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Original article

Clinical outcome of endoscopic resection for nonampullary duodenal tumors

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Short title: Outcome of endoscopic resection for duodenal tumors

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In brief

This large case series included 113 patients with 121 nonampullary tumors who were treated with endoscopic resection. Delayed bleeding occurred in 12% of patients. Long-term follow-up after a median of 51 months showed that even piecemeal resection is oncologically safe.

Background and study aims: Compared with any other location in the gastrointestinal tract, the duodenum presents the most challenging site for endoscopic resection. The aim of this study was to analyze the clinical outcomes of duodenal endoscopic resection and to assess the feasibility of the technique as a therapeutic procedure.

Patients and methods: A total of 113 consecutive patients with 121 nonampullary duodenal tumors underwent endoscopic resection by endoscopic submucosal dissection (ESD), endoscopic mucosal resection (EMR), or polypectomy between January 2000 and September 2013. Long-term outcomes were investigated in patients with more than 1 year follow-up.

Results: The median tumor size was 12 mm (range 3–50 mm). Lesions consisted of 63 adenocarcinomas/high-grade intraepithelial neoplasias (53%) and 57 adenomas/low-grade intraepithelial neoplasias (48%). Endoscopic resection included 106 EMRs (87%), 8 ESDs (7%), and 7 polypectomies (6%). En bloc resection was achieved in 77 lesions (64%), and 43 lesions (35%) underwent piecemeal resection; one procedure was discontinued due to perforation. There were 14 cases of delayed bleeding after EMR (12%), 1 perforation (1%) during ESD, and 1 delayed perforation (1%) after ESD, which required emergency surgery. Of the 76 patients who were followed for more than 1 year, none of the patients died from a primary duodenal neoplasm, and there were no local recurrences during the 51-month median follow-up period (range 12–163 months).

Conclusions: Duodenal endoscopic resection was feasible as a therapeutic procedure, but it should only be performed by highly skilled endoscopists because of its technical difficulty. Piecemeal resection by EMR is acceptable for small lesions, based on these excellent long-term outcomes.

Introduction

The duodenum represents the most challenging and difficult site for endoscopic resection compared with other areas of the gastrointestinal tract. This is due to anatomical features, which include: a narrow lumen; a precipitous flexure that causes poor stability of the endoscope; Brunner's glands in the submucosal layer that stiffen the duodenal wall, resulting in poor mucosal lifting; a thin muscle layer that results in a higher incidence of perforation and increased risk of other complications such as delayed bleeding and delayed perforation; and difficult access if emergency surgery becomes necessary [1–3].

Endoscopic submucosal dissection (ESD) is regularly performed at expert centers in Japan for superficial lesions of the esophagus, stomach, and colorectum. ESD achieves a higher proportion of en bloc resection, which enables accurate histopathological assessment. It is our current position, however, to refrain from aggressively performing duodenal ESD because the procedure is exceptionally difficult technically, and the procedure is associated with the highest incidence of perforation, with serious consequences, compared with other sites in the gastrointestinal tract [4–6]. Meanwhile, endoscopic mucosal resection (EMR) is a safer, easier, and quicker procedure compared with ESD; however, EMR results in fewer en bloc resections [7–13]. Although there is still controversy as to which endoscopic resection method is preferable, EMR is currently recognized as the standard procedure for endoscopic treatment of nonampullary duodenal tumors.

Duodenal tumors such as primary duodenal adenocarcinoma and duodenal adenoma are rare compared with other gastrointestinal tract cancers, and consequently there are currently no established indications for endoscopic resection, the necessity of en bloc resection is controversial due to the procedural risks in this region, and there is no

definition of early cancer or pathological criteria for curative endoscopic resection [14,15]. Duodenal lesions that require endoscopic resection are so limited in number that although several reports have been published, most involve only a small number of patients [1–3,5,6,8–13]. Consequently, there are a number of issues that need to be addressed in the future. The aim of this study was to analyze the clinical outcomes of endoscopic resection for nonampullary duodenal tumors and to assess the feasibility of endoscopic resection as a therapeutic procedure.

Patients and methods

The study involved the retrospective analysis of duodenal endoscopic resection procedures that were performed between January 2000 and September 2013 at the National Cancer Center Hospital in Tokyo, Japan. Carcinoid tumors and ampullary duodenal tumors were excluded from the study. The institutional review board of the hospital approved the study, and informed consent was obtained from all patients in accordance with the institutional protocol.

Endoscopic resection included ESD, EMR, and polypectomy [16,17]. EMR was performed using either the “injection and snaring” method or the two-channel strip biopsy method. ESD also involved snaring following a circumferential incision [18–20]. No EMR procedures used a cap-fitted panendoscope or ligation.

The study measurements were divided into short-term and long-term outcomes. Short-term outcomes for all patients included patient characteristics, endoscopic findings, treatment methods, pathological findings, and complications. Histopathological diagnosis was divided into adenoma/low-grade intraepithelial neoplasia (LGIN), intramucosal adenocarcinoma/high-grade intraepithelial neoplasia (HGIN), and submucosal adenocarcinoma. Delayed bleeding was defined clinically by the

development of hematemesis or melena that required additional endoscopic treatment. Delayed perforation was defined by free air on radiograph or computed tomography examination and indicated by sudden severe abdominal pain in patients without apparent intraoperative perforation. Long-term outcomes included rates of disease-specific survival and local recurrence in patients who were followed up for more than 1 year. Local recurrence was defined as the identification of a tumor located on or adjacent to the scar of previous endoscopic resection.

Baseline and outcome data were collected from electronic medical records and prospectively collected in a computerized database. Pathological information was subsequently added after confirmation of endoscopic resection results. Incomplete and missing data for long-term outcomes were retrieved from various sources such as telephone contact or correspondence with patients, families, and referring physicians, and then checked against statistical data kept by the local government agency registries in December 2013.

Endoscopic procedures

Treatment strategies were determined during weekly conferences in the Endoscopy Division, in order to decide on the appropriate endoscopic resection method (i.e. EMR, ESD, or polypectomy). The basic hospital policy for endoscopic resection of duodenal tumors is to resect all biopsy-confirmed adenocarcinomas and adenomas of >10 mm in size. Adenomas of ≤ 10 mm in size are either followed closely or resected if this is the patient wish.

All endoscopic resection procedures were performed by highly skilled endoscopists using standard forward-viewing video endoscopes and/or a two-channel endoscope (Olympus Medical Systems Co., Ltd., Tokyo, Japan), and an electrosurgical generator

(ICC200; ERBE Elektromedizin, Tübingen, Germany). Patients received midazolam and/or propofol combined with pentazocine for deep sedation, and oxygen was administered nasally (2 L/minute) during each procedure. When performing EMR, injection solutions such as diluted epinephrine with normal saline (1:200 000) or a 10% glycerin plus 5% fructose and 0.9% saline preparation (Glyceol; Chugai Pharmaceutical Co., Ltd., Tokyo, Japan), together with a minute amount of indigo carmine dye, were used to produce a soft elevation that made snaring easier [21–24]. Three sizes of oval electrosurgical snares were used (SnareMaster: 10 mm, 15 mm, and 25 mm diameter; Olympus), and en bloc resections were attempted subject to the morphology and location of each lesion. If an en bloc resection could not be achieved, additional resection using a snare was performed to remove the residual portion of the lesion (**Fig. 1**). Additional coagulation using either hot-biopsy forceps (Boston Scientific Japan Co., Tokyo, Japan) or argon plasma coagulation (APC; ERBE) was sometimes performed to reduce the risk of any residual tumor, based on the judgment of the endoscopist when the residual portion was too small to remove using the snare [7,8,25].

When performing the “injection and snaring” method of EMR, injection into the submucosal layer underneath the lesion was initially performed to obtain sufficient elevation, and then snaring was conducted in the standard manner. When performing strip biopsy as part of the EMR procedure, the two-channel endoscope was used, with grasping forceps inserted into the right channel and the snare inserted into the left channel. Submucosal injection was performed in the same manner as standard EMR, and the grasping forceps were used to pull the lesion, which was then resected using the snare [18,19].

When performing ESD in the duodenum, sodium hyaluronate (MucoUp; Johnson & Johnson K.K., Tokyo, Japan) diluted with normal saline (1:1) or Glyceol was used to obtain a higher and longer-lasting elevation, and a transparent hood was attached to the top of the endoscope to obtain a better view for submucosal dissection (**Fig. 2**) [22,26,27]. First, marking dots were made around the lesion using a needle-knife (Olympus) or APC followed by injection to lift the submucosal layer. Next, a small initial incision was made using the needle-knife, and a circumferential mucosal incision around the periphery of the marking dots was performed with an insulation-tipped diathermic knife (IT-knife). After additional submucosal injection, the submucosal layer beneath the lesion was directly dissected using the IT-knife [16,28,29]. Although all ESDs were generally performed in this manner, some lesions were resected en bloc by using a snare as a result of technical difficulties during the procedure. The decision to use a snare following circumferential incision, a procedure that is easier and quicker to perform than standard ESD, was made by the performing endoscopist [20].

Polypectomies were performed for protruded lesions showing pedunculated morphology (e.g. 0-Ip).

Prophylactic clipping to reduce the risk of delayed bleeding and delayed perforation was always performed if technically possible, depending on the location, size, and endoscope stability [1,4,8,11]. Follow-up endoscopy was performed within 6 months following treatment, and every 6 months or annually thereafter.

Statistical analysis

All variables were described in terms of mean (\pm SD), or median and range. The chi-squared test and Fisher's exact test were used to compare baseline characteristics and

measurements. All statistical analyses were performed using statistical analysis software (SPSS, version 20; SPSS Japan Inc., Tokyo, Japan), and a *P* value of <0.05 was considered to be statistically significant.

Results

Patient characteristics

A total of 121 lesions in 113 consecutive patients were included in the study (80 males, 33 females; mean age 61.7 ± 11.9 years) (**Table 1**). Nine patients had familial adenomatous polyposis. The 121 lesions were diagnosed by biopsy as 61 adenocarcinomas/HGINs (50%) and 60 adenomas/LGINs (50%), and were located in the following regions: 20 in the first part of the duodenum (17%), 92 in the second part (76%), and 6 in the third part (5%), and 3 were located on the anal side of the anastomosis (2%) following prior distal gastrectomy with Billroth I reconstruction. The macroscopic types were 90 elevated (74%), 20 depressed (17%), and 11 combined (9%).

Endoscopic treatments and complications

Endoscopic resection was in the form of 106 EMRs (87%) including 87 “injection and snaring” (72%) and 19 strip biopsies (16%), eight ESDs (7%) that included four snarings with circumferential incision, and seven polypectomies (6%) (**Table 2**). En bloc resection was achieved successfully in 77 lesions (64%), and 43 lesions (35%) were resected in a piecemeal fashion including 22 lesions (18%) with more than three resection specimens (**Fig. 3**). One case of intraoperative perforation led to discontinuation of the ESD procedure before a resection specimen had been obtained. A total of 29 lesions (24%) underwent additional coagulation using either hot biopsy

or APC to reduce the risk of residual tumor. Immediate closure following endoscopic resection was performed in 99 lesions (82%) by means of prophylactic clipping.

There was one perforation (1%) during ESD and one delayed perforation (1%) following ESD, which required emergency surgery (**Table 3, Fig. 3**). The intraoperative perforation case involved a 45-mm intramucosal adenocarcinoma/HGIN located in the first part of the duodenum. The perforation could be treated conservatively after closure using endoclips, although the patient subsequently underwent surgery for curative purposes because the lesion had not been completely resected at the time of the perforation. The delayed perforation occurred in the case of a 14-mm adenoma/LGIN in the first part of the duodenum. An ESD procedure by snaring with circumferential incision was successfully completed without prophylactic clipping, but the patient experienced severe abdominal pain the next day, which resulted in emergency surgery being required to close the delayed perforation.

Delayed bleeding was observed in 14 EMR cases (12%; 14/121) involving 12 in the second part (13%; 12/92) and two in the third part (33%; 2/6) of the duodenum, although only one patient received a blood transfusion (**Table 3**). Bleeding in all 14 cases could be successfully controlled endoscopically. In cases involving prophylactic clipping, the delayed bleeding rate was 7% (7/99) compared with 32% (7/22) in cases without prophylactic clipping, and there was a significant difference between the two groups ($P < 0.004$).

Histopathological results

The ESD lesion that was subsequently resected by surgery due to intraoperative perforation was not included in the histopathological results. The median tumor size

as determined by histopathology was 12 mm (range 3–50 mm). There were 57 duodenal adenomas/LGINs, 60 intramucosal adenocarcinomas/HGINs, and 3 submucosal adenocarcinomas (**Table 4**). The accuracy of biopsy diagnosis was 71.1% (86/121), and the positive predictive value of biopsy for adenocarcinoma/HGIN and adenoma/LGIN was 75.4% (46/61) and 70.0% (42/60), respectively. The horizontal margin was estimated as being negative in 47 (39%), positive in 9 (8%), and inconclusive in 64 lesions (53%). The vertical margin was estimated to be negative in 115 (96%), positive in 1 (1%), and inconclusive in 4 lesions (3%). There were no instances of lymphatic and/or venous invasion in this study.

Lesion characteristics and treatment results of EMR and ESD

EMR was most frequently performed in the second part of the duodenum (80%; 90/113) whereas ESD was mainly performed in the first part of the duodenum (75%; 6/8). The median tumor size of the EMR and ESD groups was 12 mm and 18 mm, respectively, and 99 lesions (88%) in the EMR group and 4 lesions (50%) in the ESD group measured ≤ 20 mm (**Table 5**). Although en bloc resection was achieved in 71 lesions (63%) by EMR and 6 lesions (75%) by ESD, only 3 lesions (21%; 3/14) of >20 mm in size could be removed en bloc using EMR. In addition, the proportion of R0 resection was 34% (38/113) by EMR and 50% (4/8) by ESD (**Fig. 3**). No EMR patients experienced perforation, but delayed bleeding was observed in 12% (14/113), whereas there were two cases of perforation in the ESD group. The final diagnosis of histopathology revealed intramucosal adenocarcinoma/HGIN and submucosal adenocarcinoma for 58 lesions (51%) in the EMR group and for 5 lesions (63%) in the ESD group, respectively.

Long-term outcomes

All patients were followed up without requiring additional surgery, with the exception of the two ESD cases involving a perforation. Among the 113 study patients, 31 patients were followed for less than 1 year after undergoing duodenal endoscopic resection and 6 were lost in follow-up after 1 year and were excluded from the analysis of long-term outcomes. Among the 76 patients who were followed for more than 1 year, 3 died and 73 patients survived. None of the patients died from a primary duodenal tumor, resulting in a disease-specific survival rate of 100% (**Table 6**). One patient with familial adenomatous polyposis followed at our institution died from recurrence of primary colorectal cancer with multiple liver and lymph node metastases. Two other patients who were followed at other institutions died at 86 and 40 months, respectively, after endoscopic resection; however the causes of death were unknown. In addition, there were no local recurrences among the 76 patients during the 51-month median follow-up period (range 12–163 months).

Discussion

This study included the largest number of patients undergoing endoscopic resection for nonampullary duodenal tumors compared with previously published reports. The results suggest that prognoses are excellent, without any deaths caused by primary duodenal tumors. No local recurrence occurred, despite the fact that one-third of the patients underwent piecemeal EMR. Duodenal endoscopic resection is a difficult, but feasible therapeutic procedure, which can be performed safely, as only one ESD patient with delayed perforation and no EMR patient required emergency surgery.

En bloc resection was achieved in 64%, piecemeal resection in 35%, with R0 resection in 35%. Due to the risks associated with ESD, operators chose EMR including polypectomy in 93% of lesions, even for lesions >20 mm (**Table 2, Table**

5). Considering the importance of en bloc resection, this low proportion is obviously unsatisfactory; however, this was influenced by a desire to minimize the mucosal defect due to concerns about perforation or bleeding, and to allow for prophylactic clipping. Fortunately, there were no local recurrences and no deaths from primary duodenal tumor even after a median follow-up of 51 months. The median tumor size of 12 mm in this series was smaller than the approximately 3 cm in previous Western studies. The higher incidence of local recurrence (21%–25%) observed with larger lesions that were resected en bloc by EMR (EMR en bloc rate 10.5%–48.8%) is therefore understandable [8–10]. In addition, other studies have reported the incidence of local recurrence to be between 5.8% and 8.3% in cases using EMR (en bloc 69.2%–82%, R0 30%–59%) for lesions of approximately 10 mm in size [13,30,31], and no local recurrence following ESD (en bloc 85.7%–100%, R0 78.6%–90%) [5,6,30,31]. However, several reports have suggested the same good prognosis during a median follow-up of 12–71 months despite higher incidences (8%–37%) of local recurrence after piecemeal EMR for larger lesions [7–10,13].

The indications for EMR and ESD are not well established, and the final decision depends on endoscopist preference. There also are many differences between institutions in the choice of endoscopic treatment methods. Nevertheless, our current position is to refrain from aggressively performing duodenal ESD. In fact, the incidence of complications with duodenal ESD has been reported to be 6.6%–31.6% for intraoperative perforation, 0–14.3% for delayed perforation, and 0–18.4% for delayed bleeding [5,6,30,31]. Furthermore, emergency surgery was performed in 3.3%–14.3% of ESD patients in this technically difficult and dangerous situation. It is preferable, of course, to resect such lesions en bloc using ESD, but performing duodenal ESD is exceptionally difficult technically, with a higher incidence of

complications at the present time. In contrast, EMR is recognized as a safer, easier, and quicker procedure, with a lower risk of intraoperative perforation (0–2.7%), delayed perforation (0–2.0%), and emergency surgery (2.7%–4.0%) [7–11,13]. In the current study, prognosis was excellent, and therefore it is acceptable to perform EMR including piecemeal resection, particularly for small lesions of ≤ 20 mm in size, when considering each patient's specific situation. In certain cases, we believe that the risks associated with ESD are greater than the benefits of en bloc resection.

In the current study, intraoperative and delayed perforation occurred in 2% and delayed bleeding occurred in 12%, but 82% of the cases underwent prophylactic clipping because we believe it to be useful in reducing such complications by protecting the mucosal defect against exposure to pancreatic juice and bile [1,2,8,11,13]. Larger series of cases would be required to precisely determine the effect of prophylactic clipping; however, 7% (7/99) of delayed bleeding cases had undergone prophylactic clipping compared with 32% (7/22) that had not undergone prophylactic clipping ($P < 0.004$). Yamamoto et al. also reported the absence of bleeding after prophylactic clipping in duodenal endoscopic resection [30]. We continue to support the use of prophylactic clipping whenever possible depending on the technical difficulty associated with location, size, or scope instability [4,11,13].

In cases of perforation, the situation becomes more complicated, as it is sometimes very difficult to achieve closure using endoclips or a loop-snare technique [32]. Carbon dioxide insufflation should be used in duodenal endoscopic resection to reduce the distention of the gastrointestinal lumen, pneumoperitoneum, pneumoretroperitoneum, and other potentially serious conditions [33]. Particularly in cases of delayed perforation, emergency surgery is usually required immediately because of the highest severity of adverse events, including sepsis and death,

compared with other digestive tract sites [4–6,31]. The high incidence of delayed perforation is the most important issue that should be addressed in the future.

It is well known that there are many differences in histopathological diagnosis between Japan and Western countries. Differences have been elucidated in other areas of the gastrointestinal tract recently; however this has not yet been clarified for duodenal lesions. In the current study, three categories of lesions were included (i.e. adenoma/LGIN, intramucosal adenocarcinoma/HGIN, and submucosal adenocarcinoma), to ensure consistency of the histopathological diagnosis by board-certificated pathologists of the Japanese Society of Pathology. The diagnostic criteria between East and West do not correspond completely; however, we believe these criteria to be acceptable in both settings.

There were several limitations to this study. It was a retrospective, single-center study, and some patients were lost to follow-up at other institutions. In addition, some recent patients were observed for less than 1 year after duodenal endoscopic resection.

In conclusion, duodenal endoscopic resection was feasible as a therapeutic procedure, but it should only be performed by highly skilled endoscopists because of its technical difficulty and higher incidence of complications. Endoscopists must be particularly concerned about perforations, including the possibility of delayed perforation. We believe that the risks of performing an en bloc resection by ESD are greater than the benefits in some cases, and it is therefore acceptable to perform a piecemeal resection by EMR for small lesions based on the excellent prognosis identified in this study.

Competing interests: None.

References

- 1 Endo M, Abiko Y, Oana S et al. Usefulness of endoscopic treatment for duodenal adenoma. *Dig Endosc* 2010; 22: 360–365
- 2 Honda T, Yamamoto H, Osawa H et al. Endoscopic submucosal dissection for superficial duodenal neoplasms. *Dig Endosc* 2009; 21: 270–274
- 3 Oka S, Tanaka S, Nagata S et al. Clinicopathologic features and endoscopic resection of early primary nonampullary duodenal carcinoma. *J Clin Gastroenterol* 2003; 37: 381–386
- 4 Inoue T, Uedo N, Yamashina T et al. Delayed perforation: a hazardous complication of endoscopic resection for non-ampullary duodenal neoplasm. *Dig Endosc* 2014; 26: 220–227
- 5 Jung JH, Choi KD, Ahn JY et al. Endoscopic submucosal dissection for sessile, nonampullary duodenal adenomas. *Endoscopy* 2013; 45: 133–135
- 6 Matsumoto S, Miyatani H, Yoshida Y. Endoscopic submucosal dissection for duodenal tumors: a single-center experience. *Endoscopy* 2012; 45: 136–137
- 7 Abbass R, Rigaux J, Al-Kawas FH. Nonampullary duodenal polyps: characteristics and endoscopic management. *Gastrointest Endosc* 2010; 71: 754–759
- 8 Alexander S, Bourke MJ, Williams SJ et al. EMR of large, sessile, sporadic nonampullary duodenal adenomas: technical aspects and long-term outcome (with videos). *Gastrointest Endosc* 2009; 69: 66–73

- 9 Apel D, Jakobs R, Spiethoff A et al. Follow-up after endoscopic snare resection of duodenal adenomas. *Endoscopy* 2005; 37: 444–448
- 10 Fanning SB, Bourke MJ, Williams SJ et al. Giant laterally spreading tumors of the duodenum: endoscopic resection outcomes, limitations, and caveats. *Gastrointest Endosc* 2012; 75: 805–812
- 11 Lepilliez V, Chemaly M, Ponchon T et al. Endoscopic resection of sporadic duodenal adenomas: an efficient technique with a substantial risk of delayed bleeding. *Endoscopy* 2008; 40: 806–810
- 12 Sohn JW, Jeon SW, Cho CM et al. Endoscopic resection of duodenal neoplasms: a single-center study. *Surg Endosc* 2010; 24: 3195–3200
- 13 Maruoka D, Arai M, Kishimoto T et al. Clinical outcomes of endoscopic resection for nonampullary duodenal high-grade dysplasia and intramucosal carcinoma. *Endoscopy* 2013; 45: 138–141
- 14 Cortese AF, Cornell GN. Carcinoma of the duodenum. *Cancer* 1972; 29: 1010–1015
- 15 Jepsen JM, Persson M, Jakobsen NO et al. Prospective study of prevalence and endoscopic and histopathologic characteristics of duodenal polyps in patients submitted to upper endoscopy. *Scand J Gastroenterol* 1994; 29: 483–487
- 16 Gotoda T. Endoscopic resection of early gastric cancer. *Gastric Cancer* 2007; 10: 1–11
- 17 Oda I, Saito D, Tada M et al. A multicenter retrospective study of endoscopic resection for early gastric cancer. *Gastric Cancer* 2006; 9: 262–270

- 18 Obata S, Suenaga M, Araki K et al. Use of strip biopsy in a case of early duodenal cancer. *Endoscopy* 1992; 24: 232–234
- 19 Tada M, Murakami A, Karita M et al. Endoscopic resection of early gastric cancer. *Endoscopy* 1993; 25: 445–450
- 20 Sakamoto T, Matsuda T, Nakajima T et al. Efficacy of endoscopic mucosal resection with circumferential incision for patients with large colorectal tumors. *Clin Gastroenterol Hepatol* 2011; 10: 22–26
- 21 Fujishiro M, Kodashima S, Goto O et al. Endoscopic submucosal dissection for esophageal squamous cell neoplasms. *Dig Endosc* 2009; 21: 109–115
- 22 Fujishiro M, Yahagi N, Kashimura K et al. Different mixtures of sodium hyaluronate and their ability to create submucosal fluid cushions for endoscopic mucosal resection. *Endoscopy* 2004; 36: 584–589
- 23 Fujishiro M, Yahagi N, Nakamura M et al. Successful outcomes of a novel endoscopic treatment for GI tumors: endoscopic submucosal dissection with a mixture of high-molecular-weight hyaluronic acid, glycerin, and sugar. *Gastrointest Endosc* 2006; 63: 243–249
- 24 Saito Y, Uraoka T, Matsuda T et al. Endoscopic treatment of large superficial colorectal tumors: a case series of 200 endoscopic submucosal dissections (with video). *Gastrointest Endosc* 2007; 66: 966–973
- 25 Kedia P, Brensinger C, Ginsberg G. Endoscopic predictors of successful endoluminal eradication in sporadic duodenal adenomas and its acute complications. *Gastrointest Endosc* 2010; 72: 1297–1301

- 26 Fujishiro M, Yahagi N, Kashimura K et al. Comparison of various submucosal injection solutions for maintaining mucosal elevation during endoscopic mucosal resection. *Endoscopy* 2004; 36: 579–583
- 27 Yamamoto H, Yahagi N, Oyama T et al. Usefulness and safety of 0.4% sodium hyaluronate solution as a submucosal fluid “cushion” in endoscopic resection for gastric neoplasms: a prospective multicenter trial. *Gastrointest Endosc* 2008; 67: 830–839
- 28 Gotoda T, Kondo H, Ono H et al. A new endoscopic mucosal resection procedure using an insulation-tipped electrosurgical knife for rectal flat lesions: report of two cases. *Gastrointest Endosc* 1999; 50: 560–563
- 29 Ono H, Kondo H, Gotoda T et al. Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 2001; 48: 225–229
- 30 Yamamoto Y, Yoshizawa N, Tomida H et al. Therapeutic outcomes of endoscopic resection for superficial non-ampullary duodenal tumor. *Dig Endosc* 2014; 26: 50–56
- 31 Hoteya S, Yahagi N, Iizuka T et al. Endoscopic submucosal dissection for nonampullary large superficial adenocarcinoma/adenoma of the duodenum: feasibility and long-term outcomes. *Endoscopy International Open* 2013; 1: E2–7
- 32 Matsuda T, Fujii T, Emura F et al. Complete closure of a large defect after EMR of a lateral spreading colorectal tumor when using a two-channel colonoscope. *Gastrointest Endosc* 2004; 60: 836–838

- 33 Nonaka S, Saito Y, Takisawa H et al. Safety of carbon dioxide insufflation for upper gastrointestinal tract endoscopic treatment of patients under deep sedation. *Surg Endosc* 2010; 24: 1638–1645

Fig. 1 Irregular elevated lesion, 25 mm in size, located in the second part of the duodenum and resected by piecemeal endoscopic mucosal resection (EMR). **a** White-light image. **b** Chromoendoscopic image using indigo carmine dye. **c** Piecemeal EMR. **d** EMR ulceration. **e** Prophylactic clipping. **f** Three specimen fragments removed by piecemeal resection.

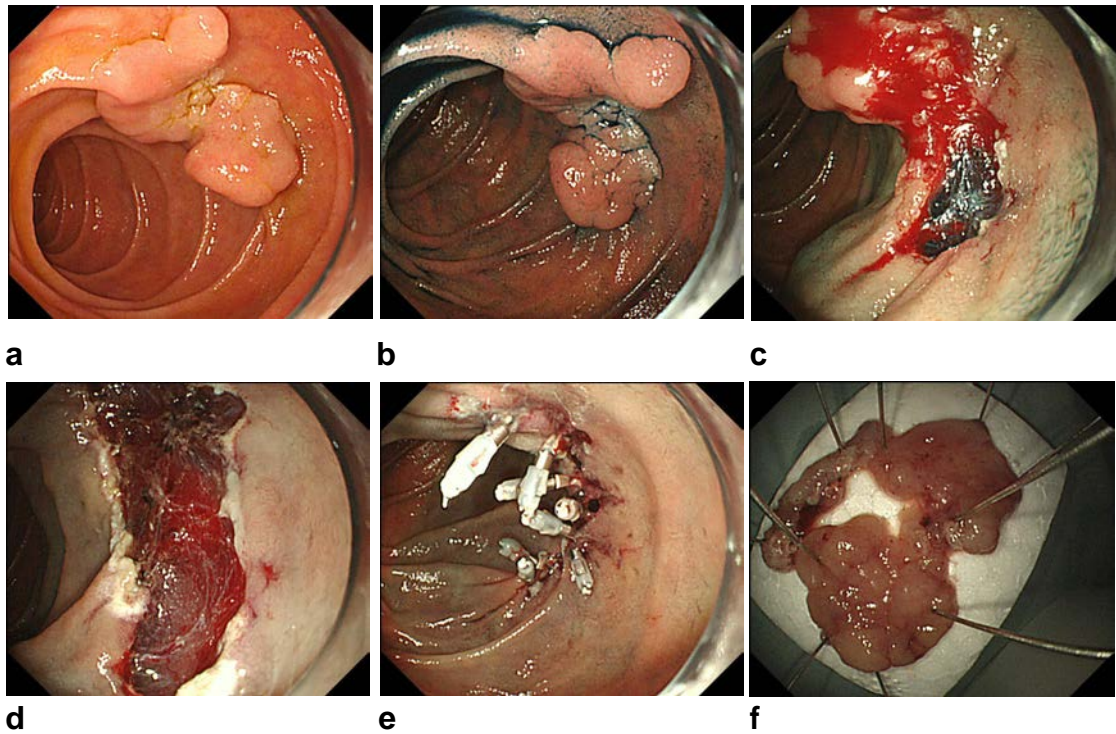
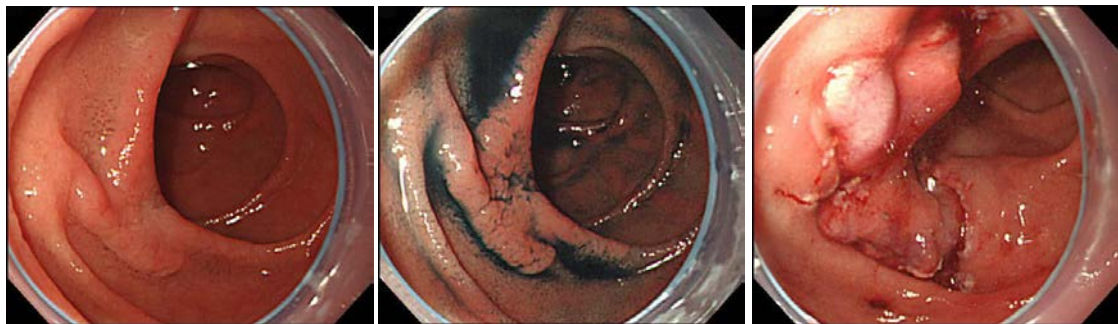


Fig. 2 Elevated lesion, 25 mm in size, located in the second part of the duodenum and resected by endoscopic submucosal dissection (ESD).

a White-light image. **b** Chromoendoscopic image using indigo carmine dye.

c Circumferential incision. **d** Submucosal dissection. **e** ESD ulceration.

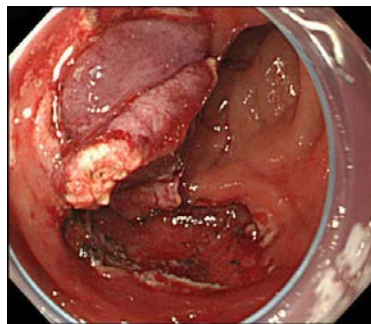
f Prophylactic clipping. **g** En bloc resected specimen.



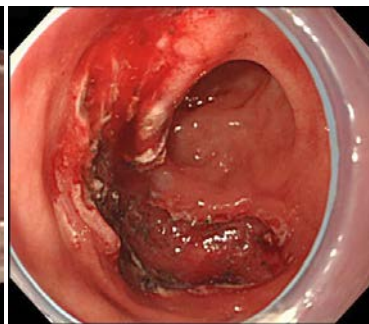
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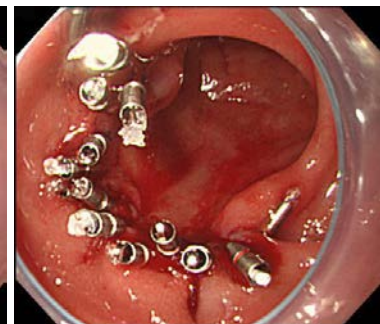
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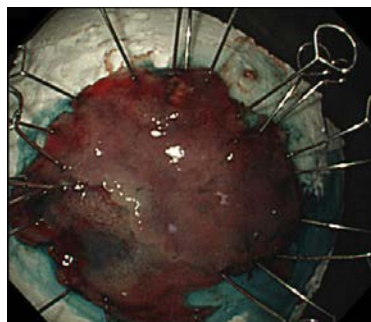
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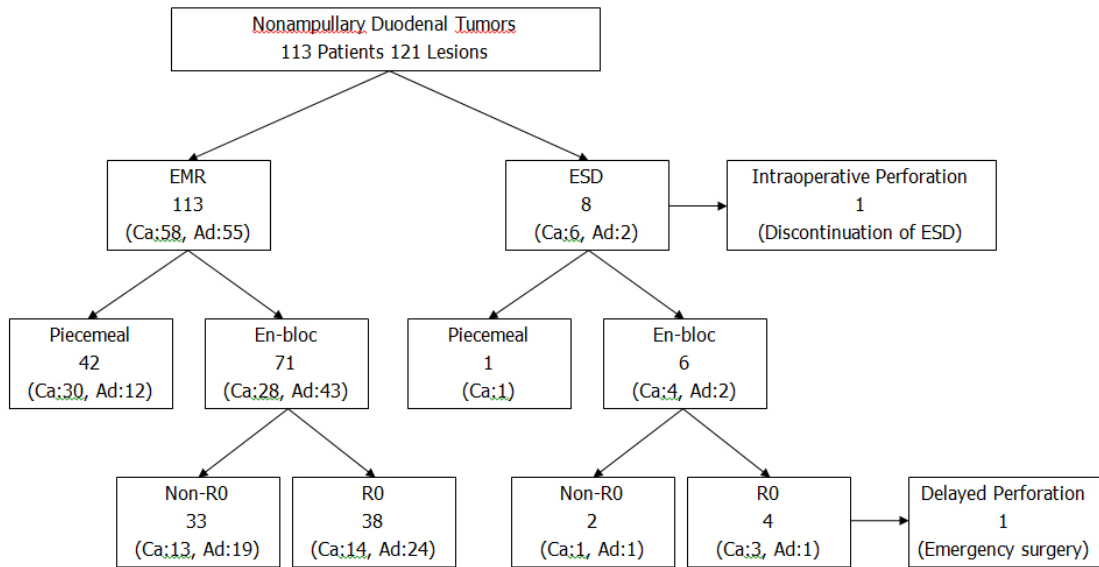


f



g

Fig. 3 The study flow diagram based on the results of endoscopic resections. EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; Ca, intramucosal adenocarcinoma/high-grade intraepithelial neoplasia and submucosal adenocarcinoma; Ad, adenoma/low-grade intraepithelial neoplasia; R0, en bloc resection with tumor-free margins histopathologically.



EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; Ca, intramucosal adenocarcinoma/high grade intraepithelial neoplasia and submucosal adenocarcinoma; Ad, adenoma/low grade intraepithelial neoplasia; R0, En-bloc resection with tumor-free margins histopathologically.

Table 1 Patient characteristics.

Patients	
Number	113
Age, mean \pm SD, years	61.7 \pm 11.9
Sex, n (%)	
Male	80 (71)
Female	33 (29)
Familial adenomatous polyposis, n (%)	9 (8)
 Lesions	
Number	121
Biopsy diagnosis, n (%)	
Adenocarcinoma/HGIN	61 (50)
Adenoma/LGIN	60 (50)
Location in duodenum, n (%)	
First part	20 (17)
Second part	92 (76)
Third part	6 (5)
Anastomosis	3 (2)
Macroscopic type, n (%)	
Elevated	90 (74)
Depressed	20 (17)
Combined	11 (9)

HGIN, high-grade intraepithelial neoplasia; LGIN, low-grade intraepithelial neoplasia.

Table 2 Endoscopic treatments in 121 lesions.

	Lesions, n (%)
Treatment methods	
EMR*	106 (87)
ESD [†]	8 (7)
Polypectomy	7 (6)
Results of resection	
En bloc	77 (64)
Piecemeal	43 (35)
Number of piecemeal specimen fragments	
2	21 (17)
≥3	22 (18)
Discontinuation of treatment	1 (1)
Additional coagulation [‡]	29 (24)
Prophylactic clipping	99 (82)

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

*Including 19 strip biopsies.

[†]Including 4 snaring with circumferential incision.

[‡]including 28 hot biopsies and one argon plasma coagulation.

Table 3 Complications following treatment of 121 lesions.

Complication	Lesions, n (%)
Perforation	2 (2)
Intraoperative perforation*	1 (1)
Delayed perforation [†]	1 (1)
Delayed bleeding	14 (12)
First part	0/20 (0)
Second part	12/92 (13)
Third part	2/6 (33)
Anastomosis	0/3 (0)
With prophylactic clipping	7/99 (7)
Without prophylactic clipping	7/22 (32)
Blood transfusion	1 (1)

*ESD was discontinued after closure using endoclips.

[†]Required emergency surgery.

Table 4 Histopathological results (n = 120*).

Tumor size, median (range), mm	12 (3–50)
Histological diagnosis, n (%)	
Adenoma/LGIN	57 (48)
Intramucosal adenocarcinoma/HGIN	60 (50)
Submucosal adenocarcinoma	3 (2)
Ductal involvements [†] , n (%)	
Negative	63 (100)
Positive	0 (0)
Horizontal margin, n (%)	
Negative	47 [‡] (39)
Positive	9 (8)
Inconclusive	64 (53)
Vertical margin, n (%)	
Negative	115 (96)
Positive	1 (1)
Inconclusive	4 (3)

HGIN, high grade intraepithelial neoplasia; LGIN, low grade intraepithelial neoplasia.

*Discontinued ESD case was not included.

[†]Adenocarcinoma only.

[‡]Including 3 with negative horizontal margin histopathologically with piecemeal resection.

Table 5 Lesion characteristics and treatment results of endoscopic mucosal resection and endoscopic submucosal dissection (n = 121).

	EMR (113)	ESD (8)
Location, n (%)		
First part	14 (12)	6 (75)
Second part	90 (80)	2 (25)
Third part	6 (5)	0 (0)
Anastomosis	3 (3)	0 (0)
Tumor size, median (range), mm	12 (3–50)	18 (5–45)
≤20, n (%)	99 (88)	4 (50)
>20, n (%)	14 (12)	4 (50)
Results of resection, n (%)		
En bloc	71 (63)	6 (75)
≤20 mm	68/99 (69)	3/4 (75)
>20 mm	3/14 (21)	3/4 (75)
R0*	38 (34)	4 (50)
Discontinuation of treatment, n (%)	0 (0)	1 (13)
Complications, n (%)		
Perforation	0 (0)	2 (25)
Delayed bleeding	14 (12)	0 (0)
Final diagnosis of histopathology [†] , n (%)		
Adenoma/LGIN	55 (49)	2 (25)
Intramucosal adenocarcinoma/HGIN	56 (49)	4 (50)
Submucosal adenocarcinoma	2 (2)	1 (13)

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HGIN, high-grade intraepithelial neoplasia; LGIN, low-grade intraepithelial neoplasia.

*En bloc resection with tumor-free margins histopathologically.

†Discontinued ESD case was not included in this analysis.

Table 6 Long-term outcomes (n = 76).

Recurrence, n (%)	0 (0)
Death by duodenal tumor, n (%)	0 (0)
Death by other causes or unknown causes, n (%)	3 (4)
Follow-up period, median (range), months	51 (12–163)
