoscopic group, 32%, P = 0.18). The 30-d mortality between the groups was also similar (9% *vs* 0%, P = 0.063). Open procedures were more likely to be emergency surgical procedures (6/11, 55% *vs* 3/37, 8%, P = 0.002).

There were no major differences in the distribution of the Clavien-Dindo grading or severity of complications between the two groups (P = 0.46). High-grade post-operative complications occurred in 9% of open procedures compared to the 6% of laparoscopic procedures.

DISCUSSION

The results of our study demonstrate that there is no significant difference between the short-term surgical outcomes between patients over 85 and those 75-85 years old who undergo colorectal cancer resection in terms of median length of stay, grading of complications and 30-d mortality. The results also indicate that the short-term outcomes from laparoscopic resection in those over 85 are similar to those of open surgery. This study is one of the first studies to utilise the Clavien-Dindo grading of complications for the assessment of short-term outcomes in this demographic.

Takeuchi *et al*[11] examined a similar cohort of patients (75-85 years old's *vs* over 85 year old's) and compared the same three short-term outcomes following colorectal cancer surgery. The results stipulated that patients over 85 years old have a significantly higher mortality when compared to those in the 75-84 years old group (24% *vs* 9%, P = 0.048). However, there was no significant difference in length of stay or post-operative complications. The paper investigated the prevalence of specific

Table 2 Surgical and pathological data of patients from 75-85 years old and those ≥ 85 years old

Feature	Number of 75-85 years old patients (% of 75-85 years old patients)	Number of ≥ 85 years old patients (% of ≥ 85 years old patients)	Total	*P* value
Patients	136	48	184	
Surgical urgency				
Emergency	24 (18)	9 (19)	33	0.35
Urgent	101 (74)	38 (79)	139	
Elective	11 (8)	1 (2)	12	
Location of cancer				
Caecum to transverse colon	83 (61)	35 (73)	118	0.24
Splenic flexure to sigmoid	43 (32)	9 (19)	52	
Rectum/anus	12 (9)	4 (8)	16	
Type of operation				
Left hemicolectomy	8 (6)	1 (2)	9	0.49
Right hemicolectomy	66 (49)	30 (63)	96	
Extended right hemicolectomy	14 (10)	4 (8)	18	
Total colectomy	1 (1)	0 (0)	1	
Subtotal colectomy	3 (2)	1 (2)	4	
High anterior resection	24 (18)	3 (6)	30	
Low anterior resection	5 (4)	3 (6)	8	
Ultralow anterior resection	2 (1)	0 (0)	2	
Hartmann's procedure	6 (4)	4 (8)	10	
Abdominoperineal resection	1 (1)	0 (0)	1	
Appendicectomy	2 (1)	0 (0)	2	
Other	4 (3)	2 (4)	5	
Approach				
Laparoscopic	60 (44)	25 (52)	85	0.50
Laparoscopic assisted	31 (23)	12 (25)	43	
Laparoscopic converted to open	14 (10)	2 (4)	16	
Open (including local excision)	31 (23)	9 (19)	40	
Histological diagnosis				
Adenocarcinoma	117 (86)	38 (79)	155	0.46
Mucinous adenocarcinoma	17 (13)	10 (21)	27	
Other	2 (1)	0 (0)	2	
Histological grade				
Low grade	97 (72)	34 (72)	131	1.0
High grade	37 (28)	13 (28)	50	
No grade	2 (0)	1 (2)	3	
Curability				
Curative	125 (91)	41 (85)	166	0.19
Palliative due to metastases	11 (8)	7 (15)	18	
Disease stage (at time of operation)				
Stage I	19 (14)	11 (23)	30	0.57

Stage IIa	39 (29)	11 (23)	50
Stage IIb	14 (10)	7 (15)	21
Stage IIIa	4 (3)	2 (4)	6
Stage IIIb	29 (22)	6 (13)	35
Stage IIIc	10 (8)	5 (10)	15
Stage IV	19 (14)	6 (13)	25

Table 3 Complications encountered in patients in the 85+ group when compared to the 75-85 years old group

Complication	Number of 75-85 years old patients (% of 75-85 years old patients)	Number of ≥ 85 years old patients (% of ≥ 85 years old patients)
Surgical Complications		
Abdominopelvic collection	3 (2)	3 (8)
Anastomotic leak	4 (3)	0
Superficial wound dehiscence	1 (1)	1 (3)
Wound infection	11 (7)	0
Prolonged ileus	26 (17)	4 (11)
Urinary retention	2 (1)	0
Post-operative haemorrhage	1 (1)	0
Anastomotic leak	4 (3)	0
Medical complications		
Deep vein thrombosis	3 (2)	0
Pulmonary embolism	1 (1)	0
Respiratory infection	15 (10)	1 (3)
Ischaemic cardiac event	1 (1)	2 (5)
Cardiac arrhythmia	20 (13)	2 (5)
Cerebrovascular event	1 (1)	1 (3)
Respiratory failure	5 (3)	3 (8)
Renal insult	6 (4)	2 (5)

complications (such as 'pulmonary complications' or 'anastomotic leak'). They demonstrated a higher incidence of pulmonary complications in the 85+ population but no other remarkable differences in complications. This study concluded that the mortality rate was higher for the 85+ population but interestingly our data demonstrates similar post-operative mortality rates between the groups.

The decision to perform a colorectal surgical resection in those over 85 is based on numerous factors including patient preference, disease stage, patient comorbid status and frailty. Although our patients over 85 have a similar comorbid burden to those aged 75-85, this may not reflect a patient's frailty which can play a large part in determining therapy for a patient. Certain surgical scales of frailty such as the Modified Frailty Index have been shown to predict mortality in general surgical procedures[12,13] for patients over 60. Unfortunately, frailty scales are rarely utilized by colorectal surgical teams but can play a large role as a factor in determining whether to offer surgery.

From our research we can conclude that the short-term outcomes from surgery in the over 85 years old's group are comparable to those who are 75-85 years old. This should serve to support surgical intervention in appropriate patients over 85.

Despite the increasing use of laparoscopic surgery for colorectal cancer resections, there is a paucity of information on its use in patients at the extremes of age. As demonstrated in Table 5, there were no significant differences in the length of stay, 30-d mortality or grading of complications between open and laparoscopic procedures in

Table 4 Short term surgical outcomes in the 85+ group when compared to those in the 75-85 years old group

Feature	Number of 75-85 years old patients (% of 75-85 years old patients)	Number of ≥ 85 years old patients (% of ≥ 85 years old patients)	Total	*P* value
Patients	136	48	184	
Median LOS (d)	8 (IQR = 6)	8 (IQR = 6)		
< 14 d	96 (71)	30 (63)	126	0.29
≥ 14 d	40 (29)	18 (38)	58	
30-d mortality	3 (2)	1 (2)	4	0.96
Clavien-Dindo complication				
No complications	50 (37)	17 (35)	67	0.93
Grade I	13 (10)	5 (11)	18	
Grade II	43 (32)	18 (38)	61	
Grade IIIa	14 (10)	5 (10)	19	
Grade IIIb	4 (3)	1 (2)	5	
Grade IVa	8 (6)	1 (2)	9	
Grade IVb	1 (1)	0 (0)	2	
Grade V	3 (2)	1 (2)	3	

LOS: Length of stay; IQR: Inter-quartile range.

those aged over 85.

There was a significantly higher proportion of open procedures for emergency operations (55% *vs* 8%, $P = 0.002$). This is understandable as the open approach affords ease of access, manoeuvrability and manipulation of distended or friable bowel in the setting of a bowel obstruction or perforation. Decisions on surgical approach are based upon multiple factors including urgency, anatomical considerations, surgeon expertise and personal preference. In general, there is a higher proportion of laparoscopic procedures performed on those aged over 85 at our institution.

These results demonstrate that there is no difference in short term outcomes between a laparoscopic or open approach in those over 85. This conclusion is supported by research from Vallribera Valls *et al*[14] who demonstrated that laparoscopic approaches in those over 85 are not associated with an increase in morbidity or length of stay. This is also mirrored by more recent studies of Ueda *et al*[15] and Hashida *et al*[16], both of whom have demonstrated laparoscopic surgery in the elderly population to be feasible, safe and have equitable outcomes to those in younger age brackets.

Despite the methodology, there are several limitations to this study. The study is a single-centre study and reflects only the practice and outcomes at our particular institution. It should be noted that patients included within this cohort were those that were deemed appropriate candidates for surgery and accepted treatment. There may have been patients who were too comorbid or frail for surgery who did not proceed with a surgical resection. Subsequently, the results should reflect the outcomes of surgery on those deemed surgical candidates and not purely those diagnosed with colorectal cancer. In order to help limit selection bias in the surgical candidate cohort, future studies could investigate the outcomes of all patients over 85 diagnosed with colorectal cancer to quantify the effect of surgery *vs* conservative management regardless of whether they may be surgical candidates. The role of frailty scores in predicting surgical outcomes is also an area for future research and may be an alternative approach to patient stratification than age alone.

CONCLUSION

Colorectal cancer resection should be offered to appropriate patients, regardless of age. The short-term outcomes of those over 85 years old are not different to those aged 75-

Table 5 Short term outcomes in laparoscopic *vs* open resection of colorectal cancer in those over 85 years old

Feature	Open procedure	Laparoscopic procedure	Total	*P* value
Patients	11 (23)	37 (77)	48	
Median LOS (d)	9 (IQR = 6)	8 (IQR = 6)		
< 14 d	5 (45)	25 (68)	30	0.18
≥ 14 d	6 (55)	12 (32)	18	
Gender				
Male	3 (28)	12 (33)	15	1.0
Female	8 (73)	25 (68)	33	
30 d mortality	1 (9)	0 (0)	1	0.063
Surgical urgency				
Emergency	6 (55)	3 (8)	9	0.002
Urgent	5 (45)	33 (90)	38	
Elective	0 (0)	1 (3)	1	
Clavien-Dindo complication				
No complications	4 (37)	13 (35)	17	0.46
Grade I	0 (0)	5 (14)	5	
Grade II	5 (46)	13 (35)	18	
Grade IIIa	1 (9)	4 (10)	5	
Grade IIIb	0 (0)	1 (3)	1	
Grade IVa	0 (0)	1 (3)	1	
Grade IVb	0 (0)	0 (0)	0	
Grade V	1 (9)	0 (0)	1	

LOS: Length of stay; IQR: Inter-quartile range.

85 and demonstrate that age alone should not be a determining factor. Our research also shows that laparoscopic resection of colorectal cancer has equitable short term post-operative outcomes to open resections.

ARTICLE HIGHLIGHTS

Research background

The global population is living longer than ever before. As a result of extended life expectancies, the prevalence of colorectal cancer in the elderly is increasing. There is a paucity of information on the role of colorectal cancer surgery in the elderly and the short term surgical outcomes associated with this demographic. There is also very little literature on the role of laparoscopic resection of colorectal cancer in those at the extremes of age.

Research motivation

This research was undertaken to determine the short-term surgical outcomes in those over 85 following colorectal cancer resection. With the increasing use of laparoscopic colorectal surgery, we also ought to investigate the viability of laparoscopic surgery in the over 85 population.

Research objectives

The main objectives was to determine whether patients over 85 had equitable outcomes following colorectal cancer surgery to those in a younger age bracket. We also sought to investigate the short term surgical outcomes from laparoscopic surgery

vs open surgery in over 85's. This research is important as older patients are at a high risk of having surgery withheld based upon age alone, without clear evidence demonstrating whether age is a determinant of poorer surgical outcomes. Furthermore, this research helps to indicate when open or laparoscopic surgery provides better outcomes in this age group.

Research methods

Patients who underwent colorectal cancer resection between January 2010 and December 2018 at The Prince Charles Hospital, Brisbane were included in the study. The study was divided into two parts. The first part examined two groups: Those over the age of 85 and those aged 75-84. The short term surgical outcomes were compared between the two groups using parametric and non-parametric tests. The second part of the study investigated the outcomes of patients over 85 who had open surgery *vs* laparoscopic surgery. The short term outcomes of each approach were compared and analyzed.

Research results

Our research demonstrated that there were no significant differences between the short-term surgical outcomes in those over the age of 85 *vs* those aged 75-85 years old. The average length of stay between the two groups was the same at eight days. There was no significant difference in severity of post-operative complications (P = 0.93) or 30-d mortality rates (P = 0.96). For patients over 85 who underwent laparoscopic resection, there was no difference in outcomes to those that underwent open resection. Between the laparoscopic and open surgical groups there was no difference in length of stay (P = 0.18), severity of post-operative complications (P = 0.46) or 30-d mortality rates (0.06).

Research conclusions

From our research we can conclude that it is safe and effective to surgically resect colorectal cancer in patients over the age of 85. There are no significant differences in post-operative outcomes between the over 85 group and the 75-84 years old group. This leads up to conclude that patients should not have surgery withheld based upon age alone. Furthermore, we demonstrated that laparoscopic surgery has equitable outcomes to open surgery and is a viable option in those over 85 years old.

Research perspectives

Further studies in this area should investigate the role of frailty scores on surgery outcomes. We have demonstrated that age is no barrier to good surgical outcomes, but the role of frailty scores on post-operative outcomes and surgical candidacy could be explored further.

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