



Endoscopic mucosal resection

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Introduction

Increasing concerns regarding the burden of cancer have led to growing efforts to achieve early endoscopic detection and treatment of cancer in the gastrointestinal mucosa. Secondary prevention of cancer depends on simultaneous detection of early malignant lesions and their premalignant precursors. The risk of developing cancer is significantly increased in individuals who have focal premalignant lesions. Early detection can be achieved either incidentally during examinations in individuals who do not have any alarm symptoms for cancer, or in mass screening programs, which increase the yield of early cases.

In Western countries, the prevention of colorectal cancer depends on detecting and resecting adenomatous polyps. In Japan, the health-care authorities have focused special attention on the early detection of gastric cancer, which is responsible for the major part of the cancer burden there, since 1965; mass screening and incidental screening have led to some 40% of all gastric cancers being detected when they are still at a localized stage. The 5-year survival rate in patients with gastric cancer in Japan is double that in other countries. Protruding premalignant precursor lesions (polyps) play a minor part in gastric carcinogenesis, and 95% of early cases of cancer (i.e., superficial tumors) are detected as flat lesions. This explains the special attention given in Japan to details of the endoscopic morphology of nonpolypoid neoplastic lesions (type 0) with the elevated, flat, or slightly depressed subtypes. Japanese researchers have also shown that the majority of early neoplastic lesions in the esophagus, as well as nearly 50% of colonic neoplastic lesions, have a nonpolypoid morphology.

The resection of nonpolypoid neoplastic lesions requires initial lifting of the lesion. Polypoid lesions are nowadays treated using polypectomy, while nonpolypoid lesions are treated using a method of strip resection known as endoscopic mucosal resection (EMR). The EMR techniques that were developed for the treatment of early gastric cancer are now increasingly being adapted for the treatment of similar lesions in the esophagus and colon.

Rationale of EMR

Established indications

Assessment of lymph-node status. EMR is a curative procedure for early cancer or lesions capable of harboring focal cancer, provided that the risk of positive lymph nodes is zero or near-zero (less than 3%). The risk is minimal when the depth of invasion is limited to the mucosa or to the superficial part of the submucosa. At a

similar depth of invasion, the risk is higher with squamous-cell cancer than with adenocarcinoma, and it is higher for poorly differentiated tumors.

Resection methods. EMR is curative if resection of the localized malignant or premalignant tumor is complete. There is no doubt that en-bloc resection of the lesion in a single fragment achieves a higher degree of complete destruction, with a lower risk of local recurrence, than piecemeal resection in multiple fragments. In the large series reported by the National Cancer Center in Tokyo [Ono et al. 2001], the rate of recurrence of early gastric cancer was 2% after en-bloc resection (244 cases), 6% after resection in two fragments (134 cases), and 26% after resection in three fragments (24 cases). This means that en-bloc resection is required for the treatment of early cancer and if technically possible is also preferable for large premalignant lesions.

■ *Treatment decision*

Even in elderly individuals, early-stage cancer requires treatment, not surveillance. Surveillance is an alternative to resection for low-grade premalignant lesions. Systematic treatment is required for intramucosal or submucosal carcinoma and high-grade, noninvasive intraepithelial neoplasia. The worldwide 5-year survival rates after treatment for early cancer by surgery or EMR are similar, but with the following differences: the postoperative morbidity rate is higher after surgery, while incomplete treatment may occur with EMR. The decision on whether to carry out surgery or EMR depends on the morphology of the lesion. Guidelines can be helpful for selecting the indications for surgical or endoscopic treatment, respectively. If the lesion meets the established criteria for endoscopic treatment, EMR is the first-line method; surgery can be offered as a second-line treatment if EMR fails. Endoscopic diagnosis involves two distinct steps: firstly, detection of irregularities on the surface, changes in color, or an abnormal pattern in the superficial vessels; and secondly, characterization of the lesion, including its size and classification in the subtypes of type 0 of the Paris classification.

■ *Data on the risk of positive lymph nodes*

Detailed studies on the risk of lymph-node invasion in relation to whether EMR is a justifiable method of treatment have been conducted for superficial gastric cancer in Tokyo. In an experience including more than 3000 cases, in which the diameter, the presence of an ulcer, and the grade of differentiation of the lesions were taken into account, EMR was found to be safe for well-differentiated intramucosal tumors even if they were larger than 2–3 cm in diameter and if there was no ulcer, and for ulcerated tumors smaller than 2 cm in diameter. EMR is safe in nonulcerated cancers less than 3 cm in size with submucosal invasion. EMR is not safe for well-differentiated intramucosal tumors that are larger than 3 cm (3%) with an ulcer; nor is it safe for poorly differentiated tumors with either an ulcer (5%) or invasion in the submucosa (10%).

The frequency of submucosal invasion depends on the morphology of the superficial carcinoma, as shown in Japanese series: in esophageal squamous-cell cancer (1562 cases) the risk of submucosal (sm) invasion is 79% in 0-I polypoid, 48% in 0-IIa slightly elevated, 15% in 0-IIb completely flat, and 27% in 0-IIc slightly depressed. The respective figures for gastric cancer (in 2098 cases) are 57% in 0-I, 29% in 0-IIa, 20% in 0-IIb and 40% in 0-IIc; and for colonic cancer (in 3680 cases) 5% in 0-Ip, 34% in 0-Is, 4% in 0-IIa, 0 in 0-IIb, and 61% in 0-IIc. The data also show

the progression of lymph-node metastases relative to the depth of invasion into the submucosa. The depth of invasion, from the lower layer of the muscularis mucosae, has been assessed in surgical specimens using a micrometer scale. The risk is very low when the invasion is less than a determined limit: 200 μm for squamous-cell cancer in the esophagus, 500 μm for adenocarcinoma in the stomach, and 1000 μm in the colon.

■ *Checking treatment efficacy*

After EMR, histopathological analysis of the specimen can be used to assess the efficacy of the procedure. In the endoscopy room, the specimen is prepared and fixed in neutral formalin. Preparation is easy with en-bloc resection, but assessment of the margins of the lesion is more difficult after piecemeal resection. For malignant lesions, there should be a 2-mm margin of nonneoplastic tissue around the lateral and bottom margins of the lesion, and the depth of invasion into the submucosa should be measured. Qualitative indices of a poor prognosis include the tumor grade, images of vascular invasion, and tumor budding.

📺 **Step-by-step method**

The method of EMR for nonpolypoid lesions has been described in a large number of publications [Inoue et al. 2002, Kudo et al. 2000, 2001, Makuuchi et al. 2001, Miyamoto et al. 2002, Ohkuwa et al. 2001, Rembacken et al. 2001, Shim 2001, Suzuki 2001, Tanabe et al. 2002, Tsunada et al. 2003, Yamamoto et al. 2001, 2002, 2003, 2005]. Despite the many technical variations that have been introduced and continuing technological developments in endotherapy devices, lesions in the esophagus, stomach, and colon are treated according to the same principles:

1. Marking the lesion. The first step is to mark the boundaries of the lesion, including the safety margin, on the surface of the mucosa. This is easily done with the point of a diathermy snare. Alternatively, clips with modified shortened arms (5.5 mm) and a maximum opening width of 6.5 mm can be used as markers.

2. Lifting the lesion. The next step is to lift the lesion above the level of the surrounding mucosa by injecting a solution of saline and epinephrine (0.025 mg/mL) into the submucosa using a special needle placed at an angle of 45°. A single injection is carried out for small lesions. With larger lesions, it is recommended that injections should be made at various points. The initial injection is made on the periphery of the lesion, at a distance from the tip of the endoscope, followed by injection into the lateral margins of the lesion closest to the tip of the endoscope. Puncture across the neoplastic lesion should be avoided. The effect of the injection in lifting the mucosa only lasts for a short time (4–5 min), and the injection may have to be repeated. Various agents have been suggested to keep the lesion raised for a longer time (over 20 min). Hyaluronic acid is effective but expensive; less expensive agents include Glyceol a glycerin solution (glycerol and fructose) and hydroxypropyl methylcellulose, which have effects equivalent to those of hyaluronic acid Fujishiro 2004, Feitoza 2003). Methylene blue (“baby blue”) or indigo carmine are often added to the solution to stain the submucosa blue, which helps assess the depth during and after resection. Lifting is also helpful for confirming whether the procedure is indicated – if the lesion fails to lift (the “nonlifting sign”), there is a strong suspicion of deep invasion into the submucosa.

3. Resection of the lesion. The third step is resection of the lesion, which can be done with a snare and blended diathermy current, or with a knife with cutting current. Most high-frequency electrosurgical generators (Olympus HF120, Erbe ICC 200) do not provide pure cutting current, and instead have an Endocut mode that makes it possible to change the ratio between cutting and coagulation current.

4. Recovering the specimen and checking the resected area. After resection, the specimen is recovered and carefully prepared for histopathological examination. All fragments have to be recovered after a piecemeal resection. The resection area is carefully scrutinized to check that the resection is complete and to detect any signs of perforation or bleeding. For hemostasis, the clip method tends to be preferred to hemostatic injections; however, Hemoclips can sometimes create obstructions if the EMR procedure is continued. Another hemostatic technique is to grasp the bleeding vessel with a hot-biopsy forceps, lift it, and coagulate it.

There is debate regarding whether the treated zone should be protected by a suture with clips. The scar heals more rapidly after suturing, and the risk of secondary stricture is reduced.

EMR procedures

■ *Snare resection*

EMR strip. This is the basic procedure [Kudo et al. 2001], used in all parts of the digestive-tract mucosa. The snare is progressively pressed and tightened around the lifted lesion and transected with blended diathermy current. Various types of improved snare have been suggested in order to prevent the snare from slipping over the surface of the mucosa – such as snares with barbs and spiral snares in which the twisted wire works in the same way as barbs. En-bloc resection of a lesion up to a diameter of 2 cm is possible. Larger lesions require the piecemeal technique.

EMR cap (EMR-C). This technique is used in the esophagus and stomach [Inoue et al. 2002] and can also be used in the duodenum, but not in the colon. A transparent attachment (cap) is attached to the tip of a single-channel endoscope, and a crescent-shaped diathermic snare is prelooped along the distal rim of the cap. The lesion is then sucked into the cap, and the base of the artificial polyp thus created is strangulated with the snare, which is then pushed outside of the scope for the final resection step using blended diathermy. With the standard cap, en-bloc resections of up to 1.5 cm are possible. En-bloc resections are possible up to 2 cm with a recently developed model that has a soft and large cap (18 mm), which is still easily swallowed. Piecemeal resection is possible for larger lesions.

EMR ligation device (EMR-L). This technique is an alternative to the cap method [Suzuki 2001]. It involves using the transparent cap of the endoscopic ligator kit for suction and placement of a ligating band. A snare is then passed through the working channel to resect the strangulated segment of mucosa above or below the constricting rubber band. This method is easier in areas that are difficult to approach in the stomach, such as the upper third of the lesser curvature. The EMR-L technique is convenient for en-bloc resection of small lesions.

EMR grasping. In this technique, the lesion is lifted by aspiration into the window of a transparent overtube, and the snare is passed through the accessory channel of the transparent tube. Alternatively, use a double-channel endoscope is used. The

lifted lesion is grasped with a jumbo grasping forceps that has been passed across the snare advanced through the other channel. This method makes it possible to resect slightly larger lesions en bloc.

■ *Needle-knife resection*

This method is based on a circumferential incision through the full thickness of the mucosa around the lesion, using a needle-knife and cutting current [Miyamoto et al. 2002, Ohkuwa et al. 2001]. It is possible to resect small lesions in all parts of the digestive tract with this method, but the specific application for it is en-bloc resection of a large surface of the gastric mucosa. A single-channel endoscope is required; a circumferential incision is made around the lesion, which is finally excised with a snare. The specimen is then removed with grasping forceps. En-bloc resection of lesions larger than 5 cm in diameter is possible in the stomach, but the procedure is quite lengthy and requires a high degree of expertise. There is a greater risk of bleeding and perforation if the cutting is excessively deep. Various types of improved needle-knife have been suggested to prevent perforation; there are triangular-tipped knives (TT knives) and hooked-tip knives (HT knives), but the most widely used type is the insulated-tip knife (IT knife), which has a small insulating sphere at the tip.

A further technical advance is shifting the boundaries between EMR and surgery. This is the method of submucosal dissection under direct vision [Yamamoto et al. 2005]. In EMR with submucosal dissection, the spontaneous retraction of the lesion that takes place after the circumferential incision is used to achieve progressive step-by-step dissection of the submucosa with the needle-knife below the surface. Dissection can progress until complete resection of the lesion has been achieved, or it can be completed with a snare. This technique is undoubtedly more precise and allows better control of invasion into the submucosa.

Complications

The overall risk of complications of EMR in the upper gastrointestinal tract has been estimated in recent statistics published by the Japanese Society of Gastrointestinal Endoscopy for the period 1993–97 at 0.5% (190 of 37 127 cases). However, higher figures (4–5%) have been reported in most individual series with defined follow-up periods. Two major complications of EMR are severe bleeding and perforation, which occur more often when the needle-knife is used. Clips for hemostasis are now available, either in single-use kits (Quick-Clip) or in packets of eight at lower cost. Clips for suturing, with a different angle in the final jaw, have also been suggested. Incomplete resection is a failure of the procedure rather than a complication.

Delayed hemorrhage (later than 24 h) after EMR in the esophagus or stomach is unusual; it may occur more often after EMR in the colon.

Alarm symptoms suggesting perforation into the peritoneal cavity during the procedure are abdominal pain (in unsedated patients), swelling of the abdomen, respiratory failure, and a drop in blood pressure on the monitor. Alarm symptoms suggesting mediastinal perforation are chest pain (in unsedated patients) and subcutaneous emphysema. Immediate treatment of perforation during the procedure is recommended, using two procedures: suturing for small perforations, or omental fixation for large ones; omentum that has herniated into the gastric lumen is fixed by clips on the mucosa surrounding the perforation. After the endoscopic procedure, the patient is kept fasting for a few days with a nasogastric tube, intravenous fluids, and

intravenous antibiotics, and consultation with a surgeon is needed. In the series reported by the National Cancer Center Hospital in Tokyo, gastric perforation occurred in 110 of 2520 EMRs (4%), 106 of which were immediately treated by endoscopic suturing.

Fibrosis and chronic stricture may occur when a large area of the mucosal surface has been resected. Suturing of the margins of the resected area at the end of the procedure reduces this risk.

Indications

Nonpolypoid premalignant and malignant precursors of advanced digestive cancer have been described in Japan; most precursor lesions in the esophagus and stomach, and 40% of those in the colon, have a nonpolypoid morphology. The EMR technique was developed in Japan to treat these lesions. In recent years, various studies in Western patients, conducted by a team including a Japanese expert, have confirmed the worldwide validity of the Japanese description. There is no doubt that the EMR technique deserves to be promoted throughout the world. The potential effect of EMR on the prevention of advanced digestive-tract cancer should be investigated. An estimate of the numbers of new (incidental) cases of digestive-tract cancer throughout the world is available in the International Agency for Research on Cancer's GloboCan database: for esophageal squamous-cell cancer, incidental cases in North America in 2002 are estimated at 15 700 in the esophagus, 24 900 in the stomach, and 183 500 in the colon and rectum. The respective figures for South America are 12 800, 52 500, and 46 300; for Africa, 24 300, 26 200, and 23 700; for Europe, including Russia, 43 000, 174 000, and 371 700; and for Asia, including Japan, 361 800, 637 000, and 369 600. The numbers of cases of early cancer in which EMR is potentially indicated represent some 10–25% of these figures. The numbers of cases of premalignant lesions in which EMR is potentially indicated are of course larger.

When EMR is carried out for confirmed or presumed nonpolypoid superficial cancer in the esophagus, stomach, or colon, resection should be complete and en bloc. When the guidelines are strictly observed, the 5-year survival is equivalent after EMR and surgical treatment. Piecemeal resection is still acceptable for low-grade and high-grade premalignant lesions and for sessile lesions (type 0-I) of the lateral spreading type in the colon.

In *squamous-cell stratified epithelium of the esophagus*, EMR is an elective treatment for intraepithelial cancer and cancer with superficial invasion of the submucosa when the diameter of the lesion is not more than 2 cm. Japanese reports show that the risk of lymph-node invasion is extremely low when the invasion of the submucosa does not exceed 200 µm.

In *esophagus lined with columnar neoplasia*, cancer in the mucosa or with superficial invasion of the submucosa is a justifiable indication for EMR if the diameter of the lesion is not more than 2 cm. As multiple neoplastic foci are frequent in the area with metaplasia, there is a trend to carry out extensive resection of the mucosa, ideally with a needle-knife and submucosal dissection; however, this technique is extremely difficult at this level, and the experience of German experts is that piecemeal resection with EMR-C or EMR-L is preferable [Pech et al. 2004, Rösch et al. 2004]. The histological distinction between inflammation and low-grade intraepithelial neoplasia is uncertain, and it is recommended that after a trial of acid-suppressive treatment, only those patients should be treated who are confirmed as

having low-grade neoplasia. Complete circumferential resection of metaplasia in patients without neoplasia is not recommended, as there is a significant risk of stricture and the risk of cancer is not eliminated.

In the *stomach*, cancer in the mucosa or with superficial invasion of the submucosa can be treated with EMR. According to the large Japanese series at the National Cancer Center in Tokyo, the risk of lymph-node invasion is extremely low when invasion of the submucosa does not exceed 500 μm . Strip biopsy and the cap method are often used, but there is a trend to use the needle-knife with submucosal dissection and en-bloc resection to achieve complete resection and a lower risk of recurrence, and to resect larger areas of mucosa. The National Cancer Center Hospital in Tokyo gathered experience with 2519 early gastric cancers in the period 1985–99. EMR was carried out according to the Japanese guidelines – lesions no larger than 2 cm for nondepressed lesions, no larger than 1 cm for depressed lesions, depth of invasion on histopathological examination no more than 500 μm . On average, the lesions treated with EMR were smaller than those treated surgically, and the proportion of intramucosal lesions was higher. Limited indications for EMR include superficial cancer up to a diameter of 20 mm for nondepressed lesions and up to 10 mm for depressed lesions. Broader indications include larger nondepressed lesions if they can be resected en bloc.

In the *small intestine*, most interventions are in the *duodenum*. High-grade and low-grade premalignant lesions in the papilla or around the papilla often have a nonpolypoid morphology and are treated by EMR using the EMR strip method after lifting of the lesion. Special attention needs to be given to surveillance of the duodenum in patients with familial adenomatous polyposis.

In the *colon*, specific attention is given to small flat and depressed lesions (0-IIc), which have a high risk of deep invasion into the submucosa. EMR is carried out for cancer in the mucosa or with superficial invasion (less than 1000 μm) for nondepressed lesions (0-IIa) no larger than 2 cm, and for depressed lesions (0-IIc) no larger than 1 cm. Other indications for EMR are being developed for nonpolypoid premalignant precursor lesions, particularly in the laterally spreading type with a large surface. For large premalignant lesions in the rectum, the piecemeal method should be replaced by the en-bloc method with a needle-knife and submucosal dissection, as an alternative to transanal surgery (Yamamoto et al. 2005).

EMR: in conclusion

In the esophagus, stomach, and colon, EMR is now a curative method of treating cancer in the mucosa, or cancer with superficial invasion of the submucosa. En-bloc resection is preferable to piecemeal resection and achieves better results. The needle-knife or IT knife with submucosal dissection requires more time and a higher degree of expertise, but is the only method that allows en-bloc resection for lesions larger than 2 cm. Second-line surgery is required if the depth of invasion into the submucosa is greater than the cut-off values of 200 μm in the esophagus, 500 μm in the stomach, and 1000 μm in the colon. Second-line surgery is also required if the resection is incomplete, with deeper involvement of the mucosa on the lateral margins. It is also required after incomplete resection on the surface and failure of repeated EMR. Surgery is still the most frequent treatment for early cancer, but the proportion of endoscopic treatments has been increasing since the introduction of the technique of submucosal dissection. Trends suggest that in the future, endoscopy will become incorporated into the sector of minimally invasive surgical procedures, possibly combined with wedge laparoscopy.

EMR is also an elective treatment for nonpolypoid premalignant precursor lesions. Most indications are in the esophagus with columnar metaplasia and in the rectum. An indication for EMR with submucosal dissection for large protruding premalignant lesions in the colon has yet to be established. In the colon, the piecemeal method with a snare is still acceptable, and EMR can be repeated if the resection is incomplete.

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The texts of all of these references are available at www.esge.com

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