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CLINICAL AND PUBLIC HEALTH CHALLENGES OF CANCER

Endoscopic mucosal resection for esophageal and gastric cancers

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Abstract Better outcomes for digestive tract cancers are likely to be possible if the tumors are detected in their earliest stages, particularly when they exist as mucosal lesions without lymph node metastases. Early esophageal squamous cell cancers can be detected with high sensitivity and specificity by iodine staining. Only mucosal cancers are suitable for the curative approach of submucosal resection; the rate of metastasis is 4%, compared to a rate of metastasis of 35% in tumors with submucosal spread. In this review, the history of endscopic mucosal resection is reviewed, including the factors that have refined the technique and technical aspects crucial for effective results. The importance of adequate submucosal injection of dilute epinephrine in saline solution is particularly emphasized. The overall efficacy, low rate of complications and such practical aspects as post-therapeutic care are discussed. In general, mucosal cancers of the gastrointestinal tract have no risk of lymph node metastases and can be curatively managed by refined endoscopic mucosal resection procedures.

Key words: Barrett's esophagus, colon cancer, curative treatment, endoscopic mucosal resection, esophageal cancer, gastric cancer, mucosal lesions, perforation, post-therapy care.

GENERAL CONCEPTUAL APPROACH TO MANAGEMENT OF GASTROINTESTINAL CANCERS

In daily clinical practice, the majority of cases of gastrointestinal cancers are detected in an advanced stage when the person presents complaining of lesion-related symptoms; these include persistent pain, gastrointestinal obstruction, and bleeding. The prognosis for patients with advanced cancer is still poor, even when major surgery with wide-area lymph node dissection has been carried out in combination with multidisciplinary treatments (e.g. see review by Law and Wong on esophageal cancer in this issue). If we would like to have better outcomes for digestive tract cancers, one solution is to detect them in their early stages, particularly when they exist as mucosal lesions without lymph node metastasis.[1]

DIAGNOSIS OF EARLY ESOPHAGEAL CANCER

Squamous cell carcinoma

Normal esophageal mucosa is observed at endoscopy as smooth and flat with a whitish lustrous surface. Early stage esophageal cancer is characterized by changes of color and luster (matte appearance), with rough surfaces and margins that show a 'step-up' or 'step-down' transition. However, to detect such cancers is extremely difficult when early stage lesions are quite minute and fail to exhibit the above-mentioned typical characteristics. In practice, for type IIb lesions, no changes can be observed even after meticulous observation using videoendoscopy.

Fortunately, a very useful diagnostic technique in the esophagus is the iodine-dye-staining method. By spraying 2% potassium iodide solution on the mucosa, normal esophageal epithelium, which contains glycogen-rich granules in the prickle cell layer, is consistently stained dark brown. Conversely, cancerous lesions lose glycogen granules and are clearly demonstrated as uncolored areas which have a clear margin juxtaposed to iodine-stained normal mucosa. Using the iodine enhancement technique, well-demarcated unstained areas can be strongly suspected as squamous cell carcinomas; the technique has a high sensitivity and specificity.[2,3] Endoscopic pinch biopsy is essential for histological confirmation of the disease.

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Indications for mucosal resection of early esophageal cancer

The first requirement is infiltration depth, which should be m1 (superficial mucosal carcinoma, *in situ*) or m2 (deep mucosal carcinoma invades into lamina propria, but does not reach muscularis mucosa). The second requirement is that superficial spread is less than half the circumference of the esophageal lumen. According to the data from the Japanese national survey for histological evaluation of surgically resected esophageal-cancer specimens, mucosal cancers in which invasion depth is limited to lamina propria mucosal layer have only a 4% incidence of lymph node involvement. As opposed to this, cancers showing submucosal invasion have a 35% rate of lymph node metastasis. Therefore, only mucosal cancers are considered as appropriate candidates for mucosal resection in attempts to permanently cure the disease.

However, even submucosal cancers can be technically resected by this procedure, after first being lifted by submucosal saline injection. It may be appropriate to treat submucosal cancers by mucosal resection if the person refuses surgery or is a poor risk for esophageal resection.

Treatment of Barrett's esophagus

One of the major interests in treating Barrett's (columnar-lined esophagus) is the application of endoscopic mucosal resection (EMR). So far, the literature dealing with this subject is limited.[4] The first experience of EMR for adenocarcinoma on short segment of Barrett's esophagus was reported in 1990 by Inoue and Endo.[5] In the near future, EMR will be applied to reduction of Barrett's esophagus in combination with photodynamic therapy or thermal ablation therapies.

DIAGNOSIS OF EARLY STAGE GASTRIC CANCER

In early stage gastric cancer, the most often encountered findings are a combinaton of color change of the mucosal surface, lusterless, rough surface, irregular step-down margin (type 0, IIc), wide-base elevation (type 0, IIa) and so forth, using the terminology from the Japanese classification of gastric cancer.[6]

Dye-enhanced endoscopy is also useful in the stomach. Spraying indigocarmine solution enhances the above-mentioned irregularity of the mucosal surface.

Indications for mucosal resection

Absolute indications of mucosectomy in gastric cancer are as follows:

- differentiated adenocarcinoma;
- less than 10 mm mucosal cancer in IIb and IIc lesions without ulcer or ulcer scar;
- less than 20 mm mucosal cancer in IIa lesion.[7,8]

The data from the Cancer Institute Hospital in Tokyo deal with more than 10 000 resected gastric-cancer cases.[9] According to this experience, less than 10 mm IIc-type mucosal cancers carry no risk of lymph node involvement, and less than 20 mm lesions of the same category still have lymph-node involvement in only 0.4% of cases. Likewise, IIa-type mucosal or submucosal cancers that are less than 20 mm have no risk of lymph-node metastasis. It should be noted that the pretherapeutic diagnosis between mucosal and submucosal cancers in IIa-type elevated lesions is relatively difficult.

In contrast to the above categories of early gastric cancer that have a good prognosis, submucosal cancers that are slightly larger (but less than 30 mm) have lymph node involvement in 29% of cases. Finally, in poorly differentiated carcinoma, there is some risk of lymph-node metastasis that exists with small lesions. It follows that this kind of lesion should be generally excluded from consideration of mucosal resection.

TREATMENT OF EARLY STAGE CANCERS IN THE ESOPHAGUS AND STOMACH BY ENDOSCOPIC MUCOSAL RESECTION

The various kinds of local treatment that can be applied to treat mucosal cancers include laser ablation, argon-plasma coagulator, and irradiation. However, EMR is the only procedure in which a resected specimen is obtained, so as to contribute to the final histopathological diagnosis. We originally developed the endoscopic mucosal resection using a cap-fitted endoscope (EMRC) procedure, which we now believe to be the simplest technique for performing mucosectomy in any part of the gastrointestinal tract.

Principle of endoscopic mucosal resection

The gastrointestinal tract basically consists of two major components, mucosal layer and muscle layers. Mucosa develops from internal germ, while the muscle layers are derived from middle germ of viviparity. These two components are attached to each other by loose connective tissue of submucosa and can be easily separated by external force. That is the reason why we can resect mucosa only from inside the cavity, leaving the remaining muscle layer intact.[10]

The wall of the gastrointestinal tract is less than 4 mm thick. Because of this, special management to avoid perforation is extremely important. It is now universally agreed that injection of saline solution into the submucosal layer is the easiest and most effective technique to avoid muscle involvement. Lifting of mucosa can always be demonstrated during submucosal saline injection anywhere in the gastrointestinal tract; there are no exceptions. After a sufficient volume of saline has been injected, the mucosa, including the target lesion, can be safely captured into the cap, strangulated by snare wire, and resected by electrocauterization.

History

In 1955, during the era of rigid endoscopy, Rosenberg[10] reported the importance of submucosal saline injection during polypectomy of rectal and sigmoidal polyps. Mucosal resection for early gastric cancer was first performed in Japan around 1983. The original strip-off biopsy technique advocated by Tada *et al*. was 'injection and snaring'[11] (Table 1). By this method, submucosal injection makes a bleb which is then cut by snare strangulation. This procedure was reported by Dehle *et al*. in 1973 as a technique for resection of sessile colonic polyps.[12]

Another technique of EMR recommended by Takekoshi *et al*. was 'grasping and snaring'[7] (Table 1); this involves retracting the mucosa by a grasper and then strangulating it by use of a snare wire. This technique was reported by Martin *et al*. in 1976.[13] 'Injection and snaring' and 'grasping and snaring' have now been combined and integrated into a so-called 'strip biopsy', that is, submucosal saline injection creating a bleb, and then mucosal retraction by grasper and capturing by snare loop. Hirao *et al*. reported the 'injection, precutting and snaring' technique.[14] This means that, after submucosal injection, target mucosa is cut by an electrocautery needle knife, and then the isolated mucosa is captured by snare wire (Table 1).

Monma and Makuuchi reported the first experience of EMR in the esophagus, utilizing a so-called 'strip-biopsy' technique in 1989 (injection, lifting and snaring).[15,16] At the same time, Inoue and Endo reported the EMR tube (EMRT) procedure which performs the 'lift and cut' method; a specially designed EMRT tube is employed[5] (Table 1). In this paper, the first experience of EMR for adenocarcinoma present in short segment Barrett's esophagus was reported. Makuuchi also developed an endoscopic esophageal mucosal resection (EEMR) tube method.[17] This method allows a larger specimen to be obtained compared to other techniques. A modified Makuuchi tube is used in Kawano's technique. This modified tube has a lateral window that serves as the mucosal trap[18] (Table 1).

We refined our EMRT approach[5] to develop the EMRC procedure[19–22] (Table 1). Endoscopic mucosal resection using a cap-fitted endoscope made the procedural techniques simpler and easier, and made its application more readily applicable to any part of the gastrointestinal tract from the pharynx to the anus, but precluding the small intestine. The principle of the EMRC procedure is based upon the endoscopic variceal ligation (EVL) technique developed by Stiegmann.[23]

Endoscopic mucosal resection utilizing variceal ligating device (EMRL) is a technically simple and safe procedure (Table 1). Masuda *et al*. in Japan, Chaves *et al*.[24] and Freischer *et al*.[25] have all reported experience with the EVL device. This method is basically similar to the EMRC procedure by dividing the EMRC procedure into two steps. It is technically simple, but is appropriate only to resect relative small lesions (less than 10 mm) because the size of the specimen is limited by the small capacity of the ligation cap.

Soehendra *et al*. introduced an extremely simple technique (simple suction technique) of mucosectomy[26] (Table 1). In their method, no accessory device is necessary to perform the procedure except for a specially designed snare. The snare is made of monofilament stainless steel wire and has a diameter of 0.4 mm. A large-channel endoscope (Olympus GIF-1T; Olympus, Tokyo, Japan) is utilized in combination with the special snare because the GIF-1T endoscope provides adequate suction alongside an inserted snare. The size of the resected specimen seems to be smaller than other techniques, but the simplicity of this procedure is potentially interesting. Ohkuwa *et al*. developed an insulated-tip diathermic knife.[27] This device makes precutting procedures easier and safer.

Table 1 Classification of endoscopic mucosal resection techniques

I. Without suction techniques
1. 'Strip-off biopsy' (injection and snaring)[11,12]
2. 'Lift and cut biopsy', 'double-snare polypectomy' (grasping and snaring)[5,13]
3. 'Endoscopic resection with hypertonic saline-epinephrine solution' (injection, precutting and snaring)[14,27]
4. 'Endoscopic mucosal resection using a transparent overtube' (grasping and snaring using an overtube)[5]*

II. With suction techniques
1. 'Endoscopic esophageal mucosal resection tube method' (injection and snaring using an overtube)[16]*
2. 'Endoscopic esophageal mucosectomy under negative-pressure control' (injection and snaring using an overtube)[17]*
3. 'Endoscopic mucosal resection using a transparent plastic cap' (injection and snaring using a cap)[18,19]
4. 'Endoscopic mucosal resection using a ligating device' (endoscopic variceal ligation and snaring)[24,25]
5. 'Simple-suction technique' (snaring using stiff snare)[26]*

*Techniques are only available to the esophagus.

Our technique of endoscopic mucosal resection using a cap-fitted endoscope

'Cap' refers to a distal attachment onto the tip of a forward-view endoscope. The cap is made from transparent plastic material. The EMRC procedure will now be described in eight steps.

• Step 1. In preparation for the EMRC procedure, a cap is attached to the tip of the forward-view endoscope and fixed tightly with adhesive tape. The cap is commercially available worldwide (Distal attachment®; Olympus). The author prefers to use the largest cap in upper gastrointestinal endoscopy. For the initial session of EMR in the esophagus or stomach, an oblique-cut large-capacity cap with rim (MAJ297; Olympus) is selected and fixed onto the tip of the standard-size endoscope (Q240, Q160; Olympus). This allows a larger sample to be obtained. For the trimming of a residual lesion, a straight-cut medium-size cap with rim (MH595; Olympus) is appropriate.

• Step 2. Superficial extension of mucosal cancer is often difficult to recognize accurately by routine endo-

scopic observation, but is clearly delineated by chromoendoscopy. For squamous cell carcinoma of the esophagus, iodine dye solution (2% potassium iodide) is the most promising dye. It demonstrates the lesion clearly as an uncolored area. In the stomach and colon, spraying of indigocarmine solution emphasizes the surface relief. The mucosal surface that surrounds the margin of the lesion is carefully marked by the tip of the snare wire. Markings are positioned 2 mm apart from the actual lesion margin. Color enhancement at chromoendoscopy disappears within a couple of minutes, and therefore marking by electrocoagulation becomes essential, especially for a flat lesion.

• Step 3. The submucosa is injected with epinephrine saline solution (0.5 mL of 0.5% epinephrine diluted into 100 mL of normal saline) with an injection needle (23 gauge, 4 mm tip length). It is technically easy to control the position of a needle tip into the submucosal layer. To achieve this, puncture the mucosa at a sharp angle; the key point is to avoid transmural penetration of the needle tip. The total volume of injected saline depends on the size of the lesion; it is necessary to inject enough saline to lift the whole lesion. Usually, more than 20 mL is injected. In principle, normal mucosa distal to the lesion is punctured first. When saline is accurately injected into the submucosal layer of any part of the gastrointestinal tract, lifting of the mucosa or bulging of the mucosa is always observed. The injected area is also recognized as a whitish swelling. By injecting a sufficient volume into the submucosal space, any type of EMR procedure can be performed quite safely.

• Step 4. A specially designed, small-diameter snare SD-7P (1.8 mm outer diameter; Olympus) is essential to the 'prelooping' process. The snare wire is fixed along the rim of the EMRC cap. To create prelooping conditions, moderate suction is at first applied to the normal mucosa to seal the outlet of the cap (Fig. 1, top). After this, the snare wire that passes through the instrumental channel of the endoscope is opened (Fig. 1, middle). The opened snare wire is fixed along the rim of the cap, and the outer sheath of the snare sticks up to the rim of the cap (Fig. 1, bottom). This completes the prelooping process of the snare wire.

• Step 5. When the endoscope approaches the target mucosa after submucosal saline injection has been made (Fig. 2, top), the target mucosa, including the lesion, is sucked fully inside the cap (Fig. 2, middle). It is then strangulated by simple closing of the 'prelooped' snare wire. At this moment, the strangulated mucosa looks like a snared polypoid lesion (Fig. 2, bottom).

• Step 6. The pseudopolyp of the strangulated mucosa is cut by blend-current electrocautery. The resected specimen can be easily captured by keeping it inside the cap without using any grasping forceps.

• Step 7. The smooth surface of the muscularis propria layer can now be observed at the bottom of the artificial ulcer. Bleeding is usually minimal or not at all. If there is any bleeding, it stops spontaneously after compression of the lateral wall of the transparent cap. To confirm complete resection of the lesion, iodine dye spraying is useful.

• Step 8. If additional resection is necessary to remove any residual lesion completely, all the above procedures,

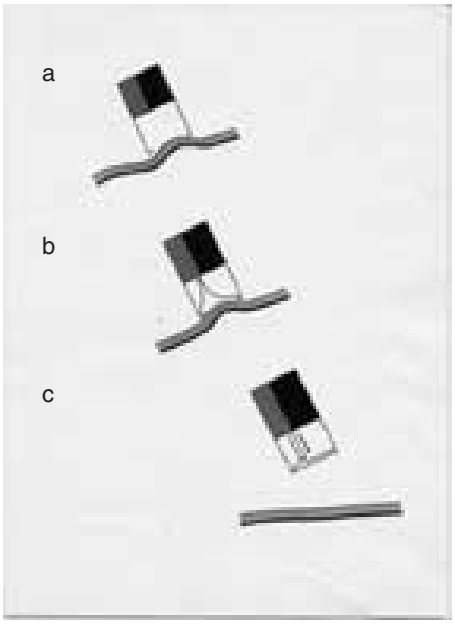

Figure 1 Schema of the endoscopic mucosal resection using a cap-fitted endoscope (EMRC) procedure. 'Pre-looping'. (a) Suck the normal mucosa and seal the outlet of the EMRC cap. (b) Open the snare wire and then it goes along the rim of the cap. (c) 'Pre-looping' condition is created. Outer sheath of the snare is pushing up to the distal end of the cap.

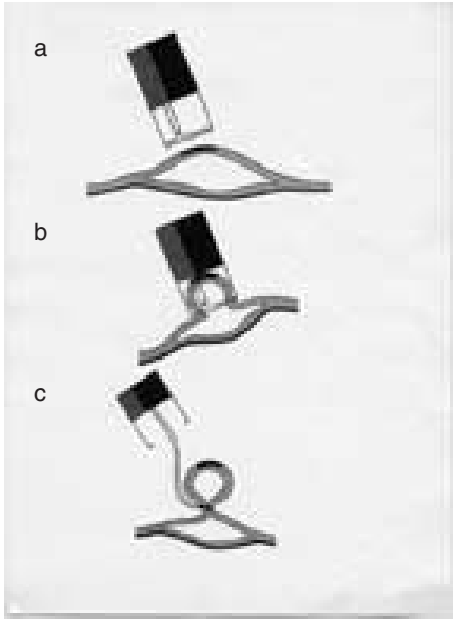

Figure 2 Schema of the endoscopic mucosal resection using a cap-fitted endoscope procedure. Approach to the target mucosa. (a) Approach onto the target mucosa. (b) Draw the target mucosa inside the cap. (c) Close the snare wire and then create an artificial polyp. The snared mucosa is cut by electrocautery.

including saline injection, should be repeated step by step. Injected saline usually infiltrates and disappears from the initial injection site within approximately 5 min, thereby terminating the role of the saline as a cushion between the mucosal and muscle layers. Therefore, repeated saline injection is necessary to reduce the risk of muscle involvement during extension of the resection procedures. In our single experience of esophageal perforation, this happened at the second strangulation without there having been an additional saline injection.

Histopathological assessment

Resected specimens should be stretched and fixed on a rubber plate using fine needles, and then bathed in 10% formalin. Formalin-fixed specimens are divided into 2 mm columns. Histopathological analysis of semiserial sections makes it possible to reconstruct the superficial extensions of the cancer.

Healing processes after endoscopic mucosal resection

Three days after EMR, the artificial ulcer is covered by a white coat. Twelve days later, the ulcer is almost recovered with thin but normal squamous epithelium.

Almost all patients complain of minor throat and retrosternal pain after EMR of the esophagus. This resolves within a couple of days if medication is given.

Just after EMR, a mucosal protective agent (sodium alginate) should be started. Antibiotics are also administered intravenously for the first 2 days, followed by oral antibiotics for 7 days. In our experience, one patient who was treated by near-total circumferential resection in the esophagus and who then received only antibiotics for only 2 days developed a severe stricture. That stricture was considered to be caused by chronic persistent inflammation.

A few hours after treatment, the patient may drink cold water. On the following day, they can eat a soft meal. On the second day after treatment, a normal diet can be resumed.

Quality of life after endoscopic mucosal resection

In almost all cases of mucosal resection, a good quality of life can be maintained.[28] Because of these excellent results, we believe that early detection of cancerous lesions and treatment of them by EMR is the ideal goal of cancer treatment in the gastrointestinal tract.

CLINICAL RESULTS

In our institute, more than 250 cases of early stage esophageal cancer have been treated with mucosal resection, mainly by two techniques.[28]

Among all cases, 72% exhibited absolute indications for mucosal resection according to our criteria described earlier. The rest were relatively indicated cases because of poor risk for surgery or refusal to have curative surgery. In absolutely indicated cases, no local or no distant metastases occurred during the follow-up period. The 5-year survival rate was 95%, including all causes of death. All those who died during the 5-year follow-up period suffered from other fatal diseases such as myocardial infarction, liver cirrhosis and stroke.

Among major complications in the esophagus, one patient in our early series encountered perforation during the second cauterization. Recovery followed conservative treatment (parenteral hyper-alimentation and antibiotics) and, 8 years later, she is healthy, with no complaints related to this complication. Another patient who received near total circumferential mucosal resection developed persistent stenosis that could not be controlled by repeated balloon dilatation; it was finally treated surgically by esophagectomy. Five years after esophagectomy, he is alive and well. The final major complication was persistent stenosis after healing of the artificial ulcer. This disaster can happen when near total circumferential resection is performed in the esophagus or prepyloric region of the stomach. We therefore try to avoid near total or total mucosal resection at all times.

In the stomach, we have treated more than 100 cases by the same procedure without encountering major complications. In three cases with lesions on the lesser curvature of the gastric body, resected specimens included small particles of muscle; all three were treated conservatively by prolonging the period before resumption of oral intake. In all but two of the more than 100 cases, the mucosal lesions were completely resected. These two cases had residual lesions after the initial EMR that were successfully treated by laser ablation therapy. During more than a 5-year follow-up period, we encountered no local recurrence of tumors among absolutely indicated cases of gastric cancers treated.[29]

In the duodenum, the wall is thinner than the esophagus and stomach. Therefore, it is considered to be easily perforated. However, inducing mucosal bleb formation by submucosal saline injection produces a prominent elevation, so that achievement of EMR in the duodenum is not technically difficult. Some cases of EMR for duodenal tumors have been reported.[22,30,31]

Mechanism of perforation

In order to evaluate the mechanism of perforation during EMR objectively, surgically resected specimens of human esophagus, stomach and colon were studied *ex vivo*. Specimens were stretched on a rubber board and then sunk into a basin filled with de-aerated water. The EMRC procedure was performed on the fixed specimens and the whole process was sonographically recorded on videotapes. In the EMR procedure without saline injection, the muscle layer beneath the surface mucosa was also drawn into the cap together with the covering mucosa. This indicates the potential risk of muscle involvement at the moment of closure of the

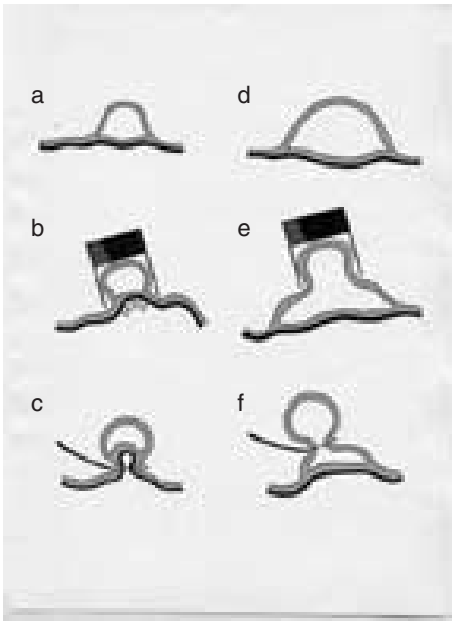

Figure 3 (a) Small-volume injection of saline creates a small bleb. (b) During suction of the target mucosa, muscle layer is also sucked into the cap. (c) Muscle layer involvement. (d) Large volume saline injection creates a large bleb. (e) Even during full suction, only the top of the bleb is captured inside the cap. (f) Mucosa is strangulated at the middle part of the bleb. This makes the procedure safe.

snare loop. Even if saline is injected, small volume injection is not sufficient to avoid the muscle involvement; it only creates a small bleb (Fig. 3a).

Full suction on a small bleb causes muscle movement into the cap. This results in muscle strangulation with the mucosa (Fig. 3b,c). Extra-large volume saline injection creates a large bleb (Fig. 3d). This large cushion mechanically prevents the muscle involvement during snare strangulation (Fig. 3e,f). In other words, snaring of the mucosa should not be done at the base of the lifted mucosa (Fig. 3b) and should always be done at the middle part of the lifted mucosa (Fig. 3e).

As is mentioned above, the largest risk factor that potentially causes perforation is the lack of submucosal saline injection. In order to prevent perforation, large-volume saline injection is considered to be important. In the esophagus, around 20 mL saline causes more than half-circumferential mucosal dissection, keeping the mucosal surface about 1 cm apart from the muscle layer. Endoscopic mucosal resection can generally be performed safely in the stomach because it has a relatively thick muscle layer. But at the lesser curvature in the upper and middle thirds, special attention should be paid to avoid muscle involvement, because stretching of the mucosa is primarily limited. Use of either a small-capacity cap, or reduction of the suction power makes the procedure safer.

In the colon, much attention should be paid to avoid perforation. This is because a relatively large-size cap is utilized for EMR in the colon, while the muscle layer is thinner than in the wall of other parts of the gastrointestinal tract. As has been already described, we have so far experienced two perforations, one of which was in the colon. The case of colonic perforation happened early in our experience; only 5 mL saline was injected and, as a consequence, only small lifting of the mucosa was observed. This case received laparoscopic closure of the perforation by utilizing a mechanical stapler. After this experience, the author started to inject usually at least 10 mL for each snaring. Thus, especially in the colon, larger volume injection and controlled suction is recommended.

Large volume saline injection is a safe procedure. In our experience, during removal of a creeping tumor in the rectum, a total of about 100 mL of saline was injected. The whole lesion was removed safely after inducing half-circumferential ulceration. In this case, the post-therapeutic course was uneventful, and it is therefore considered that large volume injection of saline is a safe procedure.

Control of bleeding from the ulcer bed

Low-concentration epinephrine saline solution is impressively effective in the control of bleeding during EMR. In the esophagus, submucosal injection of that solution results in almost complete hemostasis. However, in the stomach, bleeding from the artificial ulcer can sometimes not be controlled. At the moment, placing a hemostatic clip is the most reliable and safe therapeutic modality to control spurting bleeding from the ulcer bed.[28] In the colon, bleeding is quite rare; pure saline without epinephrine is enough to prevent bleeding. As a result, bleeding from ulcer bed can be relatively easily controlled.

CONCLUSION

In general, mucosal cancers of the gastrointestinal tract have no risk of lymph node metastases. Therefore, they can be curatively managed by EMR procedure.

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