Evaluation of additional gastrectomy after noncurative endoscopic submucosal dissection for early gastric cancer

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Research Article

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Abstract

Background

Performing additional surgery after noncurative endoscopic submucosal dissection (ESD) for early gastric cancer is controversial. Our aims are to clarify the risk factors for lymph node metastasis (LNM) and local residual cancer (RC) after noncurative ESD and to determine recommendations for additional treatment.

Methods

Of the 1483 patients who underwent ESD for early gastric cancer between January 2012 and April 2020, we retrospectively analyzed 151 patients diagnosed as having a lesion not meeting the curative criteria after ESD. Of these patients, 100 underwent additional gastrectomy, and 51 were observed without surgery.

Results

Surgical specimens showed LNM in 14 patients (14.0 %) and local RC in 7 (7.0 %). However, 81 patients (81.0 %) had neither of these malignancies. Multivariate analysis revealed that a positive lymphatic invasion ($P = 0.035$) and an undifferentiated type ($P = 0.047$) were independent risk factors for LNM, whereas a positive horizontal margin ($P = 0.017$) was an independent risk factor for local RC. In the additional gastrectomy group, 3 patients (3.0 %) had recurrences, and 2 (2.0 %) died of gastric cancer. In the observation group, 1 patient (2.0 %) had distant recurrence, and 2 patients (3.9 %) had local recurrences.

Conclusion

Following noncurative ESD for early gastric cancer, we recommend an additional gastrectomy with lymph node dissection for patients with lymphovascular invasion and/or undifferentiated type. Careful follow-ups without additional surgery may be acceptable for patients with advanced age, severe comorbidity, or no lymphovascular invasion.

Introduction

Endoscopic submucosal dissection (ESD) is a standard treatment for early gastric cancer with a negligible risk of lymph node metastasis [1, 2]. According to Japanese gastric cancer treatment guidelines, resection of a lesion that does not meet the curative criteria is considered a noncurative resection and radical gastrectomy with lymph node dissection or additional endoscopic treatment is the recommended course of treatment [1–3]. In general, it is difficult to determine if there are patients with clinically positive nodes after ESD. Therefore, the necessity for additional surgery is determined based on the histopathologic findings of the endoscopically resected specimens [3]. If positive horizontal margin is the only non curative factor, additional ESD is considered [1, 2]. Especially for elderly patients and those

with complications, an additional gastrectomy is invasive and potentially fatal. Therefore, whether an additional gastrectomy is necessary for all patients not meeting the curative criteria after ESD is controversial [4, 5].

In this study, we evaluated the predictive factors for LNM and local residual cancer (RC) in patients not meeting the curative criteria after ESD and, based on these findings, recommend criteria to determine additional treatment strategies.

Patients And Methods

A total 1483 patients underwent ESD for early gastric cancer at the Department of Gastroenterology at Kishiwada Tokushukai Hospital between January 2012 and April 2020. Of these, we analyzed 151 patients diagnosed as having a lesion not meeting the curative criteria after ESD, including 100 who underwent additional gastrectomy, and 51 who were observed without surgery. All cases of ESD were en bloc resection; piecemeal resection was not included in these cases.

This study was approved by the institutional ethics committee of Kishiwada Tokushukai Hospital. Written informed consent was obtained from all patients before ESD and surgery.

Curative criteria

Tumors were classified by invasion depth as either mucosal (M) or submucosal (SM). Submucosal cancers were subclassified, according to the depth of the tumor invasion into the submucosa measured from the muscularis mucosae, as either superficial (SM1; depth < 500 μ), or deep (SM2; depth ≥500 μ) submucosal invasion. Results of histopathological examination of the ESD specimen were evaluated according to the Japanese classification of gastric carcinoma [1, 3] for curative criteria based on several indicators.

Curative resection was indicated for a case of an en bloc resection with 6 coexisting indicators, including (1) a tumor size ≤2 cm, (2) differentiated tumor type, (3) pT1a (M), (4) negative horizontal margin (HM0), (5) negative vertical margin (VM0), and (6) no lymphovascular invasion (ly[-], v[-]).

Curative resection for tumors of expanded indication was defined for an en bloc resection with 3 indicators, including (1) HM0, (2) VM0, (3) ly(-), v(-), and (4) either of four types of constellation of an additional set indicators, including 1) a tumor size > 2 cm, differentiated tumor type, pT1a, with a negative ulcerative finding (UL[-]); 2) a tumor size ≤3 cm, differentiated tumor type, pT1a, and UL(+); 3) a tumor size ≤2 cm, an undifferentiated tumor type, pT1a, and UL(-); or 4) a tumor size ≤3 cm, differentiated tumor type, and pT1b (SM1) [3].

Noncurative resection was the resection of a lesion that does not meet any of the above curative criteria [3]. Whether additional gastrectomy or observation was finally chosen depended on patient’s age, comorbidities, and decision.

Pathological evaluation

Following resection, ESD specimens were immediately fixed in 10 % buffered formalin, serially sectioned to 2 mm thickness, and the sections mounted on slides were stained with hematoxylin and eosin. Stained sections were examined by a pathologist, and a pathological diagnosis was made and the depth of tumor invasion was measured according to the Japanese classification of gastric carcinoma [1]. Lymphatic invasion and vascular invasion were assessed by D2-40 staining and Elastica van Gieson staining, respectively.

Additional surgery and follow-up

Following noncurative ESD, patients were evaluated for additional surgery with lymph node dissection. In principle, a radical gastrectomy with concomitant lymph node dissection is recommended after noncurative ESD [1–3]. In our institution, a lymph node dissection is performed with D1+ as standard treatment. D2 lymph node dissection was performed in patients whose ESD specimens showed SM2 invasion with a positive vertical margin or who had clinical suspicion of LNM. With the patient's informed consent, either open or laparoscopic surgery was performed. After the additional gastrectomy, we planned to follow-up the patients for at least 5 years, with abdominal imaging (computed tomography (CT) scanning and ultrasonography) performed every 6 months to monitor distant metastases.

For patients who did not undergo additional gastrectomy, surveillance endoscopy was performed following noncurative ESD at every 6 months in the first two years, and annually later. Abdominal CT was performed every 6 months to monitor LNM and distant metastases.

Statistical analysis

Differences of means between categorical variables were analyzed using Fisher's exact test. Statistical significance was indicated by P value <0.05. All statistical analyses were performed using R version 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

We retrospectively analyzed data from 1483 patients who underwent ESD for early gastric cancer at our hospital over an 8-year period, and 179 patients were diagnosed as not meeting the curative criteria after ESD (Fig. 1). Of the 179 patients, 23 patients underwent surgery at other hospitals, 3 patients of remnant gastric cancer, and 2 patients with missing data, were excluded from this study. Of the remaining 151 patients, 100 patients underwent additional gastrectomy, and 51 patients were observed without surgery.

The clinicopathological characteristics of the gastrectomy and observation groups are shown in Table 1. In the observation group, the patients' clinicopathological characteristics did not differ significantly from additional gastrectomy group, but age ($P < 0.001$) and American Society of Anesthesiologists physical status (ASA-PS) ($P = 0.027$) were significantly higher. There was no difference in tumor size and histopathological type between the two groups. The cancer depth in the ESD specimens in the

gastrectomy group indicated invasion class M in 11 patients (11%), SM1 in 9 (9%), SM2 in 78 (78%), and musculus propria (MP) in 2 (2%). On the other hand, the cancer depth in the observation group indicated invasion class M in 6 patients (11.8%), SM1 in 2 (3.9%) and SM2 in 43 (84.3%). The rate of positive lymphatic invasion and positive vertical margin tended to increase in the gastrectomy group compared to the observation group.

Most of the gastrectomy performed was distal (60 patients), but we also performed total (29), and proximal (11) gastrectomy (Table 2). Most of the operations were laparoscopic surgery (89%; 89/100). Lymph node dissection was performed with D1 + as standard treatment. The number of positive lymph nodes was only observed in 14 patients (14%). In 14 patients (14%), postoperative complications greater than grade Ⅲ Clavien-Dindo (CD) classification were observed, including anastomotic leakage in 3 (3%), intraabdominal abscess in 3 (3%), and pancreatic fistula in 2 (2%). One patient died from aspiration pneumonia 51 days after surgery (1% postoperative mortality rate). The median postoperative hospital stay was 11 days. Analyses of surgical specimens showed a residual tumor in 19 patients (19%), including LNM alone in 12 patients (12%), local RC alone in 5(5%), and both in 2 (2%) (Table 3). Half of the 14 patients with LNM had 2 or more metastasized lymph nodes (Table 4), including the 3 patients who recurred after the additional surgery.

The results of risk factor analysis of the 14 patients with LNM are shown in Table 5. Among the 14 patients with LNM, a lymphatic invasion was observed in 12 patients (85.7%), and vascular invasion was observed in 7 patients (50.0%). Univariate analysis identified significant correlations with LNM for both a positive lymphatic invasion ($P < 0.001$) and positive vascular invasion ($P = 0.012$). In contrast, tumor size, depth of invasion, and the resection margin were not correlated with LNM. Multivariate factor analysis confirmed the significant correlation of a positive lymphatic invasion ($P = 0.035$) and an undifferentiated type ($P = 0.047$) with LNM. Although a positive vascular invasion tended to be associated with LNM, the association was not statistically significant. In addition, relationship between lymphatic invasion and vascular invasion for LNM are shown in Table 6. LNM was observed in patients with both lymphatic and vascular invasions (41.2%, 7/17), patients with a lymphatic invasion but without vascular invasion (19.2%, 5/26), patients with a vascular invasion but without lymphatic invasion (0%, 0/5), and patients without both lymphatic and vascular invasions (3.8%, 2/52), respectively. The prevalence of LNM was significantly higher in patients with both positive lymphatic and vascular invasions.

The risk factors for local RC in surgical specimens are shown in Table 7. Local RC was observed in 7 patients (7%). According to histopathological examination of the ESD specimens from these 7 patients, 3 patients had a positive horizontal margin, 3 patients had a positive vertical margin, and 1 patient had a negative margin. The pathological examination of the patient with the negative margin showed a tumor size of 76 mm with ulceration and positive lymphatic invasion. Univariate analysis identified significant correlations with Local RC for a positive horizontal margin ($P = 0.004$), tumor size > 30 mm ($P = 0.008$), and positive ulceration ($P = 0.019$). Although, multivariate factor analysis indicated that having local RC was significantly correlated with only positive horizontal margin ($P = 0.017$).

The median follow-up period in the additional surgery group was 44 months (interquartile range, 20.5–65.5 months). During follow-up, 3 patients (3%) had recurrences: 1 each in the peritoneum, bone, and lymph nodes (Table 2)Two patients (2%) died of gastric cancer, and 6 patients (6%) died of other diseases. The 5-year overall survival rate was 87.4% and the cancer specific survival rate was 97.2% in the 100 patients who underwent additional gastrectomy (Fig. 2, 3).

Of the 51 patients in the observation group, 1 patient (2.0%) died as a result of gastric cancer, and 10 patients (19.6%) died from other diseases. As mentioned above, overall, these were older patients than gastrectomy group. The median follow up period in the observation group was 31 months (IQR 16.0-47.5 months), shorter than in the gastrectomy group. Recurrence was observed in 3 patients (5.9%). One patient (2.0%) who had liver metastasis died of gastric cancer. Of the 2 patients (3.9%) who had local recurrence, one underwent additional ESD, and is alive without recurrence, and the other one died of myocardial infarction.

Discussion

Endoscopic submucosal dissection is a minimally invasive and effective procedure for early gastric cancer with a negligible risk of LNM. When the pathological findings do not meet the curative criteria, an additional gastrectomy with lymph node dissection is recommended [1—3]. However, certain patients, such as older adults, may have additional risks with this surgery [6, 7]. Furthermore, an additional surgical resection may amount to overtreatment for approximately 90% or more of the patients identified in ESD with noncurative treatment [8]. Therefore, whether additional surgery should be performed after noncurative ESD for early gastric cancer is controversial [4, 5, 9]. This retrospective analysis revealed that the incidence rate of LNM in patient receiving additional gastrectomy was 14% (14/100), which is slightly higher but comparable to incidence rates previously reported by others (ranging from 6.3–12.7%) in studies on additional gastrectomy after ESD [2, 10–14].

Previous reports identified several predictive factors for LNM in cases of early gastric cancer, including a submucosal invasion, a positive lymphatic invasion, a positive vascular invasion, an undifferentiated tumor type, and a tumor size > 30 mm [14–16].

These factors are critical in determining whether to perform an additional gastrectomy with lymph node dissection in patients not meeting the curative criteria after ESD. In this study, lymphatic invasion and undifferentiated type were independent risk factors for LNM in patients not meeting the curative criteria after ESD.

Furthermore, having a vascular invasion was correlated with LNM in a univariate analysis. LNM was observed in 41.2% (7/17) of patients with both lymphatic invasion and vascular invasion and in 19.2% (5/26) of those with a lymphatic invasion but without a vascular invasion. In contrast, LNM was only observed in 3.8% (2/52) of patients who had neither a lymphatic nor vascular invasion. Of patients not meeting the curative criteria after ESD, those without both lymphatic and vascular invasions are considered to be at low risk of LNM. Therefore, both factors being positive are thought to be a markedly

high-risk factor for LNM. Neither the tumor size > 30 mm nor deeper submucosal invasion (SM2) was correlated with LNM in this study. Hatta et al [15] established the eCura scoring system to predict the risk of LNM in patients after a noncurative ESD. This system evaluates patients on 5 factors, and patients are categorized into 3 risk groups. Salvage surgery is expected to benefit those in the high-risk group, while follow-ups alone are sufficient for those in the low risk group [15]. When evaluating the eCura scores in our study, the incidence of LNM was 31.3%(10/32)in the high-risk group and 2.9% (1/34) in the low risk group (data not shown). Therefore, follow-ups without additional surgery may be sufficient not only for patients of advanced age, or those with severe comorbidities, but also for patients in whom lymphovascular invasion is absent.

In this study, local RC after an additional gastrectomy was observed in 7% (7/100) of patients. Multivariate analysis identified as an independent risk factor for local RC after ESD included having a positive horizontal margin. Our result is consistent with previous studies that reported having a positive horizontal margin is a risk factor for local RC, but a positive vertical margin is not [14, 17]. This may be explained by the weaker cautery effect in the horizontal compared to vertical direction [14, 17]. Furthermore, having an undifferentiated tumor type was not significantly related to the risk of local RC in this study. After noncurative ESD, treatment options include additional surgery and additional endoscopic procedures. Because of the low risk of LNM in cases with a positive horizontal margin and a differentiated tumor type without positive lymphatic invasion, local treatment, such as a secondary ESD, can be considered [2, 14, 18]. Confirming the utility of this approach, one of 2 patients in the observation group who had local recurrence underwent secondary ESD and is alive without recurrence.

The local recurrence rate after an en bloc resection with a negative margin by ESD has been reported to range between 0% and 0.7% [19–21]. For comparison, there were two patients in our study that had local RC observed after en bloc resection with negative margin (One patient was in the additional gastrectomy group, the other in the observation group). Both of these lesions were large tumors with lymphovascular invasion. Previous reports stated that in these cases the cancer cells might have spilled out from the vessels, accumulated within the vessels due to vascular stasis, or remained after resection because the coagulated portion of the resection margin could not be assessed accurately [14, 19].

We have found that having SM2 or a deeper invasion was not associated with the risk of LNM, but the reverse was not true: all patients with LNM had SM2 or a deeper invasion. Significantly, all three patients who experienced a recurrence after the additional gastrectomy had more than 2 LNM. There is no consensus or ideal recommendation for the extent of lymph node dissection in the additional surgery [22]. A D1 + lymph node dissection was performed as standard treatment in our study. However, D2 dissection was selected, when the lesion depth was SM2 with a positive vertical margin or when LNM was clinically suspected. In our study, all LNM instances were within the D1 + level. Therefore, performing a D1 + dissection appears reasonable after noncurative ESD for early gastric cancer.

Surgery related complications classified as CD grade Ⅲ or worse occurred in 14 patients (14%) in this study. Of those who underwent additional surgery, 1 patient (1%) died due to a probable perioperative

adverse event. During the follow-up period, 3 patients(3%)had recurrences: 1 each in the peritoneum, bone, and lymph nodes Two patients (2%) died of gastric cancer, and 6 (6%) died of other diseases. In the observation group, 1 patient (2.0%) died of gastric cancer and 10 patients (19.6%) died from other diseases. Clinicopathological characteristics of the patients did not differ significantly between the two groups. Although, age and ASA-PS were significantly higher in the observation group. Therefore, careful follow-ups without additional surgery may be acceptable for patients with differentiated type without lymphovascular invasion, those at an advanced age, or those with a severe comorbidity. On the other hand, an additional gastrectomy with a lymphadenectomy may be more appropriate than simple follow-ups in noncurative ESD patients without concomitant disease who are young enough to undergo a surgical intervention [1, 23].

This study has some limitations. First, we used the relatively small sample size from a single institute. Second, the criteria of ESD differed slightly depending on doctors who performed the treatment. Third, there was resection bias in the treatment path (gastrectomy contraindicated due to patients' old age, comorbidities, or their own decision). In addition, the average age of the observation group was significantly higher than that of the additional surgery group. To address these limitations, a prospective, multicenter, large-scale further analysis should be considered.

Conclusions

In patients not meeting the curative criteria after ESD for early gastric cancer, a positive lymphatic invasion and an undifferentiated type were independent risk factors for LNM, while a positive horizontal margin was an independent risk factor for local RC. Based on our results, we recommend an additional gastrectomy with lymph node dissection for patients with lymphovascular invasion and/or undifferentiated type after noncurative ESD. Additional surgery under these circumstances has been proven to be effective and to have good long-term outcomes. However, it may be possible to use local treatment, such as a secondary ESD, for patients with a positive horizontal margin without a lymphovascular invasion, and it may be acceptable to carefully follow-up without additional surgery for those patients who have no lymphovascular invasion, or are of an advanced age or with a severe comorbidity.

Abbreviations

ESD: Endoscopic submucosal dissection, LNM: Lymph node metastasis, RC: Residual cancer, M: Mucosal, SM: Submucosal, HM0: Negative horizontal margin, VM0: Negative vertical margin, CT: Computed tomography, CD; Clavien-Dindo, ASA-PS: American Society of Anesthesiologists physical status, IQR: Interquartile range, SSI: Surgical site infection

Declarations

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Authors' contributions

SM wrote the main manuscript. SM, YM, TT, HS and NK collected the data. TM and SO analyzed the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

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

Ethics approval and consent to participate for publication.

This study was approved by the institutional ethics committee of Kishiwada Tokushukai Hospital. Written informed consent was obtained from all patients. This study was performed in accordance with the tenets of the declaration of Helsinki.

Consent for publication

Participants gave their consent for publication.

Competing interests

The authors declare no conflicts of interest in association with the present study.

References

1. Japanese Gastric Cancer Association. Japanese gastric treatment guidelines 2010 (ver.3). Gastric Cancer. 2011;14(2):113–23.
2. Oda I, Gotoda T, Sasako M, Sano T, Katai H, Fukagawa T, Shimoda T, Emura F, Saito D. Treatment strategy after non-curative endoscopic resection of early gastric cancer. Br J Surg. 2008;95(12):1495–500.
3. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver.4). Gastric. Cancer. 2017;20(1):1–19.
4. Kusano C, Iwasaki M, Kaltenbach T, Conlin A, Oda I, Gotoda T. Should elderly patients undergo additional surgery after non-curative endoscopic resection for early gastric cancer ?Long-term

comparative outcomes. Am J Gastroenterol. 2011;106(6):1064–9.

5. Li D, Luan H, Wang S, Zhou Y. (2019) Survival benefits of additional surgery after. non-curative. endoscopic resection in patients with early gastric cancer: a meta-analysis. Surg Endosc 33(3):711–716.
6. Yamada S, Hatta W, Shimosegawa T, Takizawa K, Oyama T, Kawata N, Takahashi A, Oka S, Hoteya S, Nakagawa M, Hirano M, Esaki M, Matsuda M, Nakaya N, Gotoda T. Different risk factors between early and late cancer recurrences in patients without additional surgery after noncurative endoscopic submucosal dissection for early gastric cancer. Gastrointest Endosc. 2019;89(5):950–60.
7. Yamanouchi K, Ogata S, Sakata Y, Tsuruoka N, Shimoda R, Nakayama A, Akutagawa T, Shirai S, Takeshita E, Yamamoto K, Fujimoto K, Iwakiri R. Effect of additional surgery after noncurative endoscopic submucosal dissection for early gastric cancer. Endosc Int Open. 2016;4(1):E24–9.
8. Kawata N, Kakushima N, Takizawa K, Tanaka M, Makuuchi R, Tokunaga M, Tanizawa Y, Bando E, Kawamura T, Sugino T, Kusafuka K, Shimoda T, Nakajima T, Terashima M, Ono H. Risk factors for lymph node metastasis and long-term outcomes of patients with expanded indication early gastric cancer after non-curative endoscopic submucosal dissection. Surg Endosc. 2017;31(4):1607–16.
9. Tian YT, Ma FH, Wang GQ, Zhang YM, Dou LZ, Xie YB, Zhong YX, Chen YT, Xu Q, Zhao DB. Additional laparoscopic gastrectomy after noncurative endoscopic submucosal dissection for early gastric cancer: a single-center experience. World J Gastroenterol. 2019;25(29):3996–4006.
10. Park WY, Shin N, Kim JY, Jeon TY, Kim GH, Kim H, Park DY. Pathologic definition and number of lymphovascular emboli: impact on lymph node metastasis in endoscopically resected early gastric cancer. Hum Pathol. 2013;44(10):2132–8.
11. Ryu KW, Choi IJ, Doh YW, Kook MC, Kim CG, Park HJ, Lee JH, Lee JS, Lee JY, Kim YW, Bae JM. Surgical indication for non-curative endoscopic resection in early gastric cancer. Ann Surg Oncol. 2007;14(12):3428–34.
12. Son SY, Park JY, Ryu KW, Eom BW, Yoon HM, Cho SJ, Lee JY, Kim CG, Lee JH, Kook MC, Choi IJ, Kim YW. The risk factors for lymph node metastasis in early gastric cancer patients who underwent endoscopic resection: is the minimal lymph node dissection applicable? A retrospective study. Surg Endosc. 2013;27(9):3247–53.
13. Kim 13KimH, Park JH, Lee JC, Noh YC, Kim SH H. Lymphovascular invasion is an important predictor of lymph node metastasis in endoscopically resected early gastric cancers. Oncol Rep. 2011;25(6):1589–95
14. Toyokawa T, Ohira M, Tanaka H, Minamino H, Sakurai K, Nagami Y, Kubo N, Yamamoto A, Sano K, Muguruma K, Tominaga K, Nebiki H, Yamashita Y, Arakawa T, Hirakawa K. Optical management for patients not meeting the inclusion criteria after endoscopic submucosal dissection for gastric cancer. Surg Endosc. 2016;30(6):2404–14.
15. Hatta W, Gotoda T, Oyama T, Kawata N, Takahashi A, Yoshifuku Y, Hoteya S, Nakagawa M, Hirano M, Esaki M, Matsuda M, Ohnita K, Yamanouchi K, Yoshida M, Dohi O, Takada J, Tanaka K, Yamada S, Tsuji T, Ito H, Hayashi Y, Nakaya N, Nakamura T, Shimosegawa T. (2017) A scoring system to stratify

curability after endoscopic submucosal dissection for early gastric cancer: “eCura system” Am J Gastroenterol 112(6):874–881. DOI:10.1038/ajg.2017.95, April 11, 2017.

16. Ito H, Gotoda T, Oyama T, Kawata N, Takahashi A, Yoshifuku Y, Hoteya S, Nakagawa M, Hatta W, Hirano M, Esaki M, Matsuda M, Ohnita K, Shimoda R, Yoshida M, Dohi O, Takada J, Tanaka K, Yamada S, Tsuji T, Hayashi Y, Nakaya N, Nakamura T, Shimosegawa T. Long-term oncological outcomes of submucosal manipulation during non-curative endoscopic submucosal dissection for submucosal invasive gastric cancer: multicenter retrospective study in Japan. Surg Endosc. 2018;32(1):196–203.
17. 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.
18. Ozawa 18NiwaH, Kurahashi R, Kumamoto Y, Nakanishi T, Okumura Y, Matsuda K, Ishida I, Hirota Y, Shinohara S H. The eCura system as a novel indicator for the necessity of salvage surgery after non-curative ESD for gastric cancer: A case -control study. PLoS ONE. 2018;13(10):0204039. i: 10. 137/ journal, pone,0204039, Oct 1, 2018) (:, do.
19. Park JC, Lee SK, Seo JH, Kim YJ, Chung H, Shin SK, Lee YC. Predictive factors for local recurrence after endoscopic resection for early gastric cancer: long-term clinical outcome in a single-center experience. Surg Endosc. 2010;24(11):2842–9.
20. Isomoto H, Shikuwa S, Yamaguchi N, Fukuda E, Ikeda K, Nishiyama H, Ohnita K, Mizuta Y, Shiozawa J, Kohno S. Endoscopic submucosal dissection for early gastric cancer: a large-scale feasibility study. Gut. 2009;58(3):331–6.
21. Lee H, Yun WK, Min BH, Lee JH, Rhee PL, Kim KM, Rhee JC, Kim JJ. A feasibility study on the expanded indication for endoscopic submucosal dissection of early gastric cancer. Surg Endosc. 2011;25(6):1985–93.
22. 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.
23. Suzuki H, Oda I, Abe S, Sekiguchi M, Nonaka S, Yoshinaga S, Saito Y, Fukagawa T, Katai H. Clinical outcomes of early gastric cancer patients after noncurative endoscopic submucosal dissection in a large consecutive patient series. Gastric Cancer. 2017;20(4):679–89.

Tables

Tables 1 to 7 are available in the Supplementary Files section

Figures

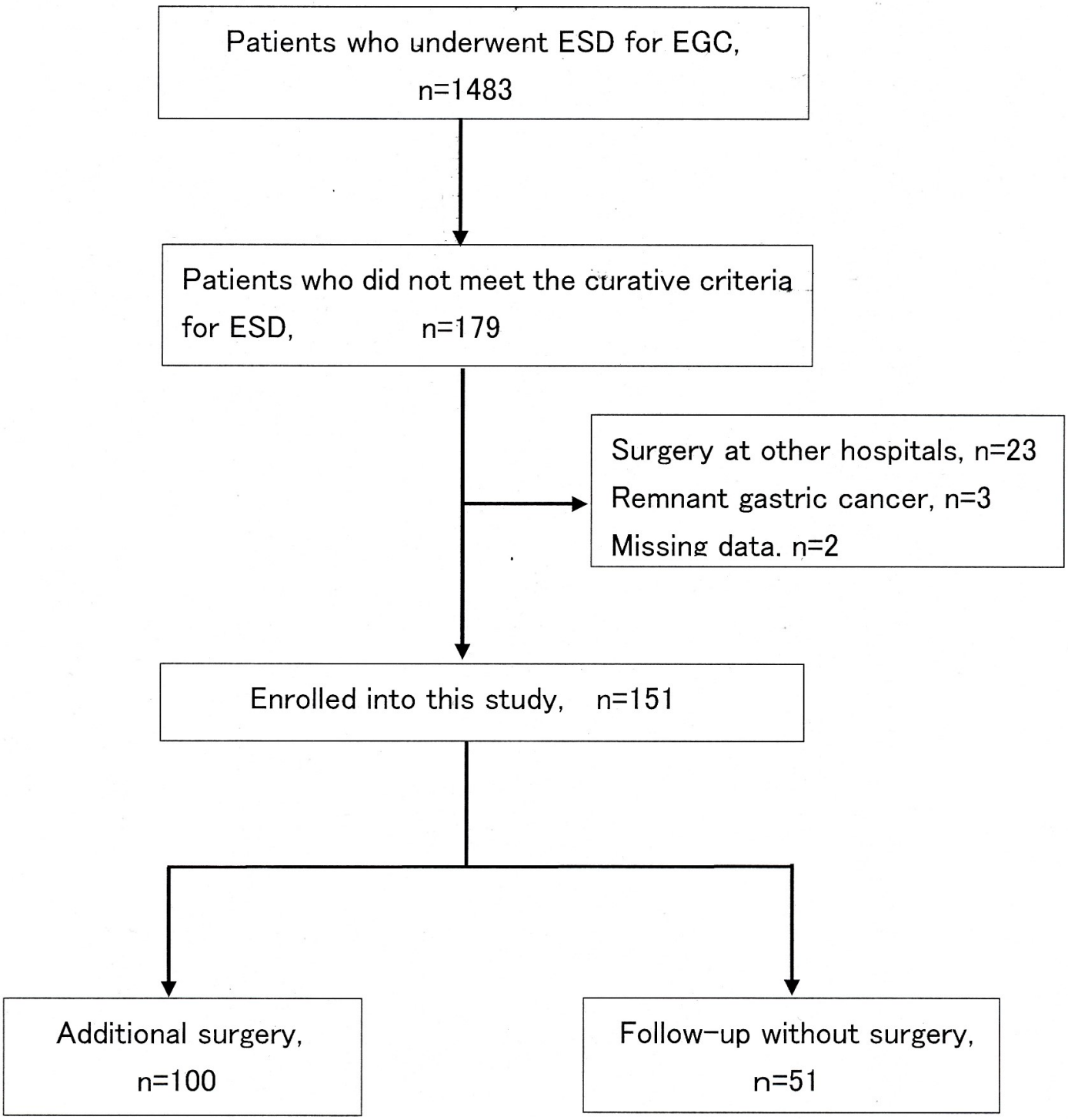

Figure 1

Flowchart of treatment strategy for patients with early gastric cancer (EGC) undergoing noncurative endoscopic submucosal dissection (ESD) .

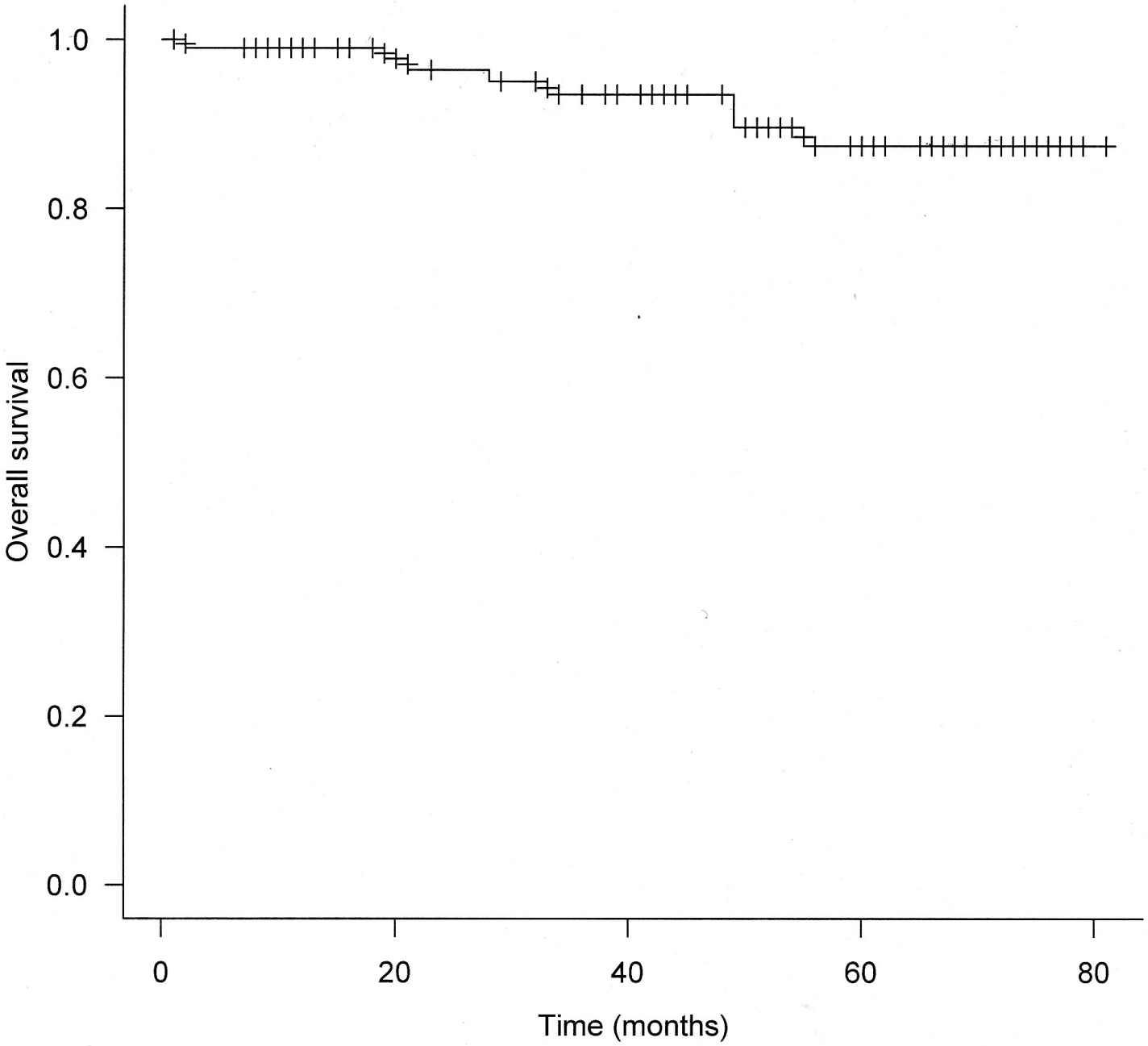

Figure 2

Kaplan-Meier analysis of overall survival rate after additional gastrectomy

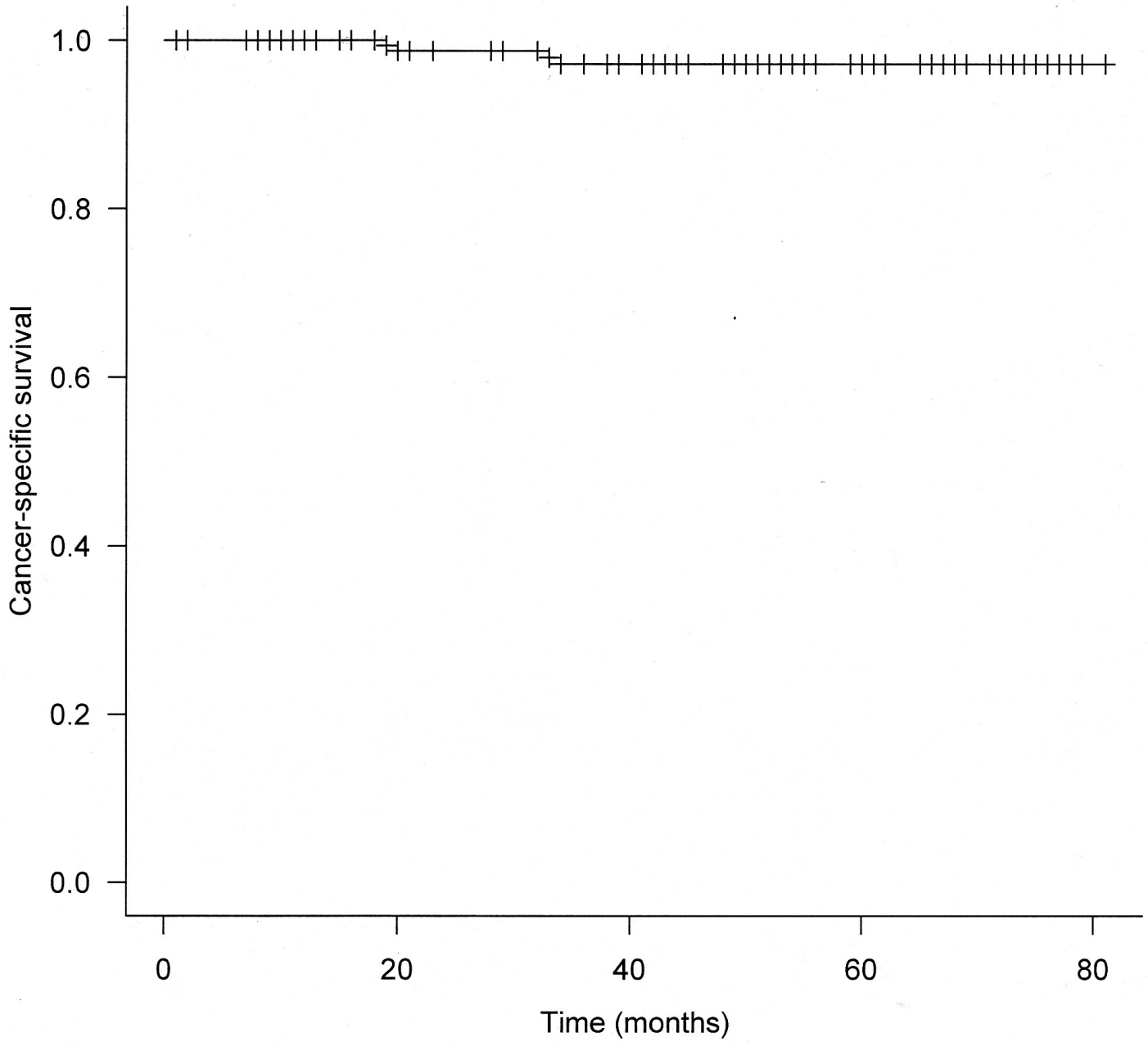

Figure 3

Kaplan-Meier analysis of cancer-specific survival rate after additional gastrectomy

Supplementary Files

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- Table17.docx