Review

ESD for duodenal carcinoma

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Abstract

Superficial non-ampullary duodenal epithelial tumors (SNADETs) are rare, but their incidence is increasing recently. Considering the invasiveness of pancreatoduodenectomy, endoscopic treatment is widely accepted as an option for maintaining patients’ quality of life. SNADETs larger than 20 mm are an indication for duodenal ESD, and intramucosal cancer can be cured by ESD. Duodenal ESD is extremely difficult with a high risk of adverse events. However, some modified treatment techniques such as the water pressure method or the pocket creation method have been proposed to improve outcomes. Furthermore, evidence is accumulating that protection of the mucosal defect reduces delayed adverse events after duodenal endoscopic treatments. Moreover, endoscopic drainage of the bile and pancreatic juice is effective as conservative management even in cases with delayed perforation.

Keywords: Endoscopic resection, duodenum, outcomes

INTRODUCTION

Superficial non-ampullary duodenal epithelial tumors (SNADETs) were considered rare¹, but, due to recent developments of endoscopic devices and increasing awareness of endoscopists, the opportunities for detecting SNADETs during screening esophagogastroduodenoscopy are increasing³,⁴. Pancreatichoduodenectomy (PD) is the standard surgery for duodenal cancer. However, morbidity and
mortality of PD range 30%-40% and 1%-4%, respectively\[5-8\]. This high morbidity makes PD too invasive for SNADETs, which has a relatively low risk of lymph node metastasis\[9\]. Endoscopic submucosal dissection (ESD) is the standard treatment for neoplasms in gastrointestinal tract because of its lower invasiveness. However, duodenal ESD is very different from that of other organs in terms of the technical aspects of the procedure and post-ESD management. In this narrative review, we focus on the current status and issues of duodenal ESD.

**INDICATIONS FOR ESD AND CURE CRITERIA**

To date, there is no established consensus on the indications for duodenal ESD. The malignant potential of the lesion is important in determining the indication for endoscopic treatment. Nakayama *et al.*\[10\] reported that the proportion of lesions diagnosed as category 4 (equivalent to high-grade dysplasia) or higher of the Vienna classification after ER of SNADETs was 6% for lesions less than 7 mm, but it gradually increased with the size of the lesion, reaching 52% for lesions 16 mm or larger. It is important to consider the resectability of each treatment method and the risk of adverse events when considering the indications for treatment. ESD is reported to accomplish secure en bloc resection for superficial epithelial tumors arising from the gastrointestinal tract irrespective of the size and location\[11-14\]. Similarly, duodenal ESD accomplishes higher en bloc resection rates in previous reports\[15-22\]. Moreover, a recent multicenter retrospective study including more than 3000 cases undergoing duodenal endoscopic treatment in Japan reported high duodenal ESD en bloc resection rates regardless of the size, location, or presence of fibrosis of the lesion, whereas other endoscopic resection techniques including endoscopic mucosal resection (EMR) and underwater EMR revealed inferior resectability, especially for lesions larger than 20 mm\[15\]. In terms of the adverse events, the delayed AE rate of ESD was significantly higher than that of the non-ESD treatments for lesions less than 19 mm (ESD 7.4% vs. others 1.9%, *P* < 0.0001); however, this difference disappeared in lesions larger than 20 mm (ESD 6.1% vs. others 7.1%, *P* = 0.6432). Based on these results, it seems reasonable to consider 20 mm or larger lesions as an indication for ESD at this time, although ESD should be performed by highly experienced endoscopists considering its high adverse event rate. As for occupied circumference, as described below, even large mucosal defects can be healed without causing stricture by complete suturing along the long axis of the intestine, so that even circumferential lesions can be treated endoscopically as long as complete suturing can be obtained. However, duodenal ESD is still technically extremely challenging, therefore piecemeal resection is still an option in institutions where en bloc resection by ESD is difficult.

Regarding curative criteria, the risk of metastasis is important, since ESD is only a local resection. Information regarding curability of duodenal ESD is still insufficient due to its rarity. There is no established concept of “early duodenal cancer”, whereas generally “early cancer” is defined as cancer with invasion limited to mucosa or submucosa in the stomach and colorectum. Regarding lymph node metastasis (LNM), intra-mucosal cancer indicates no incidence of LNM\[24\], and the LNM of submucosal cancer is about 40%\[24-26\]. Based on these facts, intra-mucosal cancer can be cured by ESD alone, while submucosal cancer cases should be referred to additional surgery with lymph node dissection.

**KNIFE**

As described below, duodenal ESD is technically extremely difficult; the most careful technique is required. especially during submucosal dissection. For this reason, a needle-shaped energy device is preferable, which enables fine dissection. Indeed, we reported that a needle type with a water irrigation function significantly shortens the procedure time for duodenal ESD\[27\]. Furthermore, recently, a scissor-type knife has also been reported to be safe and secure duodenal ESD\[28\].
KNACK AND PITFALL

ESD of the duodenum is technically more difficult compared to other organs because of various anatomical features. The endoscope maneuverability is impaired because of the distance from the oral cavity and fixed position to the retroperitoneum of duodenum. It is often difficult to approach the lesion tangentially, and only the perpendicular approach is possible, especially in the flexural position of the duodenum (e.g., superior and inferior duodenal angles). The wall of the duodenum is so thin that the outer structure can sometimes be seen through it; therefore, only a small inadvertent cautery, even hemostasis, towards the muscle layer can easily cause perforation. The submucosal layer to dissect is very narrow because of rich Brunner’s glands especially in proximal duodenum. There are rich blood vessels in the submucosal layer, and even a thin blood vessel could cause massive bleeding. In addition, only a tiny biopsy before ESD often causes severe fibrosis of the submucosal layer, which makes endoscopic resection difficult. In fact, a recent multi-center retrospective study has demonstrated an intraprocedural perforation rate of 9.3%. In that study, this high incidence was observed even though all participating institutes were high-volume Japanese centers; thus, duodenal ESD is still challenging even for highly experienced endoscopists.

The first step to overcome the abovementioned difficulties is to understand predictors for technical difficulties. We explored predictors for intraoperative perforation and the procedure requiring a long time; these were set as surrogate endpoints for technical difficulties. We found lesions located in the flexural part such as the superior or inferior duodenal angle, large lesion size, and occupied circumference of the lesion exceeding half the circumference were independently associated with technical difficulty. Knowledge of these predictors is expected to be useful when preparing for difficult duodenal ESD, for example by planning a procedure under general anesthesia.

TECHNIQUE

Although duodenal ESD is difficult, several modified techniques and recently developed devices have been proposed. Improvement of visualization of the submucosa is one of the most important keys to safe and successful ESD.

We invented the water pressure method (WPM), in which active water flow is utilized by the water jet function of a therapeutic endoscope. First, the lumen of the duodenum is filled with normal saline, and, just after the mucosal incision, the active water stream is aimed at the mucosal flap to open the tissue. Generally, it is very difficult to dissect the submucosal layer at the beginning of submucosal dissection because it is impossible to directly visualize the dissecting layer due to the narrow space. WPM enables direct observation of the submucosa even at the very early stage of submucosal dissection by exposure of the tissue using an active water stream. Another advantage of WPM is that it makes it easier to dissect the lateral edge of the lesion. It is also relatively difficult to dissect this area because of the narrow space, and WPM assists by opening the space using active water pressure. Actually, we reported that WPM significantly reduces perforation during the ESD procedure as well as significantly shortens the procedure time.

Miura et al. reported the effectiveness of the pocket creation method (PCM). In PCM, a small, tapered tip hood is used to create a pocket by dissecting the submucosa without a circumferential incision. PCM contributes to stabilizing the endoscope and improving the visibility of the submucosal layer. Moreover, there is a report addressing the effectiveness of a traction device. These newly reported modified ESD techniques are expected to improve duodenal ESD.
Figure 1. Duodenal ESD using the water pressure method: (A) a 40 mm flat elevated lesion was found in the descending duodenum; (B, C) mucosal incision; (D, E) hitting the submucosa with water contributed to improved visibility of the dissecting area; and (F) the lesion was resected without any adverse events.

SUTURING
Duodenal ESD has a high risk of delayed adverse event (AE), for example bleeding or perforation, even though the treatment is completed safely\cite{33}. Actually, a recent large-scale multicenter retrospective study indicated that delayed perforation was found in 2.3% of cases that underwent duodenal ESD\cite{23}. This incidence is more than 10-fold higher than that of other areas of the gastrointestinal tract. The high incidence of delayed AE is considered to be due to exposure of bile and pancreatic juice to the post-ESD mucosal defect\cite{18,33-35}. Protection of the post-ESD wound is a way to prevent delayed AE. Various preventive methods have been reported to reduce delayed AE after duodenal endoscopic treatment, for example simple closure by clips, the string-clip suturing method, the endoloop-clips technique, over-the-scope clips (OTSC), or covering with polyglycolic acid (PGA) sheets\cite{19,21,36-39}.

Simple closure is applied for small defects. Recently, different kinds of clips with the ability to re-open and close are available, and these clips are useful for secure closure of the wound. In the endoloop-clips technique, the mucosal defect is closed by a detachable snare (endoloop) and clips. A detachable snare is opened along the margin of the defect, and then clips are deployed on the endoloop. Next, the defect is approximated by tightening the endoloop, and the defect is closed by adding clips. In the string-clip suturing technique, a clip with string is anchored at the distal edge of a mucosal defect, and a second clip is deployed at the oral side to keep the string. The wound is finally closed by pulling the string. Subsequently, complete closure is accomplished by the placing additional clips\cite{39} [Figure 2].

Accumulating evidence shows that wound protection reduces delayed AE. We reported delayed AE was just 1.7% in cases where complete closure was achieved, whereas it was 25% and 15.6% in cases with incomplete closure or without closure, respectively\cite{36}. Similarly, a meta-analysis indicated delayed AE was reduced by more than 80% by wound protection\cite{40}.
Figure 2. The string clip suturing method for a large mucosal defect: (A) a 40 mm flat elevated lesion was found in the descending duodenum; (B, C) the wound was approximated by pulling the string tight to the clip; (D, E) the string was cut by forceps and additional clips were deployed; and (F) the wound was completely closed.

Although wound protection is effective for the prevention of delayed AE after duodenal ESD, there are some remaining issues. Devices and materials for protection are expensive: an OTSC costs about $700, a PGA sheet costs about $140, and the fibrin glue costs about $300. Moreover, the fibrin glue is derived from donated blood, which has a low but non-negligible risk of AE such as infection. The string-clip suturing method is cheap, but it demands endoscopists’ skill. Mizutani et al.\textsuperscript{[41]} explored the predictors for difficulty of closure and concluded that the tumor location of medial/anterior wall and lesion size more than 40 mm are risk factors for incomplete closure.

Another way to prevent delayed AE is suturing the wound from the peritoneal side by laparoscopy assistance in addition to flexible endoscopy from inside the duodenum lumen. This novel surgical procedure, named endoscopic cooperative surgery (D-LECS), was first reported in 2015\textsuperscript{[42]}. A retrospective case series with 206 cases undergoing D-LECS revealed 95% R0 resection rate, 1.5% perforation rate, and 1% bleeding rate, suggesting favorable outcomes\textsuperscript{[43]}. D-LECS has been covered by health insurance in Japan since April 2021.

COUNTERMEASURES FOR COMPLICATIONS

As mentioned above, various preventive measures can significantly reduce the risk of delayed AE after duodenal ESD; unfortunately, it is difficult to prevent them completely. Therefore, it is also important to know how to manage delayed AEs. The management of perforation is particularly important because it sometimes requires highly invasive treatment including surgery.

We analyzed clinical courses of cases with perforation of duodenal ESD and found that closing the whole area of mucosal defect as well as perforation site improved clinical outcomes. The maximum C-reactive protein value and length of hospital stay of cases where the mucosal defect was closed completely were almost equivalent to those without perforation\textsuperscript{[44]}. Closing the mucosal defect enables managing the patients conservatively in the case of intraprocedural perforation as well as helps avoid delayed AE [Figure 3].
Figure 3. Complete closure of a mucosal defect in a case with intraprocedural perforation: (A) a 5 mm perforation occurred during submucosal dissection; (B) the wound was approximated by pulling the string tight to the clip; and (C) the whole mucosal defect was completely closed. The post-procedural clinical course was uneventful, and the patient was discharged on Post-Procedural Day 4.

Figure 4. Endoscopic naso-biliary and naso-pancreatic drainage (ENBPD) in a case where complete closure was impossible: (A) ESD completed for lesion located on the oral side of the main papilla; (B) complete closure was impossible because the main papilla was too close to the mucosal defect; and (C) ENBPD tubes were inserted and the post-procedural clinical course was uneventful.

The situation is more complicated for delayed perforations that occur a long time after ESD. The tissue surrounding the wound becomes fragile due to inflammation, and mechanical suturing is often impossible. For such cases, drainage of the bile and pancreatic ducts using the ERCP technique has been reported to be effective. We also reported cases with delayed perforation successfully managed by only endoscopic nasobiliary and naso-pancreatic duct drainage that did not require any other invasive intervention⁴⁵. Although post-ERCP pancreatitis was observed in 16% of cases, due to the high morbidity of surgical treatment, it can be considered a salvage option for cases with delayed adverse event [Figure 4].

FUTURE PERSPECTIVE
Duodenal ESD is still a technically challenging procedure, and it is not recommended as a standard treatment, considering its high morbidity. However, it has a great advantage of secure en bloc resection irrespective of lesion size and location. Several recent studies have shown that protection of the post-ESD wound could prevent delayed AE. A simpler and more reliable method for wound protection would contribute to further improvement of the outcomes and widespread use of duodenal ESD in the future. Moreover, the process to overcome difficulty of duodenal ESD through discovering unmet medical demands would contribute to further advances of therapeutic endoscopy in any organ as well as duodenal ESD.

DECLARATIONS
Authors’ contributions
Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Kato M
Performed data acquisition, as well as provided administrative, technical, and material support: Sasaki M, Maehata T, Yahagi N

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