Endoscopic Treatment: EMR and ESD

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Abstract

Esophageal superficial cancers with negligible risk for lymph node metastasis can be cured by endoscopic local resection. Endoscopic mucosal resection (EMR) is a conventional technique, which can resect relatively small lesions by using a snare. On the contrary, endoscopic submucosal dissection (ESD) can resect superficial lesion in an en bloc fashion irrespective of size or presence of submucosal fibrosis, which has made the indication of endoscopic resection expanded. Although skillful hands of endoscopy and sufficient knowledge for management of complications such as perforation and stricture formation are required, ESD is a promising technique as a minimally-invasive treatment.

Keywords

Endoscopic mucosal resection · Endoscopic submucosal dissection · Indication · Complication

9.1 Introduction

Due to improvement of therapeutic endoscopy in recent years such as endoscopic submucosal dissection (ESD), size limitation of a resectable extent by endoscopy has disappeared. In a so-called "pre-ESD" era, endoscopic mucosal resection (EMR) using an electrocautery snare was one and only available technique. This technique, however, could be applied only to small mucosal lesions because of the

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limitation in size. In case of large lesions, piecemeal resection is unavoidable, which may make histological evaluation difficult and even inaccurate [1, 2]. Development of ESD has changed the indication of endoscopic resection, owing to the unique characteristics of this technique. That is, ESD has technically enabled early gastrointestinal cancers to be resected endoscopically in an en bloc fashion irrespective of size or presence of submucosal fibrosis [3, 4]. Indication and methods of each technique, as well as the management of complications, are summarized in this chapter.

9.2 Indication of Endoscopic Resection

According to the Japanese classification of esophageal cancer, superficial carcinoma of the esophagus is defined as one invading up to the submucosa [5]. Among them, superficial carcinoma confined to the mucosa is called early cancer of the esophagus. Indication of endoscopic resection is determined mainly by the risk of lymph node metastasis [5–9]. If early cancer invading up to lamina propria mucosae (T1a-EP or LPM), where the risk of lymph node metastasis is thought to be less than 5% [5] is resected completely, curative resection will be expected. Therefore, T1a-EP and LPM are accepted as an absolute indication of endoscopic resection. Meanwhile, superficial cancer invading to muscularis mucosae (MM) or superficial submucosa up to 200 μm (SM1) has 10 to 15% of the risk of lymph node metastasis [8]. However, other treatment options for esophageal cancer, e.g., chemoradiotherapy or surgery are generally more invasive and also inheres considerable risks for major complications, therefore, endoscopic local resection for such cancers is acceptable as a relative indication. Obviously, negative lymphovascular infiltration should be confirmed histologically after complete resection of the tumor, to be judged as curative in both conditions.

On the other hand, extensive resection of the mucosa could be accompanied with severe stricture after treatment, which causes dysphagia and consequently loses the quality of life of the patients seriously [10, 11]. Although endoscopic balloon dilatation can avoid surgical intervention, frequent dilatation, and a risk of perforation during the procedure must be a burden for the patients [12, 13]. For this reason, a general indication of endoscopic resection for lateral tumor extension is up to three-fourths of the circumference. However, complete circumferential resection can be available as a relative indication if the patient accepts the risk for severe stricture and this additional troublesome endoscopic treatment.

9.3 Endoscopic Mucosal Resection

EMR is composed of fluid injection into the submucosa and mucosal resection with part of the submucosa using an electrocautery snare. There are some technical variations in EMR (Fig. 9.1).

EMR with a ligation device (EMR-L) requires an O-ring used for esophageal varices ligation (Fig. 9.1a) [14]. In this technique, after suctioning a lesion and

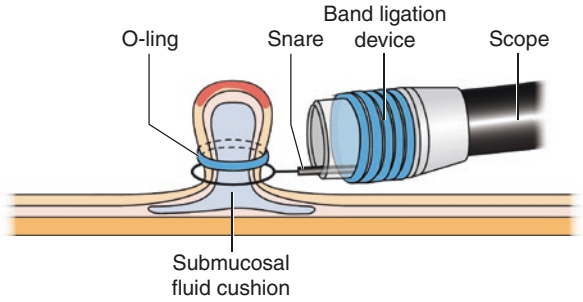

Fig. 9.1 Variety of EMRs. (**a**) EMR with a ligation device (EMR-L). A lesion is suctioned into a ligation device and ligated with O-ring before resection. (**b**). EMR using a cap-fitted endoscope (EMR-C). A lesion is suctioned into a transparent hood and resected by the snare. (**c**). Endoscopic esophageal mucosal resection (EEMR)-tube method. A long transparent silicon overtube is used for suctioning the lesion. (**d**). Two-channel EMR method. A forceps is used for grasping and pulling the lesion

ligating it with the O-ring to create a pseudopolyp, endoscopic resection is performed just below the O-ring using a snare. Although submucosal injection before the resection is desirable in order to avoid unexpected perforation, endoscopic resection using a ligation device without submucosal injection seems to be also acceptable due to its good clinical outcomes especially for early Barrett's neoplasia [15].

In EMR using a cap-fitted endoscope (EMR-C), a transparent hood attached to the tip of the endoscope is used (Fig. 9.1b) [16]. After opening a semilunar snare along the rim of the hood, an elevated lesion by submucosal injection is suctioned into the hood and resected by the snare.

In the endoscopic esophageal mucosal resection (EEMR)-tube method, a long transparent silicon overtube is used (Fig. 9.1c) [17]. After submucosal injection, the lesion is suctioned by the overtube introduced over the endoscope, and tightened by a snare preliminarily introduced through the side channel of the overtube. Resection should be done after confirming that the muscular layer is not involved because a diameter of the overtube is much larger than any other EMR caps.

A grasping and pulling technique using a two-channel endoscope is called two-channel EMR method (Fig. 9.1d) [18]. A grasping forceps from one working channel is passed through a snare introduced from the other channel. The elevated lesion by submucosal injection is grasped with the forceps and tightened with the snare at the bottom of the grasped mucosa. Again, resection should be done after confirming that the muscular layer is not involved within the captured tissue.

Because the size of snares is limited in these EMRs, the available size of en bloc resection is also limited [3, 4, 19, 20]. Expected maximal size of one specimen is thought to be approximately 2 cm. Besides, the resectable size is also limited by the diameter of the O-ring in EMR-L, the hood in EMR-C, and the overtube in EEMR-tube. Furthermore, in case of having severe fibrosis under the lesion, it usually becomes quite difficult to resect the lesion by these EMRs because a snare is easily

slipped from the target. Accordingly, early esophageal cancer in 1 cm or less without fibrosis would be suitable for a candidate of EMR in usual clinical settings.

9.4 Endoscopic Submucosal Dissection

This epoch-making technique is composed of four steps; marking around the lesion after chromoendoscopy with Lugol's iodine solution, submucosal injection, circumferential mucosal incision, and dissection of the submucosal connective tissue (Fig. 9.2). Because the operator can determine the extent of resection and dissect the submucosal tissue under the direct vision, ESD can offer reliable en bloc, margin-free resection irrespective of size or presence of submucosal fibrosis.

9.4.1 Details of Practical Skill

Since ESD takes longer procedure time than EMR, sufficient sedation is necessary for a safe and successful procedure. And in case of difficult ESD cases such as lesions located at cervical esophagus or large lesions with severe fibrosis, general anesthesia should be used to have much stable condition throughout the procedure.

Among various electrocautery knives specialized for ESD, pointed tip-type knives would be suitable, especially for esophageal ESD due to the narrow lumen and the thin wall of the esophagus[21–23]. Moreover, it is reported that the revised type of insulated knife and scissors type electrocautery knives are useful for esophageal ESD as well [24–26] (Fig. 9.3).

Successful resection requires an accurate endoscopic diagnosis of a tumor extent. Although promising image-enhancement endoscopy techniques have been introduced, conventional chromoendoscopy using Lugol's iodine solution would be still most useful for demarcating the tumor extent. Using a tip of the knife, markings are made 2–3 mm outside the lesion at intervals of approximately 3 mm.

In creating a submucosal fluid cushion, an injection needle is gently advanced into the submucosa at the outside of markings, and fluid colored with a small amount of indigo carmine, which is helpful to visualize the submucosa, is injected into the submucosa to make sufficient submucosal space for incision and dissection. Hypertonic or viscous injection fluid such as Glyceol™ (Chugai Pharmaceutical Co., Japan; consisted of 10% glycerine, 5% fructose, and 0.9% sodium chloride) or hyaluronic acid solution is desirable for long-lasting submucosal fluid cushion. Injection directly through the cancerous area should be avoided in order to prevent cancer cell implantation in the deeper layer.

The mucosa 1–2 mm outside of markings is usually cut with cutting current using a specific knife. Right after partial mucosal incision, initial submucosal dissection should be made along the incision line with coagulation current. To make sure the end point of submucosal dissection, it is better to cut the anal side of the lesion first, subsequently, mucosal incision and submucosal dissection are conducted from the oral side.

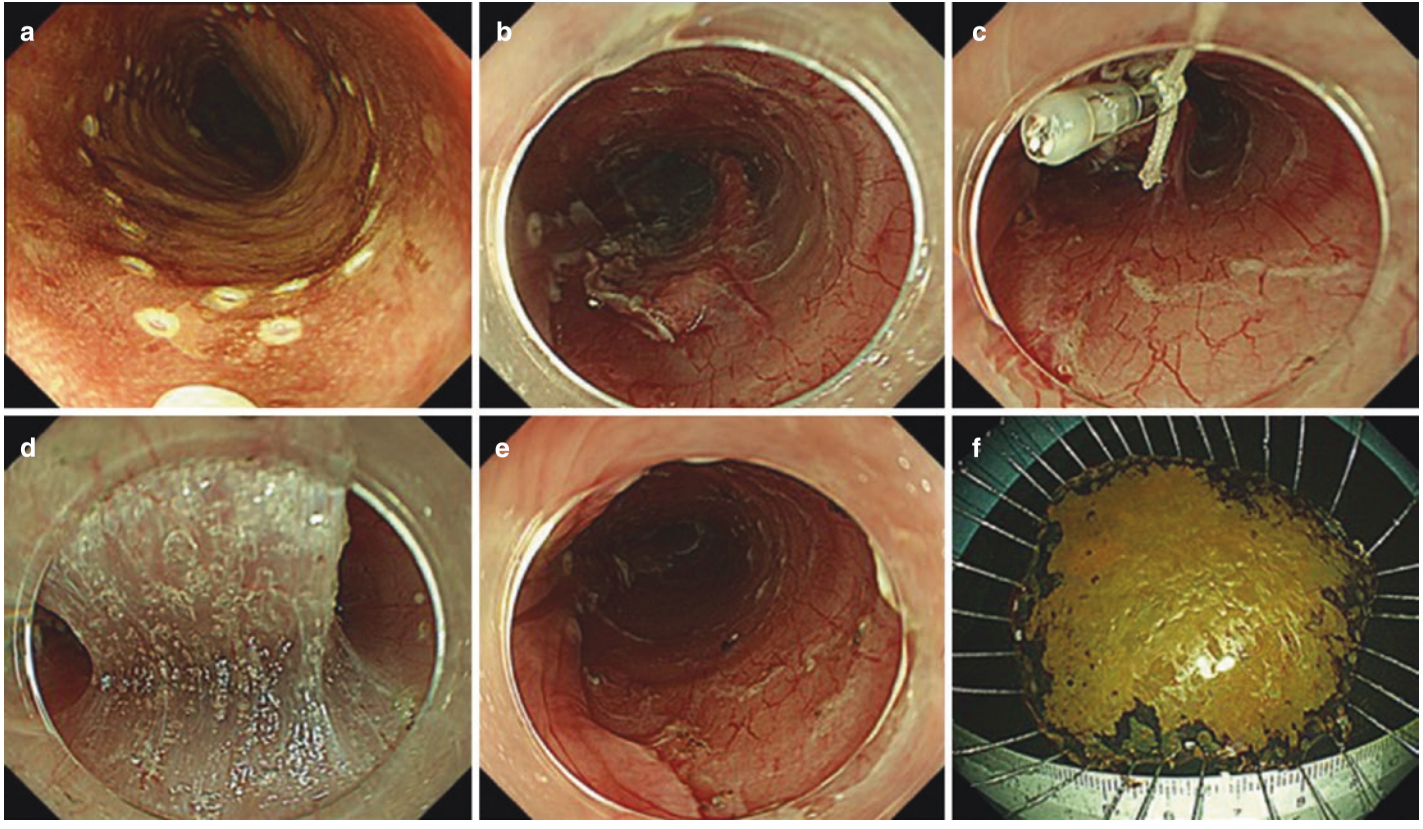

Fig. 9.2 Esophageal endoscopic submucosal dissection (ESD) using Dualknife J and clip with string traction method for large esophageal SCC. (**a**) Markings are placed around the lesion with an appropriate margin. (**b**) Submucosal dissection was started from the oral side. (**c**) A clip with string was deployed on the proximal side of the lesion. (**d**) Good visualization of the submucosal layer was obtained by pulling the string. (**e**) Resection wound after ESD. (**f**) An en bloc resection enables precise histological assessment (esophageal squamous cell carcinoma, pT1-a, 55x40mm, ly0, v0, pHM0, and pVM0)

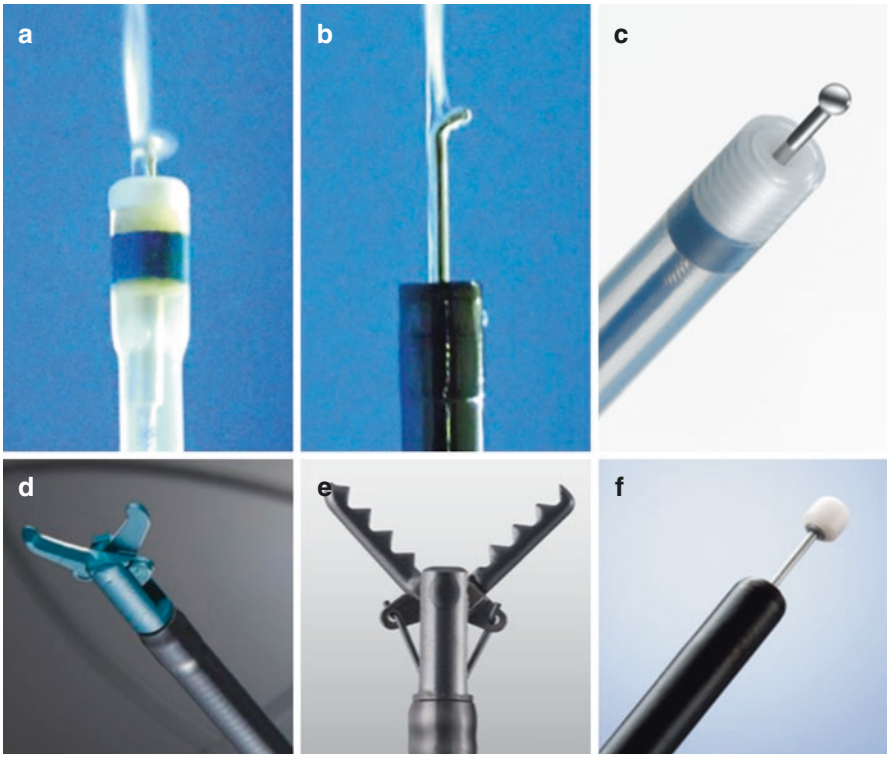

Fig. 9.3 Electrocautery knives for esophageal ESD (**a**) DualKnifeJ™. (**b**) HookKnifeJ™. (**c**): FlushKnife BT-S™. (**d**) SB knife Jr.™. (**e**) ClutchCutter™. (**f**) IT knife nano™

It is very important to conduct submucosal dissection under the direct vision, using a transparent hood. For large lesions, tunneling technique or traction device such as a clip with line is helpful to obtain good submucosal deployment (Fig. 9.2). The knife should be moved parallel to the plane of the muscular layer during submucosal dissection, to avoid muscular injury or perforation. Repeat submucosal injection, mucosal incision and submucosal dissection step by step until end of the procedure.

9.5 Management of Complications

9.5.1 Bleeding

Unlike gastric ESD, the rate of postoperative bleeding is relatively low (0–2%) [27–30]. In case of minor bleeding, hemostasis using the tip of the knife is initially attempted. When it is difficult to stop bleeding or it bleeds massively,

hemostatic forceps should be used. After the retrieval of the resected specimen, the resection wound should be thoroughly checked for visible vessels. And every thick exposed blood vessels should be carefully coagulated, avoiding excessive thermal damage.

9.5.2 Perforation

Perforation should be paid more attention, especially in esophageal ESD. Because the esophagus has no serosa, exposure of the muscular layer may cause pneumomediastinum [31, 32]. Indeed, pneumomediastinum was found by CT-scan in half of treated cases after esophageal ESD, although fortunately, these were almost subclinical [31]. Damage of the muscular layer might lead to delayed perforation, which could become fatal mediastinitis. Therefore, it is necessary to follow-up the patient carefully, especially after perforation, muscular injury and severe thermal damage. In case of perforation, we should keep patients at rest with fasting and intravenous administration of antibiotics until a fever and inflammation are relieved. Generally, emergency endoscopy for the purpose of detection and closure of a perforation site is not indicated because it may be not only ineffective but also a cause of expansion of mediastinitis.

9.5.3 Postoperative Stricture

The risk of postoperative stricture is particularly higher in esophageal ESD [10, 11]. Because the probability of stricture mostly depends on the resected size, a lesion over three-fourths of the circumference is relative indication of ESD as previously mentioned. Several attempts to prevent postoperative stricture have been tried [33–39]. Of them, locoregional injection or systemic treatment of steroids are known to be effective to prevent stricture formation after wide field ESD. Triamcinolone acetonide (TAC) is a type of corticosteroid that is used for locoregional injection as a slurry (Fig. 9.4). Some studies have revealed the significant superiority of locoregional TAC injection to historical control in preventing post-ESD esophageal stricture [33, 34]. Though it is effective to prevent post ESD stricture, the effectiveness is not enough for wider lesion such as full circumferential lesion and incidental TAC injection into proper muscle layer would cause mural necrosis [40]. Systemic administration of steroid is another option, which would prevent stricture formation even after circumferential ESD [31], but there is also a concern over adverse events of systemic administration of steroids. Moreover, preclinical trials are also considered such as adipose tissue stem cell transplantation [41] or cultured cell sheet transplantation [42, 43] and small interfering RNA with anti-fibrotic properties [44] but there has been no definitive method so far. Further investigation would be necessary to overcome this problem.

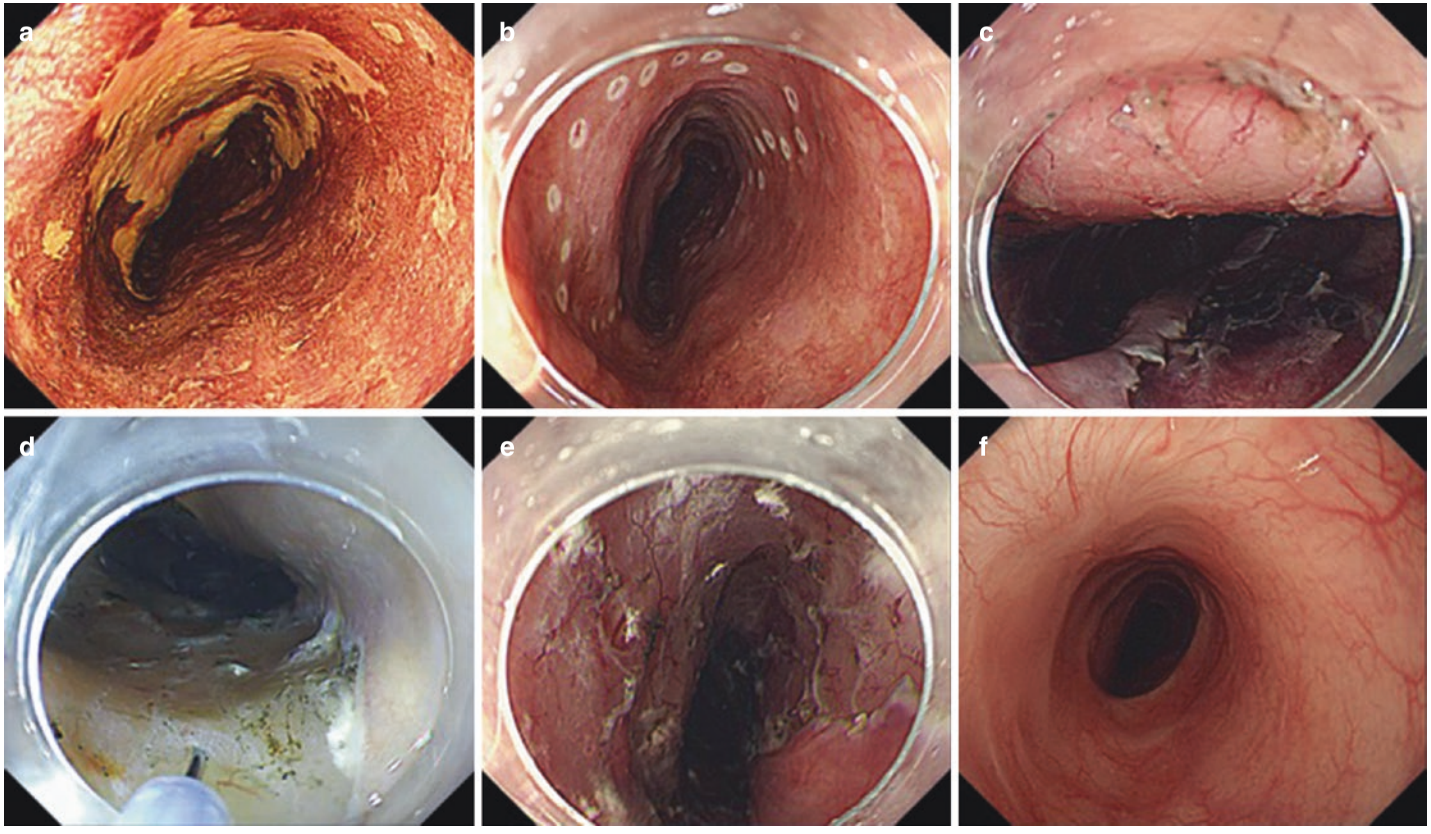

Fig. 9.4 Prevention of stricture formation after extensive resection. (**a**) Superficial cancer extending three quarters of circumference. (**b**) Placement of marking dots. (**c**) Resection wound become semi-circumferential. (**d**) Triamcinolone acetonide (TAC) is injected into the remaining submucosa in order to prevent severe stricture formation. (**e**) Artificial ulcer after resection. (**f**) Endoscopic imaging 6 months after initial ESD. The mucosal defect completely healed without severe stricture

9.6 Outcomes of ESD for Esophageal Squamous Cell Carcinoma

9.6.1 Short-Term Outcomes

Favorable treatment results have been reported from high volume centers particularly in Japan [27–30]. In short-term outcomes as a technical feasibility of esophageal ESD, over 90% of complete resection rate is obtained, whereas the rates of major complications such as delayed bleeding or perforation keep below 2% in leading centers for ESD. Even if complications occurred, it can be managed conservatively and thus hardly becomes a life-threatening condition. Considering the severity of potential post-surgical complications, ESD is an apparently less-invasive treatment option than surgery. However, in case of having severe stricture after extensive resection, multiple balloon dilatation is usually required. Stricture rate after ESD for the lesion involving over three-fourths of the circumference is reported to be 92% [12].

Technically, ESD for the lesion near the esophagogastric junction is sometimes difficult and time consuming because of intraoperative bleeding from abundant collecting vessels. The lesion located in the cervical esophagus, one of the natural constrictions, is also difficult to resect because of poor maneuverability of the endoscope and poor visibility of the lesion. Furthermore, the risk of aspiration pneumonia becomes extremely high by reflux of fluids (e.g., blood, rinsing water, and submucosal fluid). In this case, ESD with general anesthesia should be considered to avoid complications during the procedure.

9.6.2 Long-Term Outcomes

The long-term outcomes of ESD are also favorable. Five-year disease-specific survival rate is almost 100%. It means that endoscopic local resection is enough for curative resection in esophageal SCC with negligible risk for lymph node metastasis. On the other hand, close surveillance should be conducted for every patient after ESD to detect a metachronous cancer since all of them are regarded as high-risk group. Although there is no reliable evidence regarding an optimal surveillance strategy, endoscopy every 6–12 months are recommended after curative resection in cases of the absolute indication. When a treatment turned to be lateral margin positive or unknown for the absolute indication cases, endoscopy should be performed more closely (e.g., every 3–4 months) to detect local recurrence. In cases of the relative indication cases such as MM or SM1, a CT scan, as well as endoscopy every 6–12 months, is strongly recommended, if additional treatments (surgery or chemoradiatherapy) are refused after complete local resection.

9.7 Summary

Compared to other treatment options, endoscopic treatment is the most minimally invasive treatment for patients suffering from esophageal cancer with negligible risk for lymph node metastasis. To achieve successful endoscopic treatment, accurate preoperative diagnosis of the lesion, precise control of the endoscope, and adequate knowledge for possible complications are essential. ESD is far better than EMR since reliable margin free resection is available irrespective of the size or presence of submucosal fibrosis. Therefore, ESD can provide good quality of life to the patient, preserving gastrointestinal function, although it is technically demanding.

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