T stage and venous invasion are crucial prognostic factors for long-term survival of patients with remnant gastric cancer: A cohort study

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Abstract

Background

The incidence of remnant gastric cancer (RGC) after distal gastrectomy is 1–5%. However, as the survival rate of patients with gastric cancer improves due to early detection and treatment, more patients may develop RGC. There is no consensus on the surgical and postoperative management of RGC, and the clinicopathological characteristics correlated with the long-term outcomes remain unclear. Therefore, we have investigated the clinicopathological factors associated with the long-term outcomes of RGC.

Methods

We included 65 consecutive patients who underwent gastrectomy for RGC from January 2000 to December 2015 at the Osaka Medical College, Japan. The Kaplan–Meier method was used to create survival curves, and differences in survival were compared between the groups (clinical factors, pathological factors, and surgical factors) using the log-rank test. Multivariate analyses using the Cox proportional hazard model were used to identify factors associated with long-term survival.

Results

There were no significant differences in the survival based on clinical factors (age, body mass index, and diabetes mellitus) or the type of remnant gastrectomy. There were significant differences in the survival based on pathological factors and surgical characteristics (intraoperative blood loss and operation time). Multivariate analysis revealed that the T stage (hazard ratio, 4.70; 95% confidence interval [CI], 1.005–22.014; p = 0.049) and venous invasion (hazard ratio 3.047; 95% CI, 1.008–9.214; p = 0.048) were significant independent risk factors for long-term survival in patients who underwent radical resection for RGC.

Conclusions

T stage and venous invasion are important prognostic factors of long-term survival after remnant gastrectomy for RGC and may be key to managing and identifying therapeutic strategies for improving prognosis in RGC.

Background

Remnant gastric cancer (RGC) describes all cancers arising from the remnant stomach after partial gastrectomy, regardless of the initial disease or type of gastrectomy [1]. The incidence of RGC after distal gastrectomy has been reported to be 1–5% [2–4]. Although the number of patients with RGC who undergo gastrectomy for benign diseases has decreased due to improvements in treatment, more

patients with a previous malignant disease are developing RGC because of improved prognosis after gastric cancer [5].

The etiology of RGC is thought to be related to the type of reconstruction. For instance, the anastomotic site of Billroth II reconstruction, which is exposed by bile regurgitation, is a common site of recurrence [6, 7]. However, non-anastomotic carcinoma occurs more frequently in patients with previous malignancies who have undergone Billroth I reconstruction [8]. Some researchers have reported that the prognosis of advanced RGC is worse than that of primary advanced gastric cancer [9]. However, despite these findings, there is no consensus on the surgical and postoperative management for RGC, and the clinicopathological characteristics that are correlated with long-term outcomes remain unclear. Data collection on the prognoses of patients with RGC is required to establish an optimal therapeutic strategy for RGC. Herein, we have investigated the clinicopathological factors associated with the long-term outcomes of RGC.

Methods

Patients

From January 2000 to December 2015, 65 consecutive patients with RGC underwent gastrectomy at the Osaka Medical College Hospital, Japan. We performed routine workup, including esophagogastroduodenoscopy (EGD) and enhanced computed tomography (CT), for preoperative evaluation. Retrieved specimens were staged using the Japanese Classification of Gastric Carcinoma (15th edition); the depth of tumor invasion was recorded as the pathological T stage. Tumor morphology was categorized as either superficial (pT1) or advanced (pT2–pT4). Lymph node metastasis was defined using the pathological N category, and lymphatic invasion and venous invasion were also assessed.

Clinical, surgical, and pathological records of the patients were obtained from our database. Data collection (after receiving written informed consent) and analysis were approved by the institutional review board of the Osaka Medical College (acceptance number: 2020–005). Written informed consent was obtained from all participants.

Patient follow-up

After the surgery, blood tests and physical examinations were performed every 3 months, CT was performed every 6 months, and EGD was performed annually. The blood tests also included examination of tumor markers, such as the carcinoembryonic antigen and carbohydrate antigen 19 − 9. Postoperative adjuvant chemotherapy was not administered to most patients, because there is no consensus on its utility.

The duration of follow-up was 60 months. Thirty-six patients were completely followed up, and 29 were lost to follow-up due to disease-specific death (n = 19), death from other causes (n = 3), and unknown reasons (n = 7).

Statistics

All statistical analyses were carried out using JMP version 15.0 software (SAS Institute Inc., Cary, NC, USA). The Kaplan–Meier method was used to estimate survival curves, and differences in survival were compared using the log-rank test. The cutoff value was set for each factor (age, body mass index [BMI], tumor size, blood loss, operation time, and the number of retrieved lymph nodes) by using receiver operating characteristic curve analysis.

Baseline variables with $p < 0.05$ in the univariate analysis were included in the multivariate Cox proportional hazard models. $p < 0.05$ was considered significant.

Results

Patient characteristics

The clinicopathological and surgical characteristics of the 65 patients are summarized in Tables 1 and 2. The patients comprised 55 men and 10 women. The mean age was 71 years (range, 46–88 years). Forty-eight patients (74%) originally had a malignant disease, and 17 (26%) had a benign disease. The mean interval between original gastrectomy and development of RGC was 10 years (range, 1–48 years) in patients who originally had a malignant disease and 33 years (range, 3–59 years) in patients who originally had a benign disease. Total resection of the remnant stomach was performed in 49 patients, while partial resection was performed in 16 patients.

Table 1
Demographic and clinical characteristics of the patients undergoing remnant gastrectomy.

Characteristics	**patients**
	(*n* = 65)
Age, years	
Median	71
Range	46–88
Sex	
Male	55(84.6%)
Female	10 (15.4%)
ASA	
1	8(12.3%)
2	50 (76.9%)
3	7(10.8%)
Body mass index, kg/m^2	
Median	20.8
Interquartile range	14.5–30.8
Previous disease	
Benign	17
Malignant	48
Previous reconstruction	
Billroth Ⅰ	23(35.4%)
Billroth Ⅱ	20(30.8%)
Others	22(33.8%)
Years since previous surgery	
Median	12
Range	1–59
No. of comorbidities	

ASA: American Society of Anesthesiologist

Characteristics	patients
	(*n* = 65)
0	24 (36.4%)
1–2	37 (56.1%)
≥3	5 (7.5%)
ASA: American Society of Anesthesiologist	

Table 2
Demographic, pathological, and surgical characteristics of the patients undergoing remnant gastrectomy

Characteristic	**patients**
	(*n* = 65)
Histologic type	
Differentiated	38 (58.5%)
Undifferentiated	27(41.5%)
Pathological T factor	
1/2/3/4	30/7/16/12
Pathological N factor	
0/1/2/3/X	43/9/8/1/4
Pathological Stage	
I/II/III/	37/10/9/7
Type of remnant gastrectomy	
Total	49(73.2%)
Partial	16(26.8%)
Operation time, min	
Median	320
Interquartile range	160–620
Blood loss, mL	
Median	310
Interquartile range	10–1740
Number of retrieved lymph nodes	
Median	12
Interquartile range	0–43
Adjuvant therapy	
Yes	4 (6.1%)
No	61(93.9%)

Table 3
Multivariate analysis of prognostic factors using the Cox proportional hazard model

Prognostic factors	HR	95% CI Lower limit	95% CI Upper limit	P
T factor (T2-T4/T1)	4.7	1.005	22.014	**0.049**
N factor (N+/N-)	1.763	0.5925	5.221	0.306
Ly factor (Ly+/Ly-)	0.32	0.0896	1.146	0.08
V factor (V+/V-)	3.047	1.008	9.214	**0.048**
Type of histology (tub1, tub2/por, sig, others)	0.475	0.188	1.198	0.115
Tumor size (> 34 mm/<34 mm)	2.254	0.543	9.349	0.263
Blood loss (> 350 mL/<350 mL)	1.637	0.51	5.251	0.407
Operation time (> 315 min/<315 min)	1.457	0.444	4.782	0.535

Association of long-term survival with clinical, pathological, and surgical factors

The overall survival curves based on the clinical characteristics are shown in Fig. 1. There were no significant differences in the survival between patients with values above and below the cut-offs for any of clinical factors examined, including age (older [> 67 years] vs. younger [< 67 years]), BMI, diabetes mellitus, type of original reconstruction, or previous disease history.

The overall survival curves based on the pathological characteristics are shown in Fig. 2. There were significant differences in the survival between patients with values above and below the cut-offs for all pathological factors examined.

The overall survival curves based on the surgical characteristics are shown in Fig. 3. There were significant differences in the survival between patients with values above and below the cut-offs for

intraoperative blood loss and operation time. However, no significant differences in the survival were noted between patients who underwent different remnant gastrectomy procedures or between those with values above and below the cut-off for the number of retrieved lymph nodes.

Multivariate analysis of prognostic factors

Multivariate analysis revealed that the T stage (hazard ratio, 4.70; 95% confidence interval [CI], 1.005–22.014; p = 0.049) and venous invasion (hazard ratio, 3.047; 95% CI, 1.008–9.214; p = 0.048) were significant independent risk factors for the long-term survival of patients who underwent radical resection for RGC (**Table.3**).

Discussion

The survival rate of gastric cancer patients has improved due to early detection and treatment. As a result, more patients may develop RGC [5]. Despite numerous studies on RGC, its oncological characteristics, prognosis, and management remain a matter of debate due to its rarity. Previous studies have indicated that the pattern of reconstruction is associated with the incidence and location of RGC [6–8, 10, 11]. However, there are few reports on the long-term prognosis and associated clinicopathological factors of remnant gastrectomy. Therefore, in this study, we examined the clinicopathological factors associated with the long-term outcomes of RGC.

Our findings showed that the pathological T stage and venous invasion were significant independent risk factors for survival among RGC patients; however, the pathological N stage was not significantly associated with long-term survival. Many studies have suggested that endoscopic surveillance is crucial, because early detection of RGC leads to a better prognosis [5, 6, 8, 12]. Our results support this suggestion. However, there is no consensus on the extent of lymphadenectomy during surgery for RGC. Previous studies have reported the need for adequate lymph node dissection and adjuvant therapy in patients with previous malignant disease based on the final staging, including lymph node metastasis [13]. Therefore, lymph node dissection for RGC may not be associated with prognosis due to previous surgical treatments. However, in the current study, we found that venous invasion was an independent risk factor, along with the T stage. Similarly, a previous study indicated that venous invasion was a risk factor for recurrence after gastrectomy followed by adjuvant chemotherapy for stage III gastric cancer [14]. Moreover, venous and nerve invasion are prognostic factors of postoperative survival in patients with resectable cancer of the rectum [15]. Based on these results, including our analysis, we believe that venous invasion could be an important risk factor for prognosis. Thus, we recommend that RGC with venous invasion should be specifically targeted to improve the prognosis of patients and suggest the possibility of it serving as an indication for more intensive treatment, such as adjuvant chemotherapy. Some studies have reported that early diagnosis and curative resection are important to improve prognosis, but no studies have reported that venous invasion is associated with a better prognosis. Therefore, evaluating venous invasion may help determine therapeutic strategies, including adjuvant chemotherapy, for RGC.

Some limitations of this study should be acknowledged. This study was a single-institutional retrospective study with a relatively small sample size. Additionally, the number of patients in each category was unequal: the number of patients with initial malignant tumors was higher than that of patients with initial benign tumors. However, this difference may be attributable to the recent trend of prolonged survival in cancer patients.

Conclusions

Although some patients had lymph node metastasis, the important prognostic factors for long-term survival of patients with RGC were the T stage and venous invasion. Therefore, early detection of RGC may play a crucial role in improving prognosis. An annual follow-up endoscopic examination is recommended for all patients after distal gastrectomy, and venous invasion may be key to managing and identifying therapeutic strategies for RGC to achieve better prognosis.

Abbreviations

BMI: body mass index, CT:computed tomography, EGD:esophagogastroduodenoscopy, RGC:remnant gastric cancer; BMI:body mass index

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from all the participants and the study was approved by the institutional review board of the Osaka Medical College (acceptance number: 2020–005) in accordance with the tenets of the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

KM, RT, YI, KH, and HT performed the patients' care, including surgery. KM and KT designed and drafted the manuscript. SL and KU reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Figures

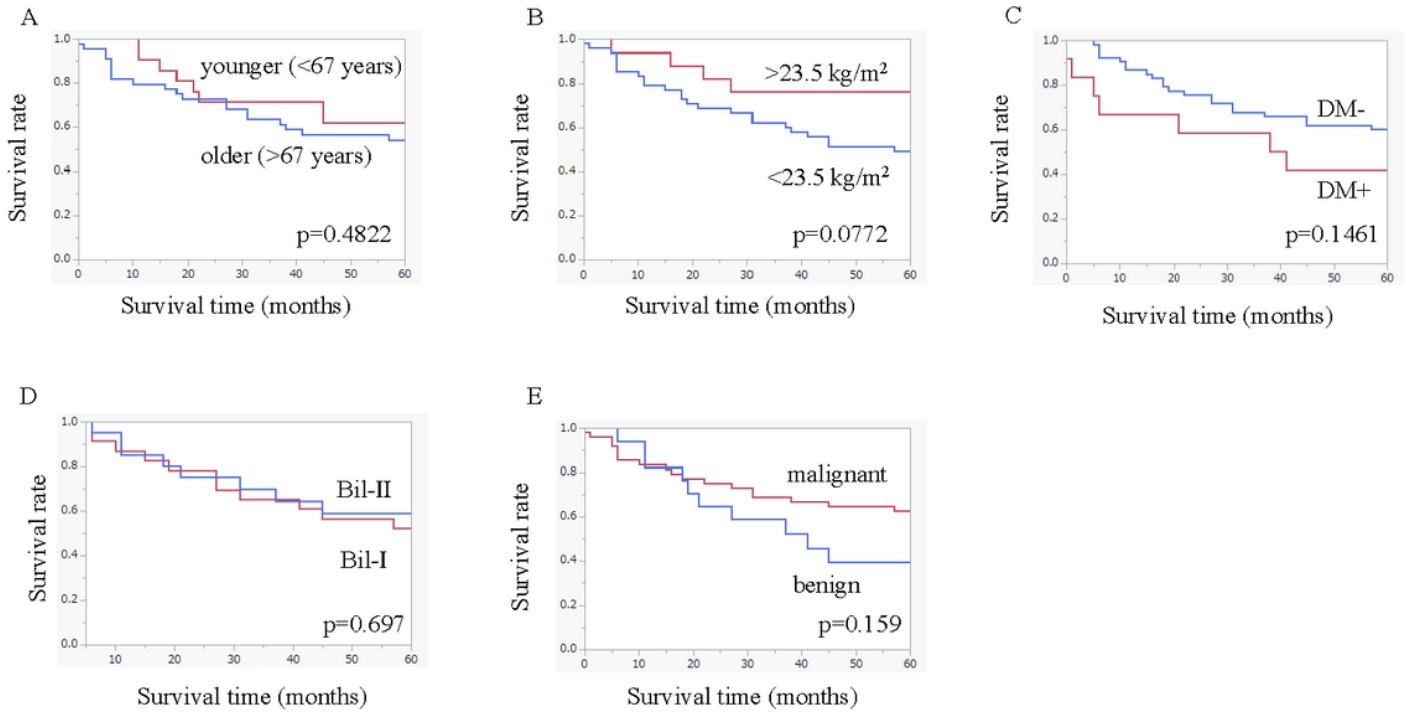

Figure 1

Long-term survival outcomes based on clinical factors: (A) age, (B) body mass index (BMI), (C) diabetes mellitus (DM), (D) type of reconstruction, and (E) previous disease.

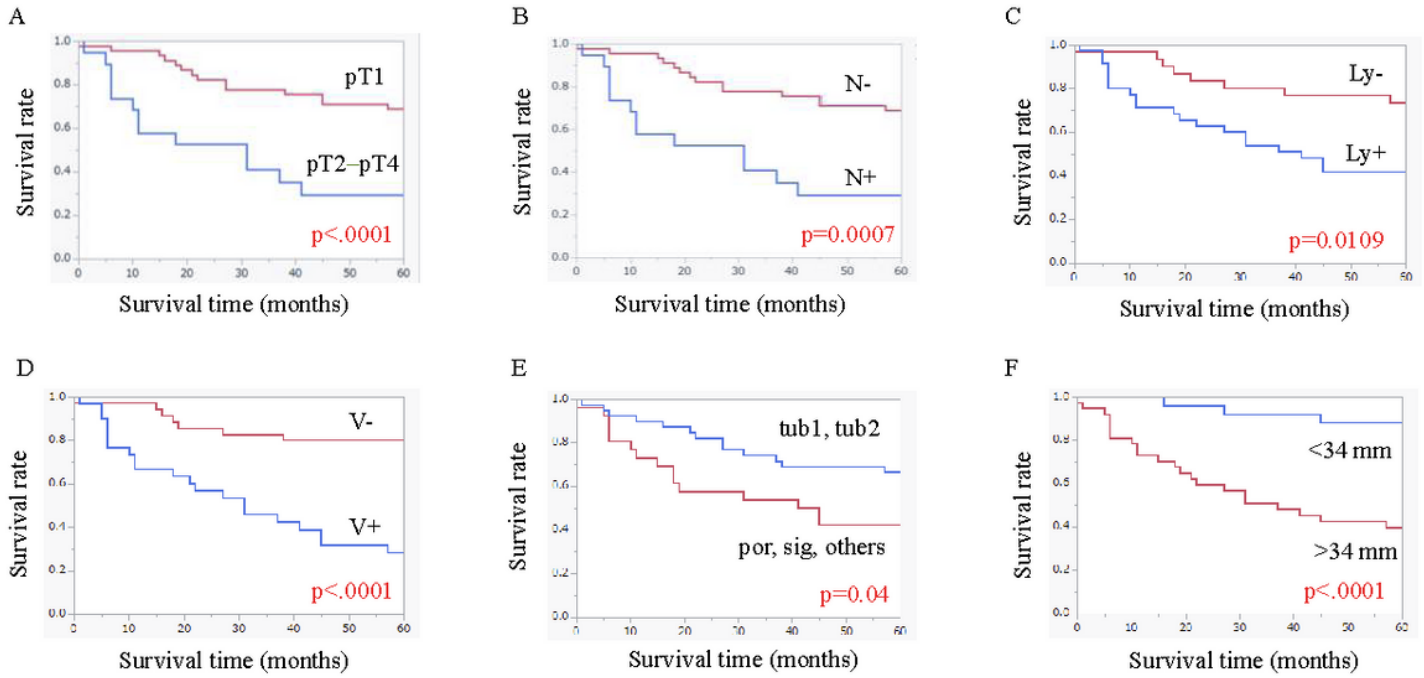

Figure 2

Long-term survival outcomes based on pathological factors: (A) pathological T stage, (B) lymph node metastasis, (C) lymphatic invasion, (D) venous invasion, (E) type of histology, and (F) tumor size.

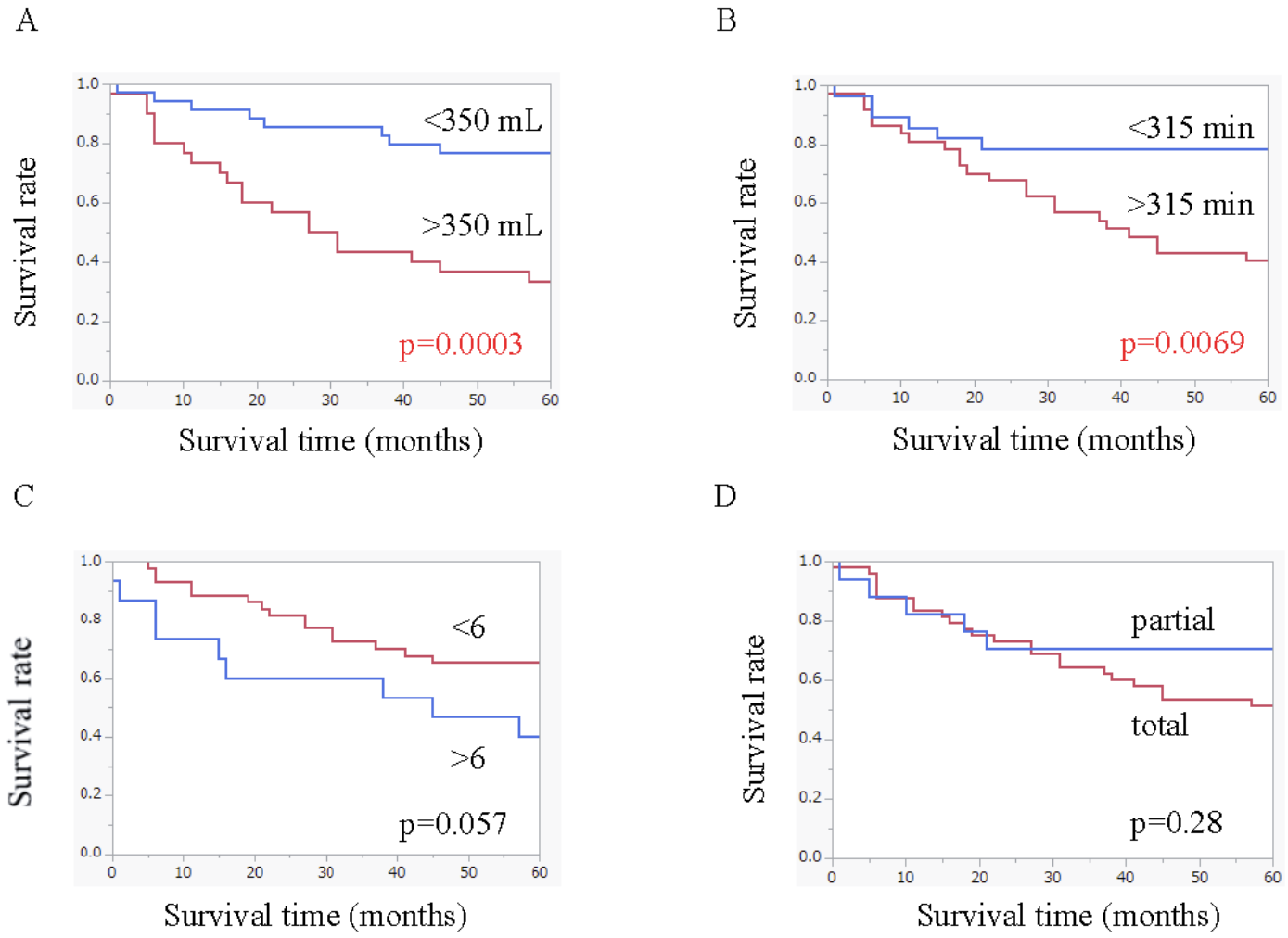

Figure 3

Long-term survival outcomes based on surgical factors: (A) intraoperative blood loss, (B) operation time, (C) number of retrieved lymph nodes, and (D) type of remnant gastrectomy.