BMC Gastroenterology

RESEARCH

Open Access

Risk factors of additional surgery after non-curative endoscopic submucosal dissection for early gastric cancer

Feng Sun[1†], Yibo Huang[2†], Yan Sun[3†], Xingzhou Wang[1], Shichao Ai[1], Wenxian Guan[1*] and Meng Wang[2*]

Abstract

Background The criteria for surgical intervention after non-curative endoscopic submucosal dissection (ESD) of early gastric cancer are unclear. We aimed to clarify the risk factors for residual cancer and lymph node metastasis after non-curative ESD and to identify recommendations for additional surgery.

Methods We collected data on 133 consecutive patients who underwent additional surgery after non-curative ESD of early gastric cancer at Nanjing Drum Tower Hospital from January 2013 to July 2022. Univariate and multivariate analyses were performed to seek risk factors of residual cancer and lymph node metastasis.

Results The incidence rates of residual cancer and lymph node metastasis were 13.5% (18/133) and 10.5% (14/133), respectively. There was neither residual tumor nor lymph node metastasis in 104 (78.2%) cases. Multivariate analyses elucidated that horizontal margin was an independent risk factor for local residual cancer, whereas lymphatic infiltration was an independent risk factor for lymph node metastasis. Patients with mixed histological types were more likely to suffer lymph node metastasis and further undergo additional surgery after non-curative ESD than pure histological type.

Conclusions Additional gastrectomy with lymph node dissection was strongly recommended in patients with lymphatic infiltration after non-curative ESD of early gastric cancer. Patients with mixed histological type have a high propensity for lymph node metastasis and should be treated as a separate subtype.

Keywords Early gastric cancer, Endoscopic submucosal dissection, Additional Surgery, Residual cancer, Lymph node Metastasis, Histologic type

†Feng Sun, Yibo Huang and Yan Sun have contributed equally to this work.

*Correspondence:
Wenxian Guan
medguanwenxian@163.com
Meng Wang
wangmeng1980@nju.edu.cn

[1]Division of Gastric Surgery, Department of General Surgery, Nanjing Drum Tower Hospital, the Affiliated Hospital of Medical School, Nanjing University, Nanjing, China
[2]Division of Gastric Surgery, Department of General Surgery, Nanjing Drum Tower Hospital Clinical College of Nanjing Medical University, Nanjing, China
[3]Department of Anesthesiology, Nanjing Drum Tower Hospital, the Affiliated Hospital of Medical School, Nanjing University, Nanjing, China

Introduction

With the popularization of endoscopic technology and early cancer screening, the proportion of early gastric cancer diagnosed is increasing. At present, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are fundamental treatments for early gastric cancer (EGC). Meanwhile, various large multicenter randomized controlled trials were carried out to expand the indications of endoscopic therapy. An important issue would ensue inevitably that a subset of patients might undergo non-curative resection.

According to the Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer updated in 2020 [1], the curable resection grades were divided into eCuraA, eCuraB, and eCuraC (Supplemental Table 1). eCura C was defined as the noncurative resection. eCuraC was further divided into eCuraC-1 and eCuraC-2, which represents non-en bloc resection or positive horizontal margins, and adjoint of high-risk factors for lymph node metastasis, respectively. For eCuraC-1 lesions, additional ESD, close follow-up, or additional surgery is optional after adequate communication with the patient [2, 3]. For eCuraC-2 lesions, gastrectomy with lymph node dissection is recommended [4].

In clinical work, it is common that neither residual tumor nor lymph node metastasis was found after additional surgery. In addition, there are some patients who hesitate to choose the following measures after non-curative ESD. Therefore, it is necessary to access accurately the risk of residual cancer and lymph node metastasis after ESD, which was fundamental for the choice of re-medical measures after non-curative ESD. In this study, we collected cases of additional surgery after non-curative ESD and analyzed the risk factors for residual cancer and lymph node metastasis.

Methods

Patients

133 consecutive patients who underwent additional surgery after non-curative ESD at Nanjing Drum Tower Hospital from January 2013 to July 2022 were analyzed in this study. All patients had pathologically confirmed early gastric cancer. Patients with synchronous other malignant tumors, previous stomach surgery, or incomplete clinical data were excluded. Patients were followed-up by phone call or outpatient clinic at 3 months after surgery and once a year thereafter. The follow-up deadline was 2023-09-15. This study was approved by the hospital ethical committee of Nanjing Drum Tower Hospital.

Data collection

The collected general data include age and gender. The collected pathological data consisted of tumor location, lesion size, differentiation type, depth of invasion, ulceration, lymphovascular invasion, perineural infiltration, and lesion margin. For differentiation type, we defined the mixed histologic type as that consisting of both differentiated and undifferentiated lesions. Postoperative characteristics included short-term complications and long-term follow-up. The postoperative short-term complications were defined as morbidity or mortality that occurred during hospitalization or within 30 days after surgery.

Non-curative criteria

The ESD indication complied with the Japanese gastric cancer treatment guidelines. The infiltration depth of early gastric cancer was divided into mucosal (T1a) and submucosal (T1b). Submucosal lesions were further classified as superficial (depth < 500 μm; SM1) and deep (depth ≥ 500 μm; SM2) submucosal infiltration. The non-curative criteria of ESD satisfied one of the following items: non-en bloc resection, positive margins, lymphovascular infiltration, SM2 submucosal invasion, differentiated type (diameter > 3 cm) with ulceration or SM1 submucosal invasion; undifferentiated type with submucosal invasion or ulceration or diameter > 2 cm.

Statistical analysis

The categorical variables were presented as numbers. Differences between categorical variables were compared with the Chi-squared test or Fisher exact test. Univariate analyses were performed first to seek risk factors of residual cancer and lymph node metastasis. Further multivariate analyses were performed on variables that were statistically significant in univariate analyses. Kaplan-Meier curves and the

Table 1 Demographic and clinical features of patients

Characteristic	N = 133	Characteristic	N = 133
Age (y)		Lymphatic invasion	
≤60	46	Positive	17
>60	87	Negative	116
Gender (n)		Vascular invasion	
Male	94	Positive	17
Female	39	Negative	116
Tumor location		Perineural invasion	
Cardia and fundus	53	Positive	2
Body	27	Negative	131
Antrum	53	Horizontal margin	
Tumor size (cm)		Positive	11
≤2.0	58	Negative	122
>2.0	75	Vertical margin	
Tumor differentiation		Positive	21
Differentiated-type	67	Negative	112
Undifferentiated-type	12	Residual cancer	
Mixed-type	54	Positive	18
Tumor invasion		Negative	115
Mucosa (T1a)	45	Lymph node metastasis	
Submucosa (T1b)	88	Positive	14
Ulceration		Negative	119
Positive	17		
Negative	116		

log-rank test was conducted to compare the long-term outcome. SPSS 19.0 (Chicago, IL, USA) was used for all statistical analyses. Statistical differences were set at P value<0.05.

Results

Patient characteristics

As shown in Table 1, a total of 133 patients who underwent additional surgery after non-curative ESD were enrolled in this study. 45 cases infiltrated into the mucosal layer while 88 cases infiltrated into the submucosal layer. Postoperative pathology presented residual cancer in 18 (13.5%) patients and lymph node metastasis in 14 (10.5%) patients. There was neither residual tumor nor lymph node metastasis in 104 (78.2%) cases.

Risk factors of residual cancer in patients with non-curative ESD

The overall incidence of local residual cancer in patients who underwent additional surgery following non-curative ESD was 13.5% (18/133). In the univariate analyses, local residual cancer was correlated with histologic differentiation (differentiated type vs. undifferentiated type), and horizontal margin. Further multivariate analyses elucidated that horizontal margin (OR=10.53, 95% CI: 2.59–42.83, P=0.001) was an independent risk factor for local residual cancer (Table 2). For 18 patients with local residual cancer, we further analyzed the poor histoprognostic factors involved (Table 3). Among these 18 patients, 6 cases suffered positive horizontal margin,

Table 2 Univariate and multivariate analyses of risk factors for local residual cancer

		Univariate			Multivariate		
Characteristics	**RC (%)**	**OR**	**95% CI**	**P**	**OR**	**95% CI**	**P**
Age (y)							
≤60	8 (17.4)	1.000					
>60	10 (11.5)	0.617	0.225–1.690	0.347			
Gender (n)							
Male	14 (14.9)	1.000					
Female	4 (10.3)	0.653	0.201–2.125	0.479			
Tumor location				0.349			
Cardia and fundus	6 (11.3)	1.000	0.301–3.326	1.000			
Body	6 (22.2)	2.238	0.646–7.758	0.204			
Antrum	6 (11.3)	1.000					
Tumor size (cm)							
≤2.0	7 (12.1)	1.000					
>2.0	11 (14.7)	1.252	0.453–3.461	0.665			
Tumor differentiation				0.129			0.325
Differentiated-type	7 (10.4)	1.000			1.000		
Undifferentiated-type	4 (33.3)	4.286	1.023–17.96	0.047	3.317	0.666–16.51	0.143
Mixed-type	7 (13.0)	1.277	0.419–3.893	0.668	1.663	0.501–5.520	0.406
Tumor invasion							
Mucosa (T1a)	9 (20.0)	1.000					
Submucosa (T1b)	9 (10.2)	0.456	0.167–1.244	0.125			
Ulceration							
Positive	2 (11.8)	0.833	0.174–3.993	0.820			
Negative	16 (13.8)	1.000					
Lymphatic invasion							
Positive	2 (11.8)	0.833	0.174–3.993	0.820			
Negative	16(13.8)	1.000					
Vascular invasion							
Positive	2 (11.8)	0.833	0.174–3.993	0.820			
Negative	16 (13.8)	1.000					
Perineural invasion							
Positive	0 (0.0)	0.000		0.999			
Negative	18 (13.7)	1.000					
Horizontal margin							
Positive	6 (54.5)	11.00	2.915–41.51	< 0.001	10.53	2.590–42.83	0.001
Negative	12 (9.8)	1.000			1.000		
Vertical margin							
Positive	4 (19.0)	1.647	0.484–5.605	0.425			
Negative	14 (12.5)	1.000					

RC=residual cancer; OR=odds ratio; CI=confidence interval

Table 3 Patients with local residual cancer following additional surgery after non-curative endoscopic submucosal dissection

Case	Horizontal margin	Mixed-type differentiation
#1	-	-
#2	-	-
#3	-	-
#4	-	+
#5	+	-
#6	+	-
#7	+	-
#8	-	+
#9	-	+
#10	+	+
#11	-	-
#12	-	+
#13	+	-
#14	-	-
#15	-	+
#16	-	-
#17	-	+
#18	+	-

while 7 cases were mixed type differentiation. 6 cases had neither positive horizontal margin, nor mixed type differentiation.

Risk factors of lymph node metastasis in patients with non-curative ESD

The overall incidence of lymph node metastasis in patients who underwent additional surgery following non-curative ESD was 10.5% (14/133). As shown in Table 4, univariate analyses showed that lymph node metastasis was correlated with histologic differentiation (differentiated type vs. mixed type), lymphatic invasion, and vascular invasion. Further multivariate analyses elucidated that lymphatic invasion (OR=8.797, 95% CI: 1.051–73.64, P=0.045) was an independent risk factor for lymph node metastasis. For 14 patients with lymph node metastasis, we further analyzed the poor histoprognostic factors involved (Table 5). Among these 14 patients, 7 cases suffered lymphatic invasion, 6 cases suffered vascular invasion, and 10 cases were mixed type differentiation. Only one case had neither lymphatic invasion, vascular invasion, nor mixed type differentiation.

Clinicopathologic features associated with different histologic types

Histopathologically, there were 67 (50.4%) cases with differentiated type, 12 (9.0%) cases with undifferentiated type, and 54 (40.6%) cases with mixed type (Table 1). The lymph node metastasis rate of differentiated type, undifferentiated type, and mixed type was 6% (4/67), 0% (0/12), and 18.5% (10/54), respectively (Table 4). Univariate analyses showed that histologic differentiation (differentiated type vs. mixed type) was correlated with lymph node metastasis (Table 4).

Short-term and long-term outcomes of patients undergoing additional surgery after non-curative ESD

The short-term outcomes were evaluated based on the Clavien-Dindo (CD) classification system [5]. Of the 133 patients, 31 (22.3%) suffered postoperative short-term complications, and 4 (3.0%) suffered major complications (grade III or more). The details were presented in Table 6. The long-term outcomes were presented by Kaplan-Meier curves. The median follow-up period was 57 months. The overall survival and disease-free survival were shown in Fig. 1. No difference was detected between patients with or without lymph node metastasis both in overall survival (P=0.759) and disease-free survival (P=0.981).

Discussion

ESD was increasingly becoming a fundamental treatment for early gastric cancer because of its minimally invasive nature. Various large-scale clinical trials were carried out to expand the indications of endoscopic therapy. As more and more patients with early gastric cancer underwent endoscopic treatment, it was inevitable that more cases of non-curative resection will occur. In this case, a remedial gastrectomy with lymph node dissection would be recommended [6]. However, in approximately 90% of cases who underwent additional surgery, neither residual tumor nor lymph node metastasis was found [7]. This means that additional surgery might be over-medical for these cases. Therefore, it is necessary to screen out this subset of patients who benefit from additional surgery after non-curative ESD.

In our study, a total of 133 patients who underwent additional surgery after non-curative ESD were retrospectively analyzed. The incidence rates of residual cancer and lymph node metastasis were 13.5% (18/133) and 10.5% (14/133), respectively. There was neither residual tumor nor lymph node metastasis in 104 (78.2%) cases. Multivariate analyses elucidated that horizontal margin was an independent risk factor for local residual cancer, which was consistent with the previous studies [8–10]. Several studies showed that residual cancer was also correlated with positive vertical margin [11, 12]. However, we did not observe such a phenomenon. This might be attributable to a weaker cautery effect in the horizontal direction than that in the vertical direction [8]. Furthermore, the length of the positive margin might be more meaningful for predicting tumor residue. *Sangjeong et al.* reported that the sensitivity of a more than 6 mm positive margins length for predicting tumor residue was 85.7% [13]. As for differentiation type, undifferentiated type (compared with differentiated type) was significantly correlated with residual cancer in univariate analyses while not in multivariate analyses. An interesting finding was that

Table 4 Univariate and multivariate analyses of risk factors for lymph node metastasis

		Univariate			Multivariate		
Characteristics	**LNM (%)**	**OR**	**95% CI**	**P**	**OR**	**95% CI**	**P**
Age (y)							
≤60	8 (17.4)	1.000					
>60	6 (6.9)	0.823	0.571–1.186	0.296			
Gender (n)							
Male	8 (8.5)	1.000					
Female	6 (15.4)	1.955	0.630–6.063	0.246			
Tumor location				0.320			
Cardia and fundus	4 (7.5)	0.784	0.198–3.095	0.728			
Body	5 (18.5)	2.182	0.572–8.319	0.253			
Antrum	5 (9.4)	1.000					
Tumor size (cm)							
≤2.0	5 (8.6)	1.000					
>2.0	9 (12.0)	1.445	0.457–4.572	0.531			
Tumor differentiation				0.123			
Differentiated-type	4 (6.0)	1.000			1.000		
Undifferentiated-type	0 (0.0)	0.000		0.999	0.000		0.999
Mixed-type	10 (18.5)	3.580	1.055–12.15	0.041	2.977	0.810–10.93	0.100
Tumor invasion							
Mucosa (T1a)	4 (8.9)	1.000					
Submucosa (T1b sm1)	4(13.8%)	1.640	0.376–7.150	0.510			
Submucosa (T1b sm2)	6(10.2)	1.160	0.307–4.384	0.826			
Ulceration							
Positive	1 (5.9)	0.495	0.061–4.048	0.512			
Negative	13 (11.2)	1.000					
Lymphatic invasion							
Positive	7 (41.2)	10.90	3.181–37.35	< 0.001	8.797	1.051–73.64	0.045
Negative	7 (6.0)	1.000			1.000		
Vascular invasion							
Positive	6 (35.3)	7.364	2.159–25.11	0.001	1.126	0.126–10.07	0.915
Negative	8 (6.9)	1.000			1.000		
Perineural invasion							
Positive	0 (0.0)	0.000		0.999			
Negative	14 (10.7)	1.000					
Horizontal margin							
Positive	0 (0.0)	0.000		0.999			
Negative	14 (11.5)	1.000					
Vertical margin							
Positive	4 (19.0)	2.400	0.675–8.530	0.176			
Negative	10 (8.9)	1.000					

LNM = lymph node metastasis; OR = odds ratio; CI = confidence interval

none of the 11 cases with positive horizontal margins in our study was observed lymph node metastases in postoperative pathology. This means that for cases with positive horizontal margins and without lymphatic infiltration, repeat ESD might be optional.

Whether the lymph nodes metastasize was a critical factor in determining the treatment of early gastric cancer. In our study, the incidence rate of lymph node metastasis was 10.5% (14/133) in patients who underwent additional surgery after non-curative ESD. Multivariate analyses elucidated that lymphatic infiltration was an independent risk factor for lymph node metastasis. The proportion of lymph node metastasis was 6.9 times higher in patients with lymphatic infiltration than that without lymphatic infiltration. For 14 patients with lymph node metastasis, 7 cases suffered lymphatic invasion, 6 cases suffered vascular invasion, and 10 cases were mixed type differentiation. Only one case had neither lymphatic invasion, vascular invasion, nor mixed type differentiation. Previous studies revealed several other risk factors for lymph node metastasis in patients with non-curative ESD, including undifferentiated type, vascular infiltration, and positive vertical margin [14–16]. *Hatta et al.*

Table 5 Patients with lymph node metastasis following additional surgery after non-curative endoscopic submucosal dissection

Case	Lymphatic invasion	Vascular invasion	Mixed-type differentiation
#1	+	+	+
#2	+	-	-
#3	-	-	-
#4	-	-	+
#5	-	-	+
#6	+	+	-
#7	-	-	+
#8	-	-	+
#9	+	+	+
#10	-	-	+
#11	-	-	+
#12	+	+	+
#13	+	+	-
#14	+	+	+

Table 6 Short-term complications following additional surgery after non-curative endoscopic submucosal dissection for early gastric cancer

Characteristics	n
Overall	31
Grade I	13
Fever > 37.5 °C	9
Emesis	2
Pleural effusion	2
Grade II	15
Blood transfusions	6
Hypoalbuminemia	1
Gastroparesis	1
Wound infection	4
Pneumonia	3
Bacteremia	1
Grade III	4
Bleeding	3
Pleural effusion	1
Grade IV-V	0

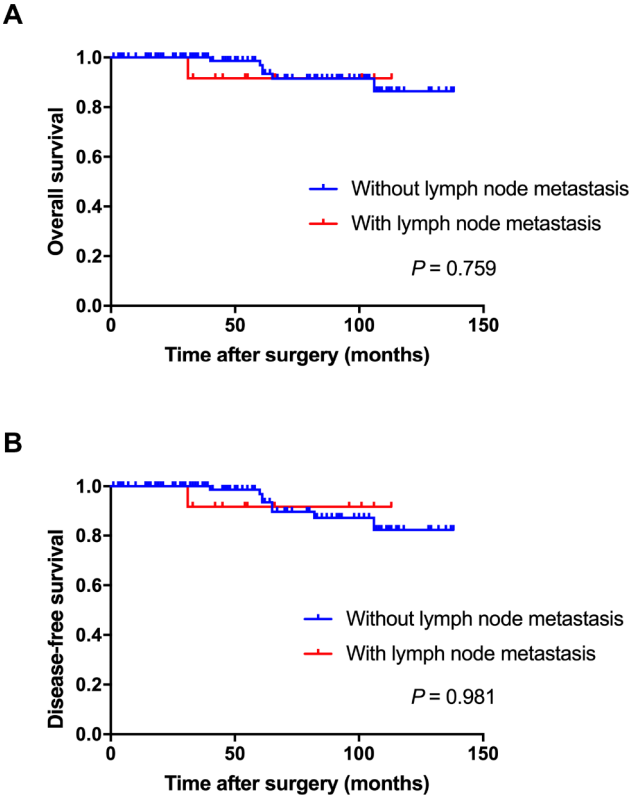

Fig. 1 Overall survival and disease-free survival following additional surgery after non-curative endoscopic submucosal dissection for early gastric cancer

constructed the eCura system to assess the risk of lymph node metastasis in patients after non-curative ESD [17]. This scoring system consisted of 5 factors: lymphatic infiltration, venous infiltration, positive vertical margin, SM2 infiltration, and tumor size>3 cm. Our findings suggest that lymphatic infiltration appeared to play a more important role among these 5 factors. Therefore, follow-ups or repeat ESD might be sufficient for patients without lymphatic invasion.

Japanese Classification of Gastric Cancer divided early gastric cancer into differentiated and undifferentiated types [18]. In practice, some lesions comprised both differentiated and undifferentiated types. Recent studies revealed that the incidence rate of lymph node metastasis was higher in patients with mixed histologic type than differentiated type or even undifferentiated type [19, 20]. From tumorigenesis to clinical features, the mixed histologic type was different from the pure histologic type. Therefore, some arguments suggested that mixed histologic type should be treated as a separate subtype [21]. The 5th edition JGCA guidelines determined whether the criteria for curative resection were met based on the size and depth of invasion of undifferentiated components in mixed histologic type EGC [1]. In this study, we considered the mixed histologic type as a separate subtype. The proportion of mixed histologic type was 40.6% (54/133) in patients who underwent additional surgery after non-curative ESD. In contrast, our previous study elucidated that the proportion of mixed histologic type was 27.7% (202/730) in all early gastric cancer who underwent radical gastric resection [22]. The above results implied that patients with mixed types were more likely to undergo additional surgery after non-curative ESD. Moreover, for patients undergoing additional surgery after non-curative ESD, the lymph node metastasis rate of differentiated type, undifferentiated type, and mixed type was 6% (4/67), 0% (0/120), and 18.5% (10/54), respectively. Univariate analyses showed that histologic differentiation (differentiated type vs. mixed type) was correlated with lymph node metastasis.

Mechanistically, former studies have made some possible explanations for why mixed type GC were more aggressive than pure type GC. These hypotheses involved genetic and epigenetic abnormalities, interactions with the tumor microenvironment, and intratumor evolution [23–25]. *Park et al.* disclosed that CpG island promoter hypermethylation was higher in mixed type GC than pure type GC [26]. *Sentani* and colleagues reported that mixed type GC showed a characteristically expression of cancer stem cell-related molecules (CD44, CD133, and ALDH1), receptor tyrosine kinase molecules (EGFR, c-MET, and HER2), and chromosomal instability compared to pure type GC [27]. Thus, it is meaningful to diagnose mixed type early gastric cancer before ESD procedures, which might reduce the incidence rates of additional surgery after ESD caused by incorrect pretreatment diagnosis of histological type. Magnifying endoscopy combined with narrow-band imaging and biopsy was a promising measure for diagnosing mixed histologic type EGC [28, 29].

We acknowledged some limitations in our study. First, it was a retrospective study. The sample size was relatively small from a single center. Second, the indications for ESD have been expanding in recent years. There might be a selection bias for the criteria of ESD between different endoscopists. Third, only surgical cases were enrolled in this study, some patients who underwent follow-ups without additional surgery have not been recorded. Further study is needed to compare the prognosis between patients with follow-ups or additional surgery.

Conclusion

In conclusion, for patients who underwent non-curative ESD, positive horizontal margin was an independent risk factor for residual cancer, while lymphatic infiltration was an independent risk factor for lymph node metastasis. Early gastric cancer with mixed histologic type might have a higher rate of lymph node metastasis. Therefore, more attention should be paid to mixed histologic type when developing criteria for EDS resection.

Abbreviations

EGC Early gastric cancer
EMR Endoscopic mucosal resection
ESD Endoscopic submucosal dissection

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-023-03006-9.

Supplementary Material 1

Acknowledgements

We acknowledge and appreciate all patients enrolled in this study.

Authors' contributions

FS designed the study, collected data, and wrote the manuscript. YH and YS worked on study design and data collection. XW and SA helped collect data. WG and MW were responsible for study design and data analyses. All authors have read and approved the final manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (No. 82100593).

Data Availability

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

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Nanjing Drum Tower Hospital, the Affiliated Hospital of Nanjing University Medical School. Due to the retrospective nature, the requirement for informed consent was waived by the IRBs from Nanjing Drum Tower Hospital, the Affiliated Hospital of Nanjing University Medical School. All methods were carried out in accordance with relevant guidelines and regulations. Research involving human data was performed in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 27 April 2023 / Accepted: 19 October 2023
Published online: 10 November 2023

References

1. Ono H, Yao K, Fujishiro M, Oda I, Uedo N, Nimura S, Yahagi N, Iishi H, Oka M, Ajioka Y, et al. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer (second edition). Dig Endoscopy: Official J Japan Gastroenterological Endoscopy Soc. 2021;33(1):4–20.
2. Japanese gastric cancer treatment guidelines 2018 (5th edition). Gastric cancer: official journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association. 2021, 24(1):1–21.
3. Jeon MY, Park JC, Hahn KY, Shin SK, Lee SK, Lee YC. Long-term outcomes after noncurative endoscopic resection of early gastric cancer: the optimal time for additional endoscopic treatment. Gastrointest Endosc. 2018;87(4):1003–1013e1002.
4. Li D, Luan H, Wang S, Zhou Y. Survival benefits of additional Surgery after non-curative endoscopic resection in patients with early gastric cancer: a meta-analysis. Surg Endosc. 2019;33(3):711–6.
5. Dindo D, Demartines N, Clavien P-A. Classification of Surgical Complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205–13.
6. Japanese gastric cancer treatment guidelines. 2014 (ver. 4). *Gastric cancer: official journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association* 2017, 20(1):1–19.
7. Kawata N, Kakushima N, Takizawa K, Tanaka M, Makuuchi R, Tokunaga M, Tanizawa Y, Bando E, Kawamura T, Sugino T, et al. Risk factors for lymph node Metastasis and long-term outcomes of patients with early gastric cancer after non-curative endoscopic submucosal dissection. Surg Endosc. 2017;31(4):1607–16.
8. Toyokawa T, Ohira M, Tanaka H, Minamino H, Sakurai K, Nagami Y, Kubo N, Yamamoto A, Sano K, Muguruma K, et al. Optimal management for patients not meeting the inclusion criteria after endoscopic submucosal dissection for gastric cancer. Surg Endosc. 2016;30(6):2404–14.
9. Makimoto S, Mushiake Y, Takami T, Shintani H, Kataoka N, Yamaguchi T, Oura S. Evaluation of additional gastrectomy after noncurative endoscopic submucosal dissection for early gastric cancer. BMC Surg. 2022;22(1):352.
10. Yoon H, Kim SG, Choi J, Im JP, Kim JS, Kim WH, Jung HC. Risk factors of residual or recurrent Tumor in patients with a tumor-positive resection margin after endoscopic resection of early gastric cancer. Surg Endosc. 2013;27(5):1561–8.
11. Nie RC, Yuan SQ, Li YF, Chen S, Chen YM, Chen XJ, Chen GM, Zhou ZW, Chen YB. Additional gastrectomy in early-stage gastric cancer after non-curative endoscopic resection: a meta-analysis. Gastroenterol Rep. 2019;7(2):91–7.

12. Sunagawa H, Kinoshita T, Kaito A, Shibasaki H, Kaneko K, Ochiai A, Ohtsu A, Nishida T. Additional Surgery for non-curative resection after endoscopic submucosal dissection for gastric cancer: a retrospective analysis of 200 cases. Surg Today. 2017;47(2):202–9.
13. Ahn S, Do IG, Sohn JH, Yang HJ, Yoo CH, Kim K. Total length of positive resection margins can predict remnant gastric cancer following endoscopic submucosal dissection. Pathol Res Pract. 2020;216(11):153183.
14. Duan K, Li D, Shi D, Pei J, Ren J, Li W, Dong A, Chen T, Zhou J. Risk Factors and Timing of Additional Surgery after Noncurative ESD for Early Gastric Cancer. *Canadian journal of gastroenterology & hepatology* 2022, 2022:3421078.
15. Hoteya S, Iizuka T, Kikuchi D, Ogawa O, Mitani T, Matsui A, Furuhata T, Yamashita S, Yamada A, Kaise M. Clinicopathological outcomes of patients with early gastric Cancer after non-curative endoscopic submucosal dissection. Digestion. 2016;93(1):53–8.
16. Sekiguchi M, Oda I, Taniguchi H, Suzuki H, Morita S, Fukagawa T, Sekine S, Kushima R, Katai H. Risk stratification and predictive risk-scoring model for lymph node Metastasis in early gastric cancer. J Gastroenterol. 2016;51(10):961–70.
17. Hatta W, Gotoda T, Oyama T, Kawata N, Takahashi A, Yoshifuku Y, Hoteya S, Nakagawa M, Hirano M, Esaki M, et al. A Scoring System to Stratify Curability after Endoscopic Submucosal dissection for early gastric Cancer: eCura system. Am J Gastroenterol. 2017;112(6):874–81.
18. Japanese classification of gastric carcinoma. : 3rd English edition. *Gastric cancer: official journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association* 2011, 14(2):101–112.
19. Horiuchi Y, Fujisaki J, Yamamoto N, Ishizuka N, Ishiyama A, Yoshio T, Hirasawa T, Yamamoto Y, Nagahama M, Takahashi H, et al. Undifferentiated-type predominant mixed-type early gastric cancer is a significant risk factor for requiring additional surgeries after endoscopic submucosal dissection. Sci Rep. 2020;10(1):6748.
20. Zhao B, Huang R, Lu H, Mei D, Bao S, Xu H, Huang B. Risk of lymph node Metastasis and prognostic outcome in early gastric cancer patients with mixed histologic type. Curr Probl Cancer. 2020;44(6):100579.
21. Yoon HJ, Kim YH, Kim JH, Kim H, Kim H, Park JJ, Youn YH, Park H, Kim JW, Hyung WJ, et al. Are new criteria for mixed histology necessary for endoscopic resection in early gastric cancer? Pathol Res Pract. 2016;212(5):410–4.
22. Sun F, Zhang S, Wang X, Yao M, Zhang C, Liu Z, Ai S, Guan W, Wang M. Mixed histologic type is a risk factor for Lymph Node Metastasis in Submucosal Invasive Early gastric Cancer. J Surg Res. 2023;282:160–7.
23. Tajiri R, Ooi A, Fujimura T, Dobashi Y, Oyama T, Nakamura R, Ikeda H. Intratumoral heterogeneous amplification of ERBB2 and subclonal genetic diversity in gastric cancers revealed by multiple ligation-dependent probe amplification and fluorescence in situ hybridization. Hum Pathol. 2014;45(4):725–34.
24. Arai T, Sakurai U, Sawabe M, Honma N, Aida J, Ushio Y, Kanazawa N, Kuroiwa K, Takubo K. Frequent microsatellite instability in papillary and solid-type, poorly differentiated adenocarcinomas of the stomach. Gastric cancer: Official Journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association. 2013;16(4):505–12.
25. Lee HW, Kim K. Acquisition of histologic diversity contributes to not only invasiveness but also lymph node Metastasis in early gastric cancer. Pathol Res Pract. 2017;213(9):1023–8.
26. Park S-Y, Kook MC, Kim YW, Cho N-Y, Kim T-Y, Kang GH. Mixed-type gastric cancer and its association with high-frequency CpG island hypermethylation. Virchows Arch. 2010;456(6):625–33.
27. Sentani K, Imai T, Kobayashi G, Hayashi T, Sasaki N, Oue N, Yasui W. Histological diversity and molecular characteristics in gastric cancer: relation of cancer stem cell-related molecules and receptor tyrosine kinase molecules to mixed histological type and more histological patterns. Gastric cancer: Official Journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association. 2021;24(2):368–81.
28. Horiuchi Y, Tokai Y, Yamamoto N, Yoshimizu S, Ishiyama A, Yoshio T, Hirasawa T, Yamamoto Y, Nagahama M, Takahashi H, et al. Additive effect of magnifying endoscopy with narrow-Band imaging for diagnosing mixed-type early gastric cancers. Dig Dis Sci. 2020;65(2):591–9.
29. Ozeki Y, Hirasawa K, Kobayashi R, Sato C, Tateishi Y, Sawada A, Ikeda R, Nishio M, Fukuchi T, Makazu M, et al. Histopathological validation of magnifying endoscopy for diagnosis of mixed-histological-type early gastric cancer. World J Gastroenterol. 2020;26(36):5450–62.

Publisher's Note