Extragastric metastasis of early gastric cancer after endoscopic submucosal dissection with lymphovascular invasion and negative resected margins

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Research Article

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Abstract

Background: Lymphovascular invasion is a criterion for noncurative resection in patients who have undergone endoscopic submucosal dissection (ESD) for early gastric cancer (EGC). We aimed to determine the rate of extragastric metastasis (EGM) and identify predictors of EGM in patients with negative resected margins (R0 resection) and lymphovascular invasion in their post-ESD pathology.

Methods: Among 2,983 consecutive patients, 110 were treated with ESD with follow-up pathology of R0 resection and lymphovascular invasion. Patients received additional gastrectomy (*n*=63) or further follow-up without gastrectomy (*n*=47).

Results: The 110 patients were assigned to one of three groups according to ESD indications based on post-ESD pathology. Group 1 satisfied the absolute indication of ESD (*n*=18), group 2 satisfied the expanded indication of ESD (*n*=34), and group 3 was beyond indication (*n*=58). The number of occurrences of EGM in each group was 1 (5.6%), 3 (8.8%), and 3 (5.2%), respectively. The logistic regression analysis, which adjusted for age, sex, tumor size, and indication of ESD, showed that larger tumor size was associated with EGM (odds ratio 1.76, 95% confidence interval 1.00–3.10, *p*=0.048). By contrast, ESD indication criteria did not affect EGM (*p*=0.349).

Conclusions: Tumor size was the only predictive indicator for EGM in patients with R0 resection and lymphovascular invasion in their post-ESD pathology. Even patients with pathology corresponding to the absolute indication criteria of ESD had lymphovascular invasion, which means they require an additional gastrectomy due to the risk of EGM.

Introduction

Endoscopic submucosal dissection (ESD) is a standard treatment for patients with early gastric cancer (EGC) who have negligible risk of lymph node metastasis [1–3]. Additional surgery may be required after ESD in cases of noncurative resection, such as deeper submucosal invasion than predicted, positive lymphovascular invasion, or worse histologic differentiation [4–6]. Lymphovascular invasion is one of the criteria for noncurative resection in patients who underwent ESD for EGC [7, 8]. However, all patients who were treated with noncurative ESD with negative resected margins (R0 resection) do not have lymph node metastasis. Thus, identifying patients with high risk of lymph node metastasis is important for determining whether additional gastrectomy is required. Liu et al. [9] reported that lymphovascular invasion-positive patients had a significantly lower 5-year survival rate than lymphovascular invasion-negative patients [9]. By contrast, Pyo et al. [10] reported that additional surgery after endoscopic resection might be unnecessary for lymphovascular invasion-positive patients who meet the absolute criteria for endoscopic resection. Here, we aimed to determine the rate of extragastric metastasis (EGM) and identify predictors of EGM in EGC patients with R0 resection and lymphovascular invasion in their post-ESD pathology.

Materials And Methods

Study population and data collection

This was a single-center retrospective study performed at Seoul National University Hospital, Korea. From January 2005 to July 2020, 2,983 consecutive patients underwent ESD for EGC at Seoul National University Hospital with at least 12 months of follow-up. ESD was performed for well-differentiated or moderately differentiated tubular adenocarcinoma no larger than 3 cm, which is expected to be confined to the mucosa [3, 11]. Patients without obvious medication history, past medical history, or pathologic report were excluded. Basic demographic data, comorbidities, medications, laboratory data, endoscopic findings, and pathologic findings of the ESD specimen were reviewed retrospectively. The Charlson comorbidity index was used for evaluation as described previously [12].

The ESD procedure was performed using an electrosurgical IT knife (KD-610L, KD-611L; Olympus), dual knife (KD-650Q; Olympus), or both. Among 2,983 consecutive patients, 350 patients did not meet the expanded curability criteria. The curability of ESD was based on the Korean practice guideline for gastric cancer [3]. Criteria for a curative resection by absolute indication include the following: (1) lesion resection *en bloc*; (2) lesion < 2 cm diameter, predominantly differentiated type, pathologically intramucosal carcinoma (pT1a), without ulcerative findings [UL(−)]; (3) not associated with lymphovascular invasion (ly0, v0); and (4) negative resected margins (R0 resection). Criteria for a curative resection by expanded indications include the following: (1) lesion resection *en bloc*; (2) either of four possibilities including (i) lesion ≥ 2 cm diameter, predominantly differentiated type, pT1a, and UL(−), or (ii) lesion < 3 cm, predominantly differentiated type, pT1a, and UL(þ), or (iii) lesion < 2 cm, predominantly undifferentiated type, pT1a, and UL(−), or (iv) lesion < 3 cm, predominantly differentiated type, pathologically minute submucosal (SM) cancer less than 500 mm (pT1b/ SM1); (3) no lymphovascular invasion; and (4) negative resected margins (R0 resection).

We defined curative ESD as cases that met either absolute or expanded indications and noncurative ESD as cases that did not satisfy any of those criteria. We excluded patients with history of gastrectomy for gastric cancer (n = 2), patients without obvious medication history, past medical history, or pathologic report (n = 29), and patients with positive resection margin (n = 209). Finally, 110 patients were enrolled in the study (Fig. 1). The enrolled patients were treated with noncurative ESD with R0 resection with lymphovascular invasion in their post-ESD pathology. The Institutional Review Board of Seoul National University Hospital approved the study protocol (IRB number 2106-114-1227) and waived the need to obtain informed consent. This study was conducted according to the principles of the Declaration of Helsinki.

Statistical analysis

Categorical data were analyzed by Pearson's chi-square test or Fisher's exact test and are presented as numbers with percentages. Continuous data were compared using Student's t-test, and are presented as the mean ± standard deviation or as the median with interquartile range (IQR). Survival curves were

plotted using the Kaplan-Meier method, and differences in survival among the three groups were tested by log-rank tests.

Overall survival was measured from the date of ESD to the date of death from any cause or to the censoring date of 31 Aug 2021. Disease-free survival was measured from the date of ESD to the date of recurrence with lymph node metastasis or to the censoring date of 31 Aug 2021. A Cox proportional hazard model was used to estimate the hazard ratio (HR) and two-sided 95% confidence interval (CI). A p value < 0.05 was considered as statistically significant. All statistical analyses were performed using SPSS version 22 (SPSS Inc., Chicago, IL, USA).

Results

Demographics and clinicopathologic characteristics

A total of 110 patients were treated with ESD with pathology showing R0 resection and lymphovascular invasion: 98 (89.1%) had only lymphatic invasion, 9 (8.2%) had only venous invasion, and 3 (2.7%) had both lymphatic and vascular invasion. Patients received either additional gastrectomy (n = 63, surgery group) or follow-up without gastrectomy (n = 47, observation group). All patients were followed during the median period of 53 months (range 12–171 months). The patient baseline characteristics are summarized in Table 1. Patients in the observation group tended to be older (70.2 ± 9.8 vs. 63.6 ± 8.5 years, p < 0.001), had higher (5≤) Charlson comorbidity index (70.2% vs. 39.7%, p = 0.002), and had less submucosal invasion (51.1% vs. 87.3%, p < 0.001) than those in the surgery group. No significant difference was observed between the groups with respect to sex, tumor location, macroscopic appearance of tumor, tumor size, presence of ulceration, and tumor histology.

Table 1
Comparison of clinicopathologic features between patients followed up without gastrectomy and patients received additional gastrectomy

Variables	Observation	Surgery	*p* value
Total	47 (42.7)	63 (57.3)	
Age (years)	70.2 ± 9.8	63.6 ± 8.5	< 0.001
Charlson Comorbidity index			0.002
≤ 4	14 (29.8)	38 (60.3)	
5≤	33 (70.2)	25 (39.7)	
Sex			0.270
Male	33 (70.2)	50 (79.4)	
Female	14 (29.8)	13 (20.6)	
Tumor location			0.475
Upper third	1 (2.1)	5 (7.9)	
Middle third	13 (27.7)	15 (23.8)	
Lower third	33 (70.2)	43 (68.3)	
Macroscopic appearance			0.803
Elevated	10 (21.3)	16 (25.4)	
Flat	11 (23.4)	12 (19.0)	
Depressed	26 (55.3)	35 (55.6)	
Tumor size	2.2 ± 1.3	2.1 ± 1.1	0.425
Ulceration			> 0.999
(-)	44 (93.6)	60 (95.2)	
(+)	3 (6.4)	3 (4.8)	
Depth of invasion			< 0.001
Lamina propria	3 (6.4)	1 (1.6)	
Muscularis mucosa	20 (42.6)	7 (11.1)	
Submucosa, SM1	14 (29.8)	20 (31.7)	
Submucosa, SM2	10 (21.3)	35 (55.6)	

IQR = Interquartile range

Variables	Observation	Surgery	*p* value
Histology			0.121
Differentiated	43 (91.5)	51 (81.0)	
Undifferentiated	4 (8.5)	12 (19.0)	
Follow-up duration (months, range, IQR)	57 (12–171, 53)	51 (14–157, 77)	0.356
IQR = Interquartile range			

Comparison of EGM in the observation and surgery groups

Five patients (7.9%) in the surgery group had lymph node metastasis in the gastrectomy specimen. One patient (1.6%) in the surgery group who had SM1 invasion with lymphatic invasion on the initial ESD specimen did not have lymph node metastasis in his postgastrectomy pathology but did have recurrence with lymph node metastasis 25 months after gastrectomy. This patient did not have lymph node metastasis pathologically on the postsurgical specimen. The patient was treated with distal gastrectomy with D1 + lymph node dissection, and the EGM occurred in the suprapancreatic node. This may be due to skip metastasis or inadequate node dissection during surgery [13–15].

The clinical features of patients who had EGM are presented in Table 2. One patient (2.1%) in the observation group had recurrence with lymph node metastasis 60 months after ESD. The Kaplan-Meier curve for overall survival and disease-free survival of the surgery and observation groups did not show significant difference between the groups ($p = 0.280$, $p = 0.804$, respectively, log-rank test) (Figs. 2 and 3).

Clinical outcomes according to ESD indications

The 110 patients were assigned to three groups according to ESD indications based on post-ESD pathology (absolute indication, $n = 18$; expanded indication, $n = 34$; and beyond indication, $n = 58$) [3]. We determined the number of occurrences of EGM in each group, which was 1 (5.6%), 3 (8.8%), and 3 (5.2%), respectively (Table 3).

Table 3
Total extra-gastric metastasis in 110 patients who had R0 resection and lymphovascular invasion in their post-ESD pathology

Depth	Ulcer	Differentiated		Undifferentiated	
M	(-)	≤ 2cm	> 2cm	≤ 2cm	> 2cm
		16 (EGM 1)	10 (EGM 2)	2	1
	(+)	≤ 3cm	> 3cm	≤ 2cm	> 2cm
		2	0	0	0
SM1		≤ 3cm	> 3cm		
		20 (EGM 1)	7	7 (EGM 1)	
SM2		36 (EGM 2)	3	6	

EGM = extra-gastric metastasis; R0 resection = negative resected margins; ESD = extra-gastric metastasis; M = mucosa; SM1 = submucosa SM1; SM2 = submucosa SM2;

Risk factors for EGM

The multivariate logistic regression analysis adjusted for age, sex, tumor size, and indication of ESD (Table 4), showed that larger tumor size was associated with EGM [odds ratio (OR) 1.76, 95% CI 1.00–3.10, $p = 0.048$]. However, ESD indication criteria did not affect EGM (OR for expanded indication referent to absolute indication, 0.398, 95% CI 0.03–5.49, $p = 0.492$; OR for beyond indication referent to absolute indication, 0.157, 95% CI 0.01–2.38, $p = 0.182$; overall $p = 0.349$).

Table 4
Multivariate logistic analysis of factors associated with extra-gastric metastasis in patients with lympho-vascular invasion and negative resected margins for gastric cancer

	Model 1			Model 2		
Variables	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	0.985	0.910–1.065	0.702	0.980	0.899–1.068	0.638
Sex	N/A	N/A	0.998	N/A	N/A	0.998
Size	1.583	0.951–2.636	0.077	1.763	1.004–3.095	0.048
ESD indication			0.778			0.349
Absolute	1			1		
Expanded	1.548	0.149–16.110	0.714	0.398	0.029–5.485	0.492
Beyond	0.857	0.803–8.813	0.857	0.157	0.010–2.375	0.182
Model 1: Non-adjusted						
Model 2: Adjusted by age, sex, tumor size and indication of ESD						
HR = hazard ratio; CI = cumulative index; N/A = not applicable; ESD = endoscopic submucosal dissection						

Discussion

This study evaluated the risk factors of EGM in patients who had R0 resection and lymphovascular invasion in the post-ESD pathology. The data indicated that patients with larger tumor size tended to have higher risk for EGM. No other predictive indicator for EGM was identified. To the best of our knowledge, this is a rare study to identify a predictive indicator and determine the risk of EGM in patients who had R0 resection and lymphovascular invasion in the post-ESD pathology. Toya et al. [16] reported no local recurrence in any patients with EGC treated with noncurative ESD with R0 resection during long-term follow-up. By contrast, we observed 7 cases (6.4%) of EGM in our retrospective study of 110 patients; 5 were detected as lymph node metastasis in the surgery group, and 2 were recurrences at 25 and 60 months post-ESD during follow-up. These findings suggest that additional surgery may be required in patients with lymphovascular invasion even though they had R0 resection.

Our study identified a patient in the surgery group who did not have EGM based on the initial surgery specimen but had recurrence with lymph node metastasis 25 months after surgery. The patient had SM1 invasion with lymphatic invasion on the initial ESD specimen, and had subtotal gastrectomy with D1 lymph node dissection. The surgical specimen did not show lymph node metastasis. However, the patient had recurrence with lymph node metastasis on the suprapancreatic lymph node 25 months after surgery. Currently, D2 dissection is considered as a gold standard of gastric cancer treatment, and D1 dissection

also is performed in EGC without risk of lymph node metastasis in Korea and Japan [1, 3]. In gastric cancer surgery, D2 dissection typically consists of a standard resection of the perigastric lymph nodes (D1) and resection of suprapancreatic lymph nodes [17]. The case we observed suggests the occurrence of skipped metastasis, which requires surgery with extended lymph node dissection or inadequate dissection of the nodes. The prognostic importance of the suprapancreatic node is well documented in gastric cancer [13], and the suprapancreatic node is a target of D2 dissection in gastric cancer patients. The role of D2 dissection is debated for patients with EGC [18, 19], especially for additional surgery following gastric ESD due to noncurative resection of EGC. However, a rigorous stage-by-stage comparison of D1 and D2 dissection in patients with definite suprapancreatic lymph node positivity is impossible because dissected node information cannot be acquired from retrospective data. Further studies are needed to answer this question about the optimal extent of node dissection in additional surgery following gastric ESD due to noncurative resection of EGC.

We aimed to identify a predictive marker for EGM in patients undergoing ESD for EGC whose pathology showed negative resection margins and positive lymphovascular invasion. A previous study suggested that ESD may be sufficient to treat patients with lymphovascular invasion-positive EGC according to the absolute criteria instead of additional surgery [10]. However, that study only included 28 patients with positive lymphovascular invasion. Our study included 110 patients who were lymphovascular invasion-positive and resection margin-negative, suggesting the previous study missed the potential for lymph node metastasis because it observed only a small number of patients. The results of our study indicate that, regardless of ESD indication criteria, EGM may occur as node metastasis or recurrence after a few years.

Our study showed that overall survival and disease-free survival did not significantly differ between the surgical and observation groups (Figs. 2 and 3). However, patients in the surgery group tended to have more submucosal invasion than those in the observation group (Table 1), suggesting that patients in the surgery group might have had more advanced stages than those in the observation group. Although the survival rate did not differ between the two groups, this does not mean that observation without surgery in EGC patients who have R0 resection and lymphovascular invasion in their post-ESD pathology is possible. A previous study by Toya et al. [16] concluded that follow-up without additional gastrectomy may be a feasible strategy for these patients as there was no recurrence during the follow-up period. However, EGM cases were found in our study, which require careful follow-up.

Our study had some limitations. First, it was a small sample, single center, retrospective study, which potentially affects selection bias. A larger sample, multicenter, prospective study is needed to verify the results. Second, we were unable to follow-up with most (61.8%) of the patients after 60 months, which is the standard period of cure. Thus, our results may be underestimated because of the relatively short follow-up duration. Additional cases of EGM may develop after longer follow-up periods, although previous studies showed that most EGCs recur within five years after curative intent surgery [20, 21]. Therefore, our results are unlikely to be substantially different even with longer follow-up periods. The present study included only patients who were uniformly lymphovascular invasion–positive and

resection margin–negative in their post-ESD pathology. Further study is required to determine whether a longer observation period would identify more patients with EGM.

Conclusions

Tumor size was the only predictive indicator of EGM in patients with R0 resection and lymphovascular invasion in their post-ESD pathology. Even patients with EGC whose pathology corresponded to absolute indication criteria of ESD had lymphovascular invasion, they required an additional gastrectomy due to the risk of EGM.

Declarations

Acknowledgements

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Ethics approval and consent to participate

The Institutional Review Board of Seoul National University Hospital approved the study protocol (IRB number 2106-114-1227) and waived the need to obtain informed consent. This study was conducted according to the principles of the Declaration of Helsinki.

Availability of data and materials

Data access can be made available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests

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Authors' contributions

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Formal analysis: L.H.M.

Investigation: L.H.M.

Methodology: K. Y., K.S.G., C.H., C.S.J.

Resources: K.Y., K.S.G., C.H., C.S.J.

Supervision: C.S.J.

Validation: L.H.M., C.S.J.

Visualization: L.H.M., C.S.J.

Writing - original draft: L.H.M.

Writing - review & editing: L.H.M., C.S.J.

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Tables

Table 2 is available in the Supplementary Files section.

Figures

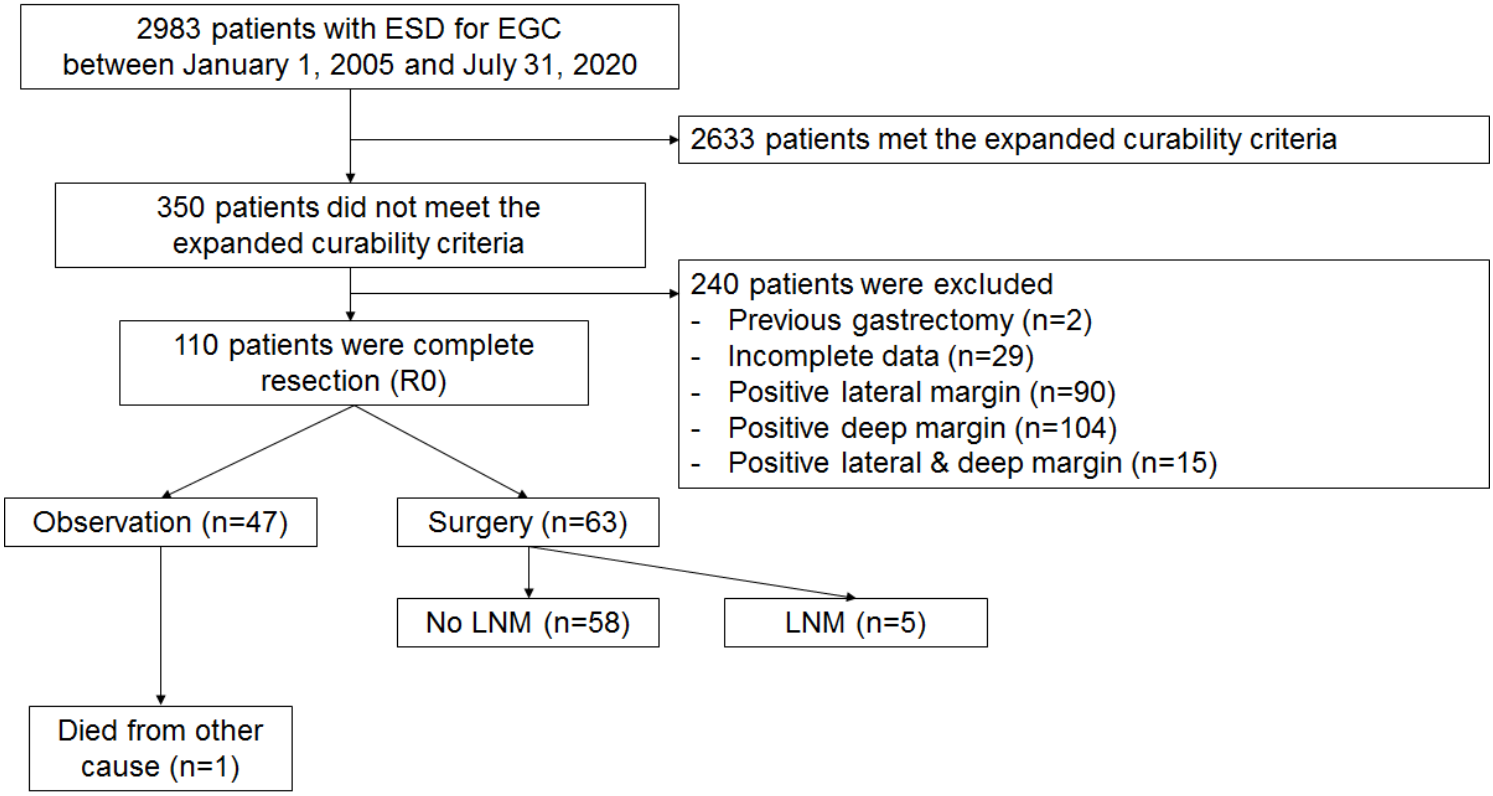

Figure 1

Flowchart and clinical outcomes of patients enrolled in this study

EGC= early gastric cancer; ESD = endoscopic submucosal dissection; LNM = lymph node metastasis

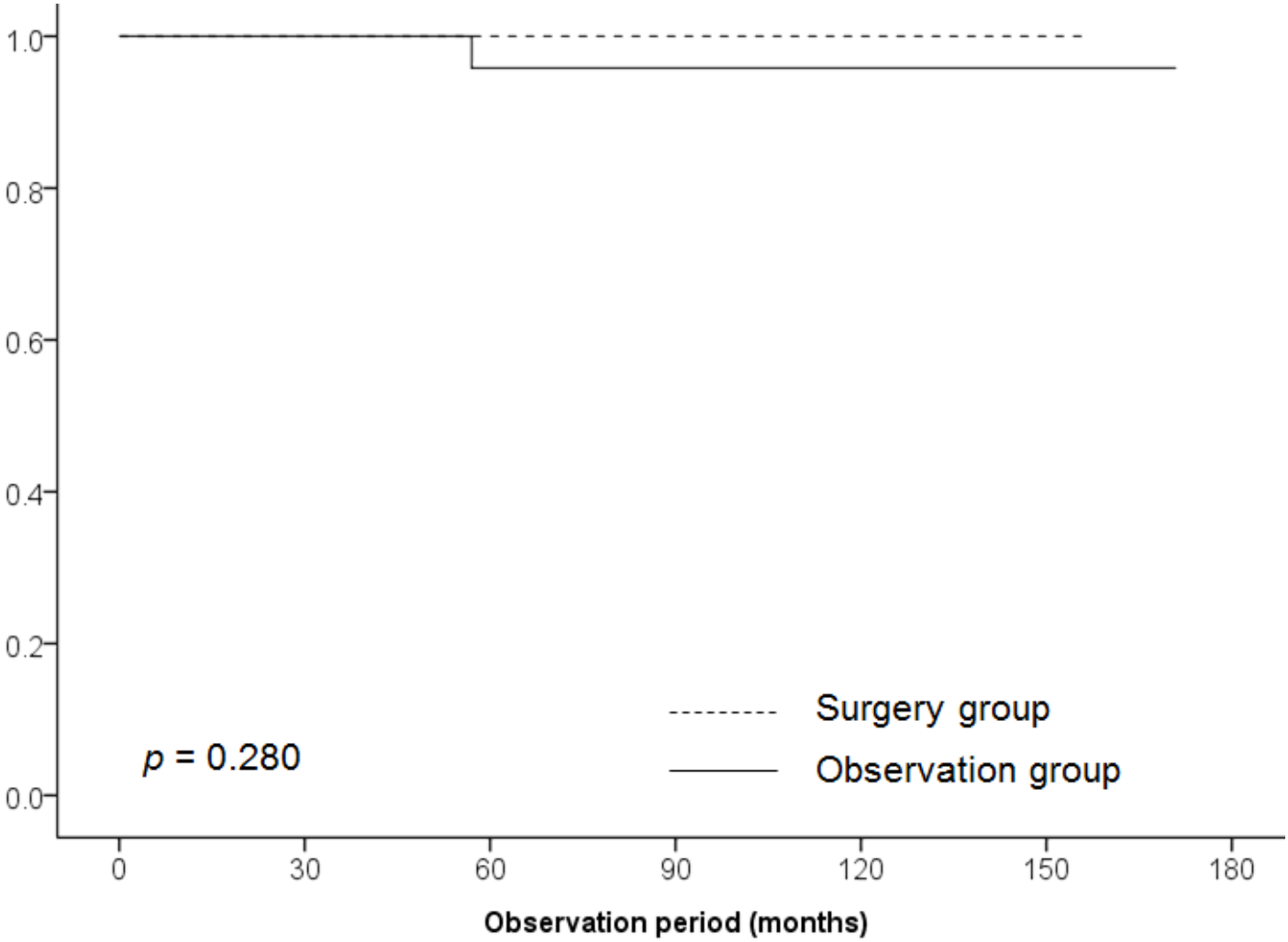

Figure 2

Overall survival curves for patients in observation group and surgery group

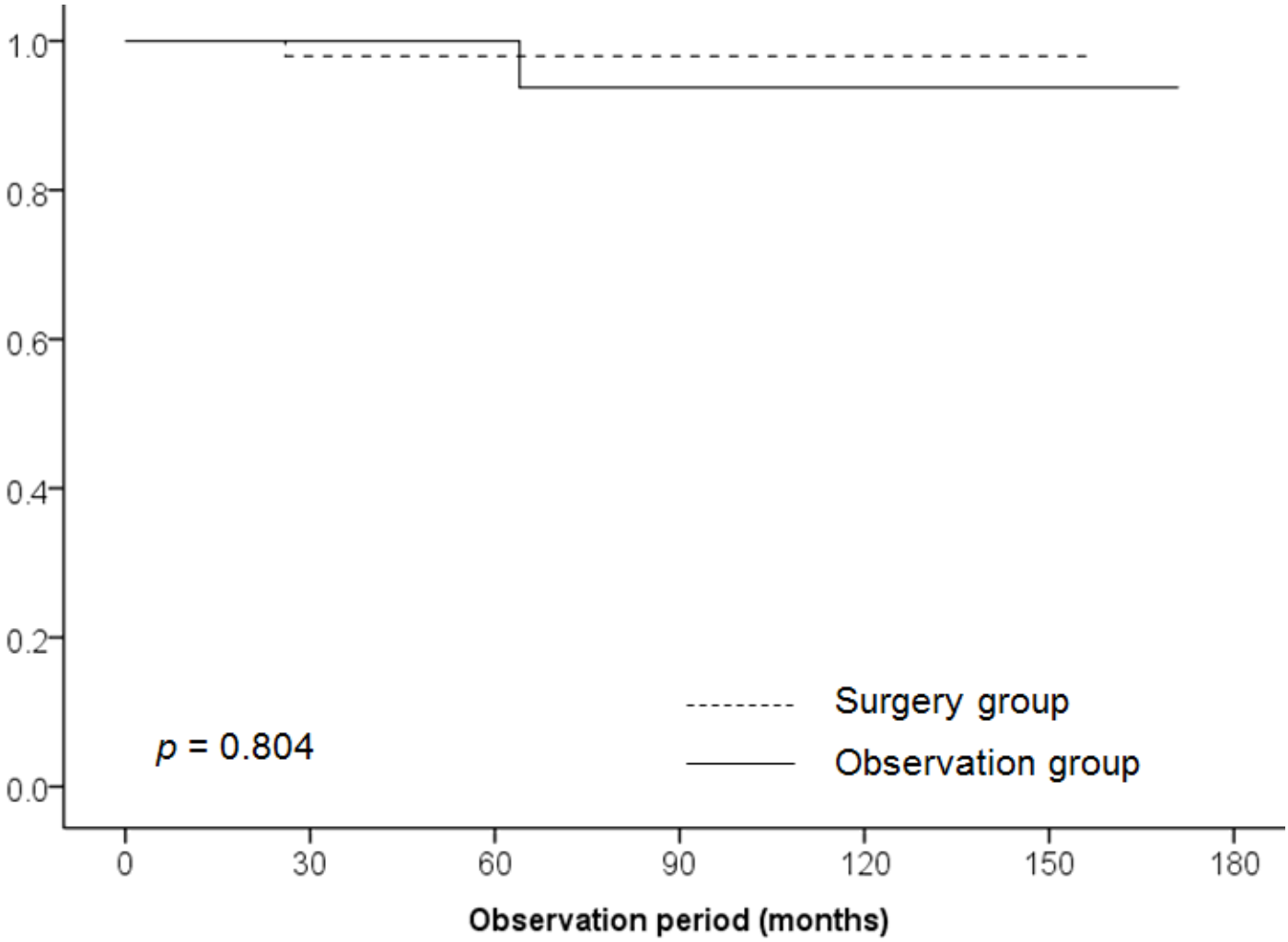

Figure 3

Disease-free survival curves for patients in observation group and surgery group

Supplementary Files

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- Table2.docx