Endoscopic Submucosal Dissection for Superficial Esophageal Cancer

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Tsuneo Oyama

Introduction

Esophageal endoscopic mucosal resection (EMR) was developed in the late 1980s, and it quickly became widely accepted as the premiere treatment for superficial esophageal cancers [1–4]. However, there were limitations regarding resectable size, and precise resection was impossible. Piecemeal resection was performed for larger lesions, but local recurrence rates after piecemeal EMR were high [5]. Therefore, a novel endoscopic treatment, endoscopic submucosal dissection (ESD), was developed to resolve such disadvantages of EMR [6–10]. Ten years have passed since esophageal ESD was established, and now, specially designed equipment is available to help make esophageal ESD safer and easier.

Indications

The indication of ESD for esophageal cancer is superficial cancer without lymph node metastasis (LNM).

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Squamous Cell Carcinoma

According to the guidelines of the Japanese esophageal society, indications for endoscopic resection are T1a cancers limited to the epithelium or lamina propria. Because such cancers are extremely rarely associated with lymph node metastasis, endoscopic resection is a sufficient treatment for these lesions. Lesions reaching the muscularis mucosae or slightly infiltrating the submucosa (up to 200 μm) are also amenable to mucosal resection, but the incidence of LNM is about 15 %. Therefore, cross-sectional imaging or endoscopic ultrasound should be performed to stage the LNM before ESD.

T1a lesions infiltrating the muscularis mucosa or T1b lesions confined to the upper third of the submucosal, without LNM, represent relative indications. Furthermore, 50 % of lesions invading deeper (more than 200 μm) into the submucosa (T1b) are associated with metastasis, and even superficial carcinomas should be treated in the same manner as advanced carcinomas (carcinomas exceeding the muscularis propria).

Adenocarcinoma

According to the guidelines of the Japanese esophageal association, the indication of ESD for esophageal adenocarcinoma is T1a cancers infiltrating the lamina propria or the muscularis mucosa superficially. Additionally, T1a cancers

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reaching deep muscularis mucosa are relative indication. Recently, in a meta-analysis of LNM for esophageal adenocarcinoma, 70 relevant reports were identified that included 1,874 patients who had esophagectomy performed for HGD or intramucosal carcinoma in Barrett's esophagus. Lymph node metastases were found in 26 patients (1.39 %; 95 % CI 0.86–0.92) [11]. No metastases were found in the 524 patients who had a final pathology diagnosis of HGD, whereas 26 (1.93 %; 95 % CI 1.19–2.66) of the 1,350 patients with a final pathology diagnosis of intramucosal carcinoma had positive lymph nodes [11]. Therefore, all subtypes of T1a lesions could be the indication for ESD of esophageal adenocarcinomas since esophagectomy has a mortality rate that often exceeds 2 %.

Mucosal resection covering three-fourth of the entire circumference is likely to be associated with postoperative cicatricial stenosis; therefore, sufficient explanation should be given to the patient prior to the procedure and preventive measures must be taken. In cases of superficially enlarged carcinoma, deep infiltration may occur in multiple areas, necessitating careful diagnosis of the depth of invasion.

Tools and Techniques

Endoknives

Many endoknives have been developed for ESD. The basic knives are the Hook knife (KD-620LR, Olympus, Tokyo) and the Dual knife (KD-650, Olympus, Tokyo). The insulated tip (IT) knife is widely used for gastric ESD, but is not suitable for esophageal ESD because of the increased perforation rate. Recently, however, the IT-nano (KD-612, Olympus, Tokyo) was developed for colonic and esophageal ESD. The size of the insulation tip is smaller than that of the usual IT knife, and good maneuverability in narrow space is now obtainable. However, the risk of perforation is relatively higher, and therefore hyaluronic acid is recommended for the submucosal injection.

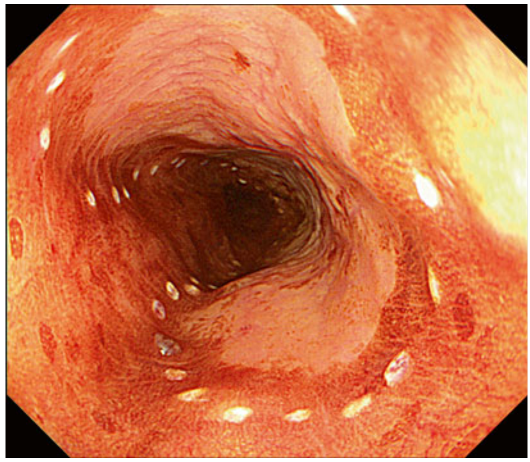

Fig. 10.1 The tip of the ESD knife is retracted within the sheath, and a mark is placed when the tip of the knife comes into contact with the mucosa

The Flush knife (Fujinon, Tokyo) is a unique device that incorporates a water flush function. It is useful for additional injection during submucosal dissection. And, even more recently, scissor-like knives such as the Clutch cutter (Fujinon, Tokyo) and the SB knife (Sumitomo Bakelite, Tokyo) have been developed. The cutting speed is slow, but they are easy for beginners to use.

Marking

The lateral extension of squamous cell carcinoma (SCC) can be visualized easily after 0.75–1 % iodine dye spray chromoendoscopy. Marks should be placed 2–3 mm away from the edge of the unstained area that represents the cancer. The esophageal wall is thinner than that of the stomach, and so perforation can occur during marking if a needle knife is used. Hook and Dual knives are useful devices for placing the marks safely. The tips of both knives can be retracted within the sheath, and a mark can be placed when the tip of knife is contacted with the mucosa and coagulated by soft coagulation (Effect 4, 20 W) (Fig. 10.1).

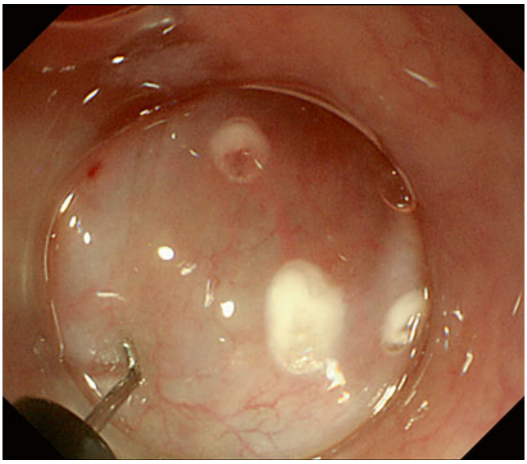

Fig. 10.2 The back side of the Hook Knife is placed so as to make contact with the mucosa, after submucosal injection of the fluid cushion, and a mucosal defect is made using the Endocut I mode

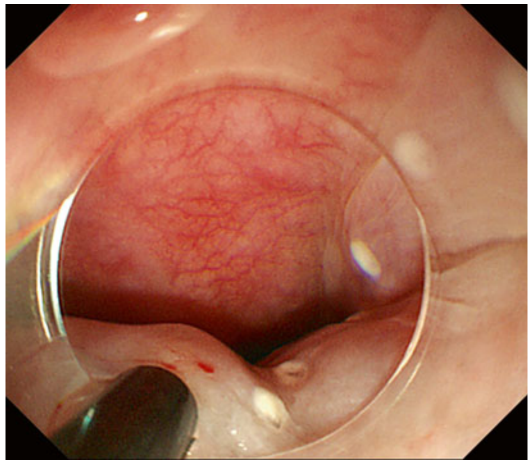

Fig. 10.4 The Hook Knife's arm is used for vertical mucosal incision. The knife is directed toward the lumen and then inserted into the submucosal. The mucosa is then elevated toward the lumen with the knife's arm, and then the mucosa is cut

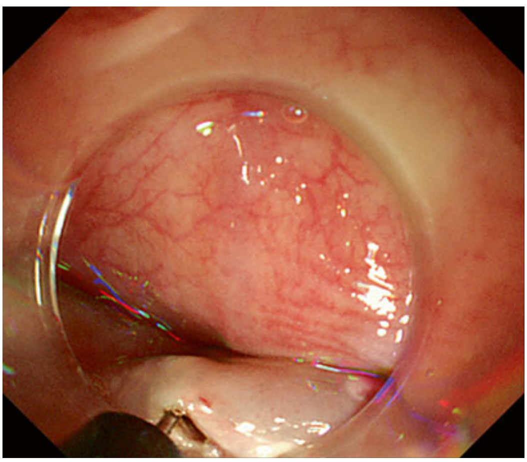

Fig. 10.3 The tip of the Hook Knife is inserted into the submucosal layer. The knife is used to hook and cut the mucosa

Mucosal Incision

The strategy for mucosal incision is dependent upon the endoknife type. When a Dual or Hook knife is used, basically the mucosal incision is performed from the oral side. At first, the backside of the hook knife is contacted with the mucosa, and a hole is made by Endocut I mode (Effect 3) (Fig. 10.2). After that, the tip of the hook knife is inserted into the submucosal layer, and the mucosa is hooked and cut with the hook part of the knife (Fig. 10.3). This is an important part of the process in order to prevent perforation. The arm part of the hook knife is used for longitudinal mucosal incision. The direction of the Hook knife is turned toward the esophageal lumen, and the knife is inserted into the submucosal layer by sliding the back side. Then the mucosa is captured by the arm part of the knife (Fig. 10.4), and, finally, the mucosa is cut with a combination of Spray coagulation (Effect 2, 60 W) and Endocut mode (Effect 3, duration 2, and interval 2). It is important in order to prevent bleeding during mucosal incision. The submucosal vessels cannot always be observed by endoscopy. Sometimes they are cut unexpectedly, and bleeding occurs during mucosal incision. Initial spray coagulation can coagulate submucosal vessels, and so such unexpected bleeding can be prevented with initial spray coagulation.

A deeper cut of submucosal fibers is performed after mucosal incision. The Hook knife is inserted into the submucosal layer, and the submucosal fibers are hooked and cut. The lesion then shrinks by the contraction of muscularis mucosa (Fig. 10.5). After that, mucosal incision

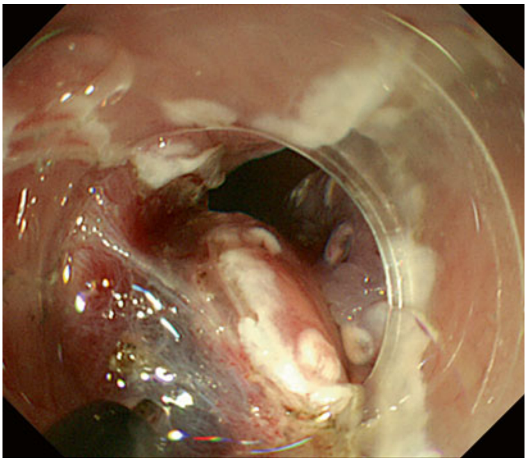

Fig. 10.5 The knife is inserted into the submucosal, and then the submucosal fibers are hooked and cut

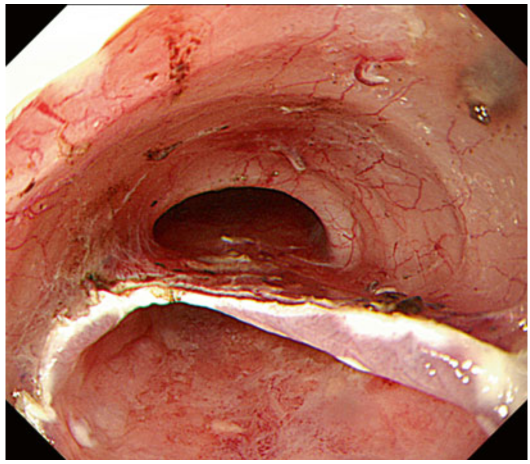

Fig. 10.7 After mucosal incision, a submucosal tunnel is made from the oral to anal side

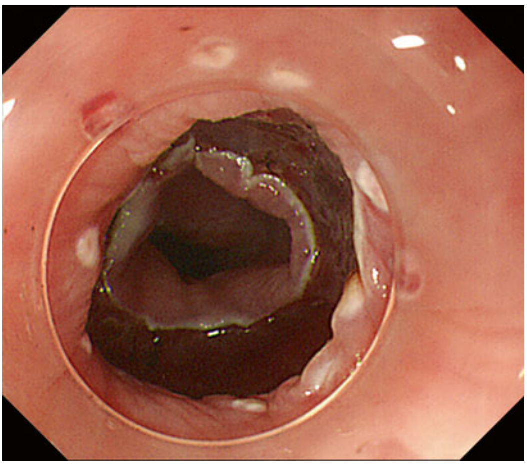

Fig. 10.6 Both oral and anal circumferential mucosal incisions were made

of the distal side is performed and then circumferential incision is completed. When an IT-nano knife is used, the mucosal incision should be started from the anal side. The initial mucosal incision at the anal side is made by a needle knife after submucosal injection. After that, the mucosal incision is made with IT-nano knife by Endocut mode. The operator cannot see the next mark well, because the cutting direction is always from distal to proximal. Therefore, the operator should take care to avoid cutting inside of the marks.

Submucosal Dissection

The direction of gravity should be checked before submucosal dissection is started. Basically, submucosal dissection should be started from the lower side, because water and blood flow to the lower side causing the field of vision to become worse. Therefore, the operator should try to shift the lesion to the upper side. If submucosal dissection is begun from the upper side, the resected part will shift to the lower side, and submucosal dissection of the later half becomes difficult.

Tunneling Method

Tunnel-like dissection is necessary for circumferential ESD [12]. At first, a circumferential mucosal incision of the anal and oral parts is performed (Fig. 10.6). After that, a mucosal tunnel is made from oral to anal [12] (Figs. 10.7 and 10.8), and the second tunnel is made at the opposite side. Finally, the remaining submucosal fibers are dissected between the two tunnels (Fig. 10.9).

Clip-with-Line Method

If you can pull the target lesion, good countertraction can be made. The clip-with-line method was first reported in 2002 (Fig. 10.10) [13]. It is a simple and useful method for achieving countertraction during ESD. A long, 3-0, silk line is

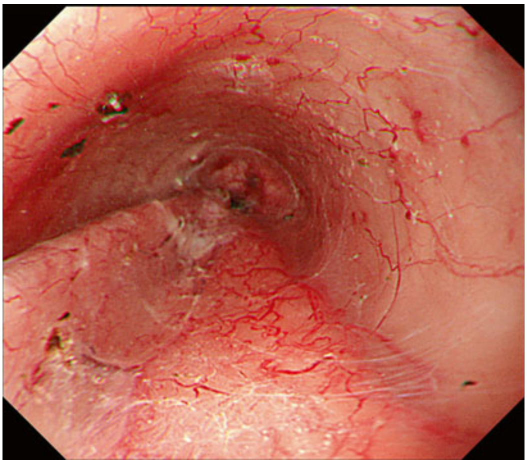

Fig. 10.8 At the opposite side, a second submucosal tunnel is made. The submucosal fibers remaining between the two tunnels are subsequently dissected

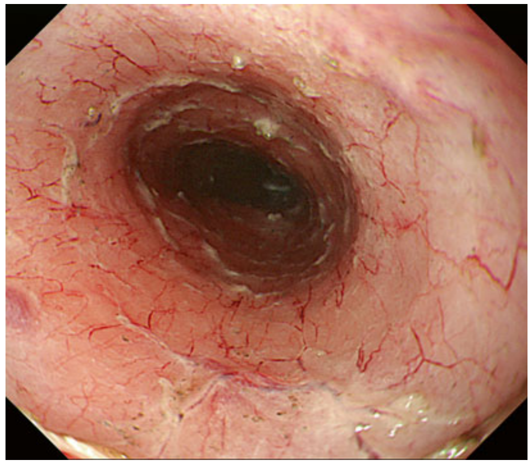

Fig. 10.9 En bloc ESD upon completion

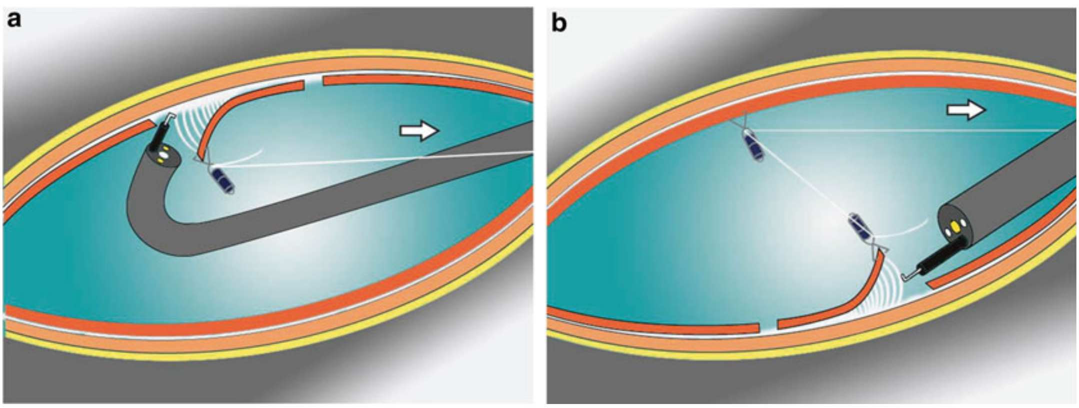

Fig. 10.10 Clip-with-line method. (**a**) A clip is placed at the distal edge of the target lesion once circumferential mucosal incision is complete. Countertraction and a clear field of view are obtained by pulling very gently on the line. (**b**) A second clip can be used to change the direction of the countertraction. (Originally from *Oyama T*, *Yuichi K*, *Shimaya S*, et al. *Endoscopic mucosal resection using a hooking knife—intra gastric lesion lifting method. Stomach and Intestine. 2002;37:1159. Japanese with English summary*)

tied to the arm part of the clip (HX-610-135; Olympus, Tokyo, Japan) (Fig. 10.11). Then the clip-with-line is reset in the cassette. The scope is withdrawn when the circumferential incision is finished. A clip applicator device (HX-110QR; Olympus) is inserted into the accessory channel of the endoscope, and the clip-with-line is mounted onto the tip of the applicator. The scope is inserted again, and the submucosal side of the target lesion is grasped (Fig. 10.12). After that, the line is pulled very gently. Only a small amount of tension is required to create countertraction. This method also creates a clear field of vision (Figs. 10.13 and 10.14). During submucosal dissection, tension is maintained with a 10 g weight, such as a bite block mouthpiece, attached to the line. The 10 g weight creates sufficient countertraction and tension without threatening to tear the submucosal layer [14].

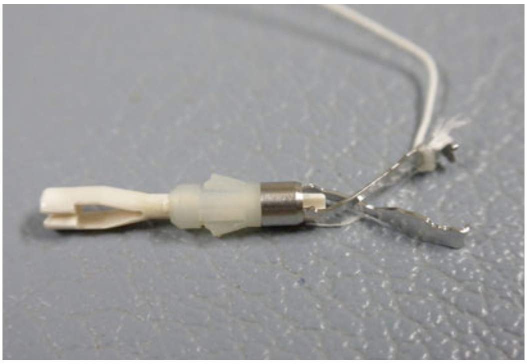

Fig. 10.11 A long silk line is attached to the arm part of a clip (HX-610-135, Olympus, Tokyo, Japan)

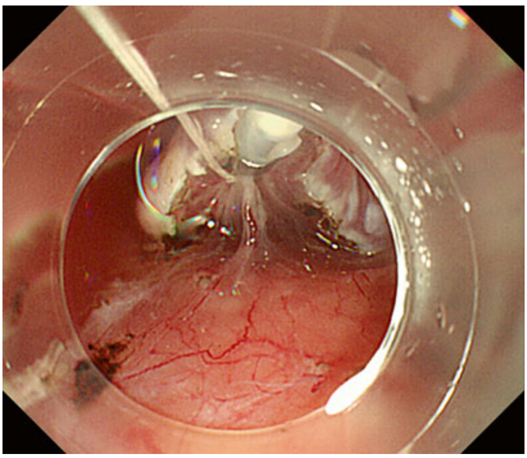

Fig. 10.12 The clip is used to grasp the submucosal side of the target lesion

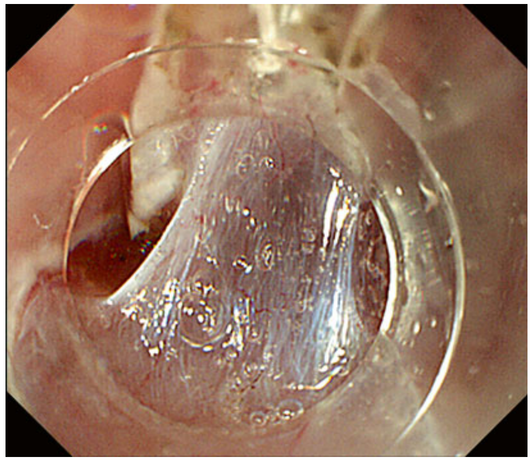

Fig. 10.13 Gentle pulling of the clip with traction line is used to provide countertraction

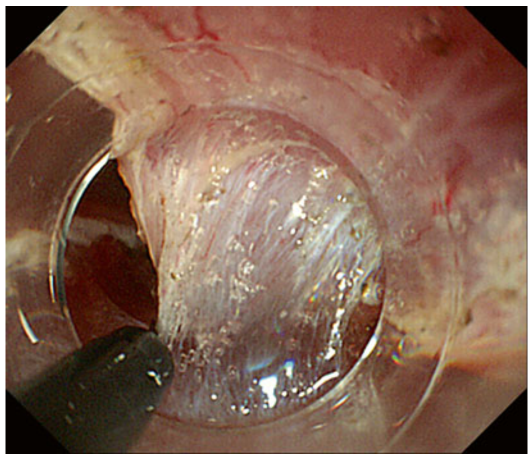

Fig. 10.14 Gentle pulling of the clip to provide countertraction facilitates submucosal dissection

Hemostasis

Bleeding makes the visual field worse; therefore hemostasis should be performed as early as possible. When bleeding occurs during mucosal incision or dissection, the area should be flushed to find the origin of bleeding.

Hemostasis Using Knife

Hemostasis using an endoknife is useful for controlling oozing bleeds [15, 16]. The tip of the knife is brought close to the origin and electrical discharge is done with Spray mode to obtain hemostasis (Effect 2, 60 W) [16, 17]. Since prolonged electrical discharge may cause perforation, electrical discharge should be performed very briefly. Therefore, it is important to maintain optimal distance using a transparent hood. A scope equipped with a water jet should be selected for esophageal ESD as it is used to confirm the precise origin of the bleeding.

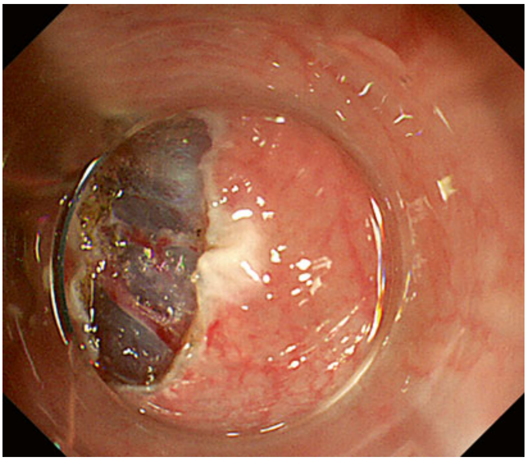

Fig. 10.15 If a vessel is large (≥1 mm), precut coagulation to prevent bleeding should be performed

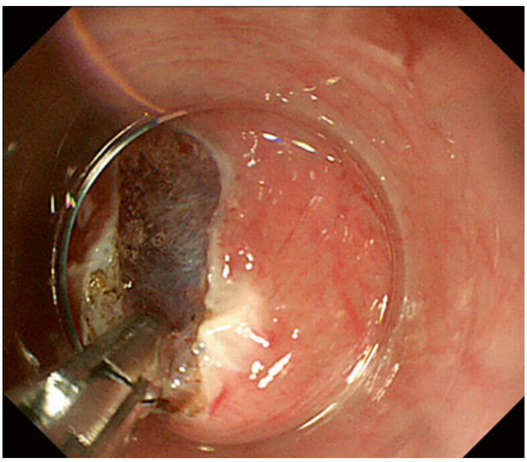

Fig. 10.16 Hemostatic forceps are used to grasp the large vessel, and it is coagulated with soft coagulation (Effect 5, 60 W)

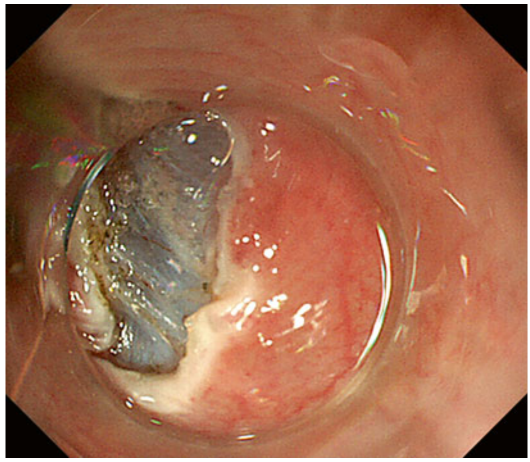

Fig. 10.17 The vessel can then be cut using the ESD knife and spray coagulation (Effect 2) without occurrence of any bleeding

Hemostatic Procedures Using Hemostatic Forceps

Hemostatic forceps, such as FD-410LR (Olympus, Tokyo, Japan), are useful in cases of more active or spurting bleeding. After flushing with a water jet to locate the origin of the bleed, the origin is grasped with the hemostatic forceps. After that, re-flushing with a water jet enables determination of whether the origin is grasped accurately. Then, the forceps are elevated a little to remove forceps from the proper muscular layer followed by electrical discharge with soft coagulation (Effect 5, 40 W), momentarily, to obtain hemostasis.

Prevention of Bleeding

Bleeding may worsen the visual field, leading to a higher risk of accidental complications. There are many vessels in the deep submucosal layer. A small vessel, 1 mm or less, could be cut using the Hook knife without bleeding when spray coagulation mode is used (Effect 2, 60 W). However, if the size of the vessel is 1 mm or larger, precut coagulation should be performed to prevent bleeding (Fig. 10.15). Larger vessels are grasped with the hemostatic forceps (Fig. 10.16) and coagulated by soft coagulation (Effect 5, 60 W). After that, the vessel can be cut using the Hook knife and spray coagulation (Effect 2, 60 W) without any bleeding occurring (Fig. 10.17).

Complications

Perforation

The major complication of EMR/ESD is perforation, as well as air embolization and aspiration pneumonia. Perforations may cause mediastinal emphysema, which increases the mediastinal pressure and crushes the esophageal lumen, leading to difficulty in securing the visual field. Severe mediastinal emphysema may be complicated by pneumothorax, which can lead to shock; therefore, electrocardiography, arterial oxygen saturation, and blood pressure (using an automated sphygmomanometer) monitoring should be conducted during ESD, as well as periodic observation for subcutaneous emphysema through palpation. CO_2 insufflation is useful for preventing such severe mediastinal emphysema.

Since the esophagus has no serous membrane and the intramediastinal pressure is lower than that of the esophageal lumen, mediastinal emphysema may occur in the absence of perforation. Dissection immediately above the proper muscular layer may damage the proper muscular layer during electrical discharge, which often causes mediastinal emphysema. Therefore, it is important to dissect the submucosal layer making sure to leave the lowest one-third without any exposure of the proper muscular layer. Under intubation general anesthesia, the mediastinal pressure is higher than the intraesophageal pressure, enabling prevention of mediastinal emphysema and/or subcutaneous emphysema. Therefore, intubation general anesthesia is preferable for large lesions that are expected to take two or more hours for complete resection.

The perforation rate caused by esophageal EMR has been reported as 0–2.4 %, and that of ESD as 0–6.4 % [7–10]. The shape and size of perforation caused by EMR is different from that caused by ESD. Muscle removed by EMR can be up to 1 cm or larger, and sometimes closure by clips is difficult. On the other hand, the shape of perforation caused by ESD is linear, without defect of proper muscle, and so closure by clips is usually easier than that of EMR. However, sometimes the clip may injure the remaining proper muscle and make the perforation larger. Therefore, the operator should be skilled at clipping. Usually such perforations can be treated by fast insertion of a nasoesophageal tube and intravenous antibiotic administration, without need for surgery.

Water jets are useful for the detection of the bleeding point. However, sometimes water reflux causes aspiration pneumonia. A flexible overtube (Sumitomo Bakelite, Akita, Japan) is a useful device for prevention of aspiration pneumonia. General anesthesia with tracheal intubation is necessary for the cervical esophageal ESD because the risk of aspiration pneumonia is high.

Stricture

Stricture is a major complication after ESD. Multivariate analysis has shown that a mucosal defect of more than three-quarters of the circumference is a reliable predictor of stricture [17–20]. Post-ESD stricture substantially decreases a patients' quality of life and requires multiple endoscopic balloon dilation (EBD) sessions. Preventive EBD has been the treatment of choice to prevent stricture; however, even after six sessions of preventive EBD, stricture is a frequent complication.

Recently, the efficacy of prophylactic oral prednisolone for prevention of post-ESD stricture was described [21]. Although this method reduced the stricture rate, the cumulative dose of prednisolone was approximately 1,000 mg, and exposure to such a high prednisolone dose raises concerns regarding adverse effects.

The efficacy of intralesional triamcinolone injection to prevent stricture after esophageal ESD has also been described [22, 23]. Especially worth noting is research by Hanaoka et al., where the effect of a single session of intralesional steroid injections immediately after ESD was studied. In this prospective study they compared the results with a historical control group of patients who underwent ESD without intralesional steroid injection. The treatment group had a significantly lower stricture rate (10 %, 3/30 patients vs. 66 %, 19/29 patients; $p<0.0001$) and a lower number of EBD sessions (median 0, range 0–2 vs. median 2, range 0–15; $p<0.0001$) [23].

A novel, unique method to prevent stricture after esophageal ESD has been published [24]. Specimens of oral mucosal tissue were collected from nine patients with superficial esophageal neoplasms. Epithelial cell sheets were fabricated ex vivo by culturing isolated cells for 16 days on temperature-responsive cell culture surfaces. After a reduction in temperature, these sheets were endoscopically transplanted directly to the ulcer surfaces of patients who had just undergone ESD. Complete re-epithelialization occurred within a median time of 3.5 weeks. No patients experienced dysphagia, stricture, or other complications following the procedure, except for one patient who had a full circumferential ulceration that expanded to the esophagogastric junction [24]. For additional discussion of stricture management, please Chaps. 14 and 15.

Conclusions

The advantage of ESD is the ability to achieve R0 resection, and a low local recurrence rate. However, esophageal ESD is technically more difficult than gastric ESD due to the narrower space of esophagus for endoscopic maneuvers. Also, the risk of perforation is higher because of the thinner muscle layer of the esophageal wall. The clip-with-line method is useful for maintaining a good endoscopic view with added counter-traction. ESD for esophageal cancer is a procedure that requires high technical ability, and therefore, only operators who have adequate skills should perform esophageal ESD.

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