Diagnosis and endoscopic resection of early gastric cancer

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ABSTRACT

The overall prognosis of gastric cancer is generally poor due to late presentation and diagnosis. When detected early, the prognosis for gastric cancer is excellent, and curative endoscopic resection may be possible, without the need for surgery. Careful endoscopic examination is important so as to avoid missed lesions. Endoscopic resection, especially with the technique of endoscopic submucosal dissection, is a viable alternative to surgery for the curative treatment of early gastric cancer, with similar long term results, as long as strict inclusion criteria are adhered to.

Keywords: diagnosis, endoscopy, gastric cancer, resection

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INTRODUCTION

Despite a temporal decrease in the incidence rates, gastric cancer (GC) remains a major clinical burden. Globally, it is the 4th most common cancer, and the 2nd most common cause of cancer death.[1] In Singapore, it is the 4th and 6th most common cancer in males and females, respectively, and the 4th most common cause of cancer deaths.[2] The age standardised rate (ASR) for Chinese males is 21.4 per 100,000, while that for Chinese females is 10.8 per 100,000. In contrast, the ASR for Malay and Indian males/females are much lower, at 6.6/3.8 and 7.8/6.1 per 100,000, respectively.[2] Chinese males are in a high-risk group, which is defined as an ASR greater than 20 per 100,000.[1] The overall survival for GC is poor due to late presentation and diagnosis. The five-year survival has been estimated to be 27% in Western Europe and 6% in sub-Saharan Africa. In Japan, the estimated survival rate, at 52%, is better due to earlier diagnosis from screening.[1]

To improve the prognosis of GC, one could attempt primary prevention by eradicating *Helicobacter (H.) pylori*, which is estimated to be responsible for 60%–85% of non-cardia gastric cancer.[3] In fact, *H. pylori* screening and eradication in high-risk populations for the purpose of GC prevention has been recommended by the Asia-Pacific consensus guidelines on gastric cancer prevention.[4] Equally important, but less contentious, would be the need to detect GC at an early stage. Early gastric cancer (EGC) may be potentially treated with endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). These endoscopic techniques were pioneered in Japan, and are now considered a standard alternative to surgery, and as a definitive therapy for patients who meet the treatment criteria.[5] Recently these techniques were introduced in Singapore. This review addresses the issues of diagnosis and curative endoscopic resection of EGC.

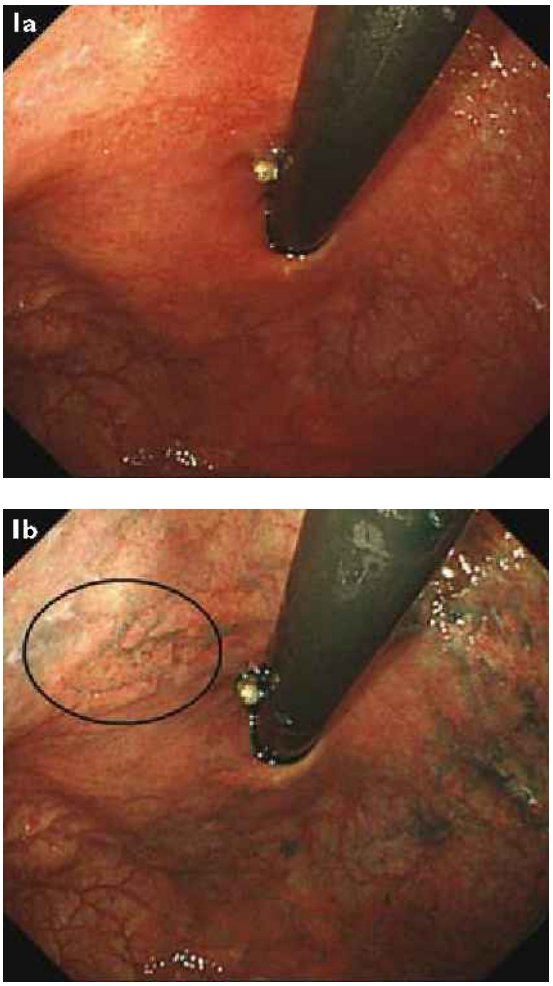

Fig. 1 Photographs show (a) early gastric cancer not clearly seen during endoscopy, (b) but highlighted by chromoendoscopy using indigo carmine.

DIAGNOSIS OF EARLY GASTRIC CANCER

High-quality endoscopic evaluation with biopsy is the key to diagnosis. Barium meal studies are alternative options,

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Table I. Endoscopic classifications of gastric cancer.

Early gastric cancer (Type 0):
Superficial protruding or non-protruding lesions
Protruding
Pedunculated: 0–Ip
Sessile: 0–Is
Non-protruding and non-excavated
Slightly elevated: 0–IIa
Completely flat: 0–IIb
Slightly depressed: 0–IIc
Elevated and depressed types: 0–IIc + IIa or 0–IIa + IIc
Excavated
Ulcer: 0–III
Excavated and depressed types: 0–IIc + III or 0–III + IIc
Advanced gastric cancer
Type 1: Protruding carcinoma, attached on a wide base
Type 2: Ulcerated carcinoma with sharp and raised margins
Type 3: Ulcerated carcinoma without definite limits
Type 4: Non-ulcerated, diffusely infiltrating carcinoma
Type 5: Unclassifiable advanced carcinoma

but they are not as sensitive. In a blinded, randomised cross-over comparative study of double-contrast barium meal and endoscopy, endoscopy was found to be significantly more sensitive (92% vs. 54%) and specific (100% vs. 91%), while the barium meal was found to have missed subtle lesions.[6] Even in Japan, where there is mass screening of GC using barium studies, most cases of EGC were detected during endoscopy.[7]

Much of the leadership in performing high-quality endoscopy comes from Japan, where the detection of early cancer is an integral part of every endoscopist's training. Western-style endoscopy training, employed in many non-Japanese Asian countries, including Singapore, emphasises the detection of gross lesions, and not subtle changes in colour, vascularity or texture, which are the hallmarks of EGC. Simple measures routinely performed in Japanese endoscopy centres may have a role to play in improving the endoscopic yield. Cleaning the endoscope lens with an alcohol-based swab before every procedure removes residues that can cause subtle degradation of the image quality. The preparation of a patient with a mixture of a defoaming agent combined with a mucolytic agent also results in improved endoscopic visibility. A systematic examination of the stomach during endoscope insertion and withdrawal, combined with an adequate air insufflation and endoscopic photography (30–40 photos in a typical Japanese esophagogastroduodenoscopy), as well as a systematic recording of the abnormalities by anatomic site, should be instituted. Approximately 10% of EGC have atypical endoscopic features and may be misdiagnosed as gastritis, erosions or ulcers. It is important that endoscopists maintain a high index of suspicion, and that a database of such endoscopic images be built up for educational purposes, especially for the less experienced endoscopists. The appropriate use of topical contrast agents, such as indigo carmine, will help to highlight subtle lesions (Fig. 1a & b).[8] Newer endoscopic imaging technologies, such as narrow-band imaging[9] and autofluorescence imaging,[10] may achieve the same results with the press of a button, and these are currently undergoing clinical evaluation.

Despite the widespread use of endoscopy worldwide, apart from Japan and Korea, the prevalence of EGC remains low. In one study, the prevalence was found to be 1%,[11] although higher rates of 15%[12] to 27%[13] have also been reported. A reported series from Singapore showed that 75% of the GC cases were in stages III or IV.[14] In Japan, where there is mass screening for GC from the age of 40 years, the prevalence of EGC ranges from 53%[13] to as high as 77%[15] to 89%,[16] in series where endoscopic screenings were performed. It must be remembered that there are no symptons in most cases of EGC,[7,15] and that detection of such cases may be incidental, through surveillance or during screening. Currently, there are no mass population screening programs except in Japan and Korea. In Singapore, a recent decision analysis based on modelling has suggested that it might be cost-effective to screen Chinese men aged 50–70 years old, who constitute a high-risk population.[17] At an individual level, endoscopy should be considered in conditions associated with increased risk for GC, such as a history of gastric adenoma, gastric intestinal metaplasia, pernicious anaemia, familial adenomatous polyposis and hereditary non-polyposis colorectal cancer syndrome.[18] Careful endoscopic examination is crucial. It is conceivable that part of the reason for the late diagnosis of GC, apart from late presentation, can be attributed to missed lesions. The estimated doubling-time for GC is 2–3 years.[19] If advanced GC were to be detected within three years of a normal endoscopy, it would imply an earlier missed lesion. The rates of missed diagnosis ranging from 4.6%[20] to 19%[21] have been reported. The measures described in the preceding paragraph can be expected to reduce these missed rates.

Once a lesion is detected, efforts should be made to describe it accurately. The macroscopic classification of early and advanced GC by the Japanese Gastric Cancer Association,[22] which has been internationally accepted,[23] is shown in Table I. EGC is described as Type 0, and may be subdivided into 3 main categories based on whether the lesion is protruding (0–I), non-protruding and non-excavated (0–II), or excavated (0–III) (Fig. 2). Type I lesions are classified as pedunculated (0–Ip) or sessile (0–Is), while Type II lesions are subdivided as slightly elevated (0–IIa), flat (0–IIb) and depressed (0–IIc).

Table II. Criteria for curative endoscopic resection in early gastric cancer.

	Mucosal cancer				Submucosal cancer	
	No ulcer		Ulcer present		Sm1 (< 500 um)	Sm2 (> 500 um)
Size (mm)	< 20	> 20	< 30	> 30	< 30	Any size
Differentiated cancer	EMR	ESD	ESD	Surgery	ESD	Surgery
Undifferentiated cancer	Surgery considered	Surgery	Surgery	Surgery	Surgery	Surgery

EMR: endoscopic mucosal resection; ESD: endoscopic submucosal dissection; Sm1: submucosal layer 1; Sm2: submucosal layer 2

Mixed patterns with elevations and depressions may also occur. The height or depth of the lesion is estimated using a pair of biopsy forceps (the diameter with closed jaws is 2.5 mm, while the diameter of a single jaw is 1.2 mm) placed longitudinally next to the lesion. Type 0–I lesions rise more than 2.5 mm above the adjacent surface, while lesions lower than this height are classified as 0–IIa. Lesions less than 1.2 mm deep are classified as 0–IIc, while deeper lesions are classified as 0–III. The classification into subtypes provides a consistent and easily understood endoscopic description of the morphology of EGC, and may help to predict the extent of invasion into the submucosa as well as guide the choice between endoscopic or surgical treatment.[23] For instance, the risk of submucosal invasion is higher with ulcerated lesions. Deep invasion to the muscularis propria is suggested if the lesion fails to lift after the submucosal injection (the non-lifting sign).

SCIENTIFIC BASIS AND CRITERIA FOR CURATIVE ENDOSCOPIC RESECTION

Surgery has traditionally been regarded as the standard of care for EGC. Endoscopic resection, whether EMR or ESD, is now well accepted in Japan and Korea, and is being increasingly recognised worldwide as a definitive therapy. The histopathological basis for endoscopic resection was established in a landmark paper that analysed 5,265 patients who underwent gastrectomy with lymph node dissection for EGC.[24] The key results were: (1) none of the 1,230 well-differentiated intramucosal cancers of less than 30 mm diameter in size, regardless of the presence of ulceration, was associated with nodal metastases (95% confidence interval [CI] 0%–0.3%); (2) none of the 929 intramucosal cancers without ulceration, regardless of size, was associated with nodal metastases (95% CI 0%–0.4%); and (3) none of the 145 differentiated adenocarcinoma of less than 30 mm in diameter, without lymphatic or venous permeation, with submucosal invasion of less than 500 um, was associated with lymph node metastases (95% CI 0%–2.5%).

The extended criteria for endoscopic resection (Table II) that is currently used in Japan[5] are based on these results. ESD for a given individual may be considered curative when the following criteria are fulfilled, following the histopathological reporting of the resected specimen: well- or moderately-differentiated histopathology; negative vertical margin (intramucosal lesion or extension into the submucosa for less than 500 micrometres; negative lateral margin; and no lymphatic or vascular invasion. These guideline criteria predict minimal or no risk of nodal metastasis, and if these criteria are met, they are therefore expected to yield long-term outcomes comparable to the gold standard of radical gastrectomy. The extended guidelines do not specify a size limit for non-ulcerated lesions that meet these criteria. If the lesion is ulcerated, ESD may be considered curative, up to a size limit of 30 mm, if all the other criteria are met.

If any of these guideline criteria are not met following the histopathological review, the patient is at risk of regional nodal metastasis, and should therefore be subjected to radical gastrectomy. An exception may be made if only the lateral margin is positive; these patients may be treated with repeat ESD or ablative therapy of the involved area, as mapped out by the pathologist. Therefore, the oral/anal orientation of the specimen that is labelled by the endoscopist is of great importance in the event that a lateral margin is found to be positive.

IS THERE A ROLE FOR ENDOSCOPIC ULTRASOUND BEFORE ENDOSCOPIC RESECTION?

Endoscopic ultrasound (EUS) visualises the wall of the gastrointestinal tract as a five-layered structure, corresponding to the mucosa (the first and second hypoechoic layers), the submucosa (the third hyperechoic layer), the muscularis propria (the fourth hypoechoic layer) and the serosa (the fifth hyperechoic layer). EUS is very useful for T-staging.[25] However, its impact in accurately predicting the suitability for ESD remains controversial, and most expert endoscopists would consider it unnecessary, relying instead on the endoscopic morphology. The accuracy of EUS in differentiating mucosal from deeper GC was addressed in a recent systemic review. Altogether, 18 studies met the inclusion

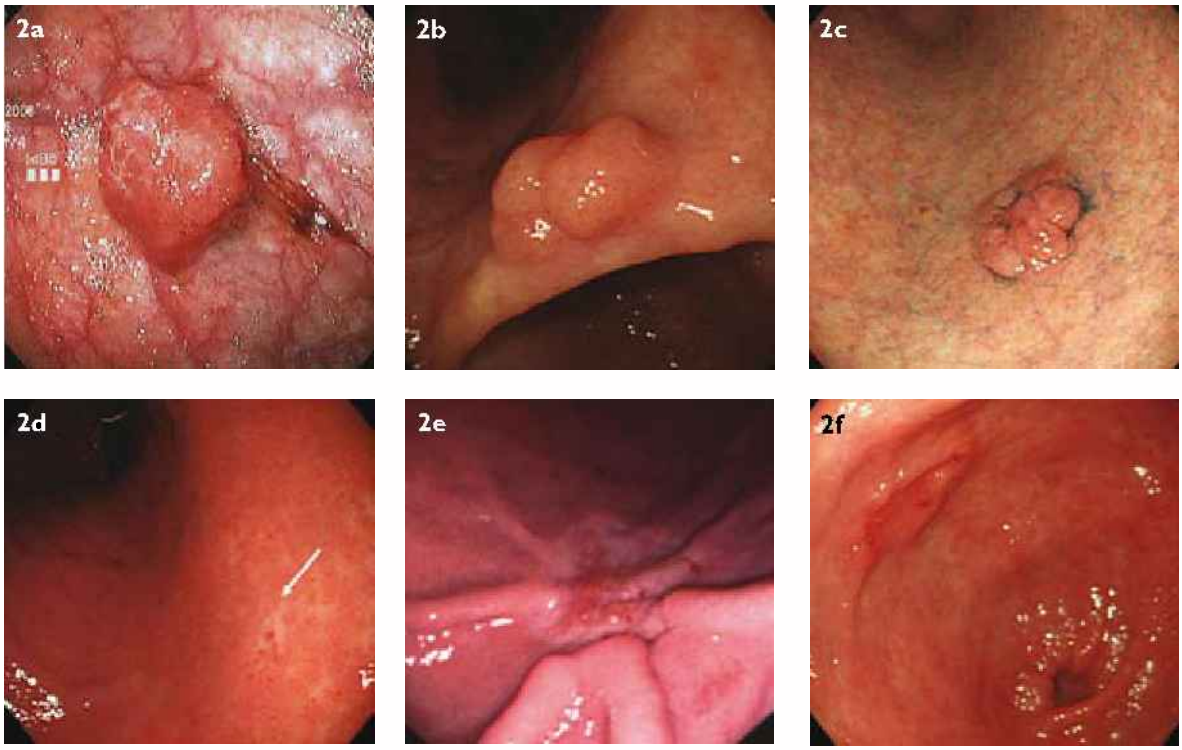

Fig. 2 Photographs show the morphology of lesions. (a) Type 0–Ip; (b) Type 0–Is; (c) Type 0–IIa; (d) Type 0–IIb; (e) Type 0–IIc; (f) Type 0–IIa + IIc; and (g) Type 0–III.

criteria and were analysed. The sensitivity and specificity of EUS in detecting tumour invasion beyond the mucosa ranged from 18.2%–100% (median 87.8%) and from 34.7%–100% (median 80.2%), respectively.[26] In a direct comparison of EUS and endoscopic assessment in predicting intramucosal cancer, the accuracies of both modalities were found to be similar (78% vs. 84%).[27] On the other hand, histopathology provides an absolute certainty in the assessment of the depth of invasion, and as such, in order not to deny approximately 20% of patients the chance of a curative endoscopic treatment, most experts would perform an ESD on the basis of the endoscopic appearance alone.

TECHNIQUE AND LIMITATIONS OF ENDOSCOPIC RESECTION

Endoscopic mucosal resection

EMR techniques are subdivided into those with and those without the use of suction. The former includes the "inject and cut" technique,[28] the "strip biopsy" technique[29] and the "simple snare resection" technique using a monofilament stainless steel wire snare.[30] In essence, the lesion is ensnared, with[28] or without[30] prior elevation with submucosal saline injection, before being resected. The latter includes cap-assisted EMR (EMRC)[31] and EMR with ligation (EMRL).[32] For these techniques, a pseudopolyp is created by suction in order to facilitate resection.[31,32] Although EMR is technically easy to perform, and has a low risk of perforation (< 1%), it is limited by the fact that en bloc resection is possible only if the lesion is less than 1.5–2 cm. For larger lesions, piecemeal resection must be performed. This precludes an accurate histopathological assessment of the vertical depth and lateral margins, and may predispose to local recurrence, which has been reported to range from 3.5% to 36.5%.[5]

Endoscopic submucosal dissection

ESD was initially pioneered in Japan for the treatment of EGC. In recent years, including the last 2–3 years in Singapore, it has been embraced by experienced endoscopists as the ideal endoscopic resection technique. ESD can achieve en bloc resection of large lesions, and is especially useful if the target lesion is larger than 1.5 cm, and if submucosal involvement is suspected or when there is fibrosis after ulcer healing. When the lesion is

Fig. 3 Photographs show the endoscopic accessories used for endoscopic submucosal dissection. (a) IT-knife; (b) IT-2 knife; (c) needle knife; (d) hook knife; (e) flex knife; and (f) triangle-tip knife.

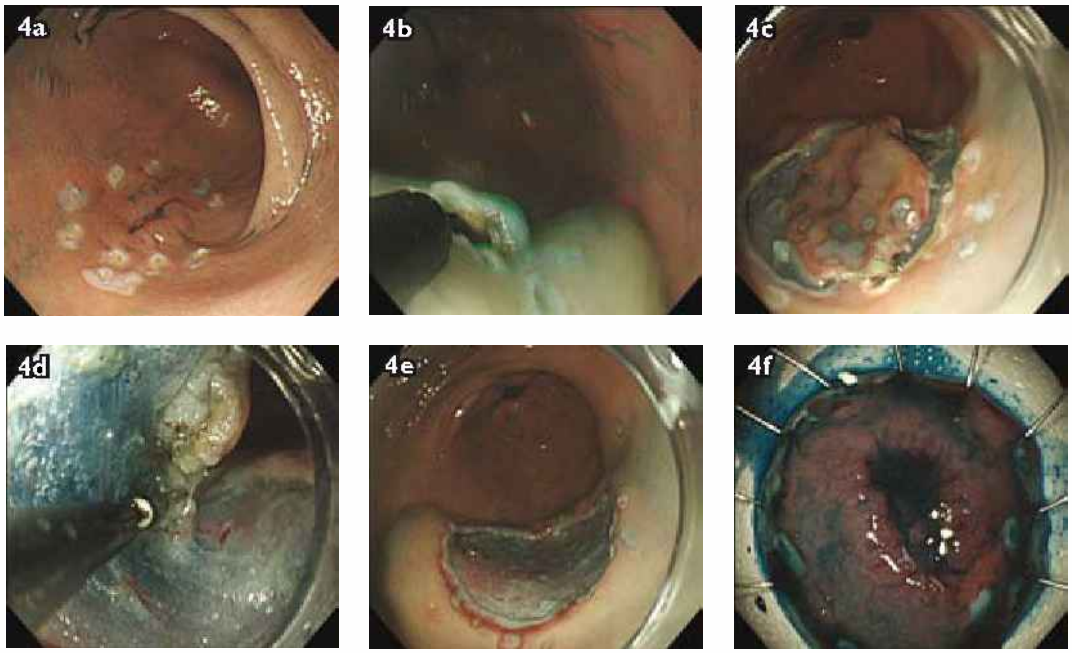

Fig. 4 Photographs show the technique used in endoscopic submucosal dissection. (a) Marking of the periphery of the lesion by the needle knife with coagulation current. (b) A small initial incision is made using the needle knife after the submucosal injection. (c) Circumferential mucosal cutting is done around the periphery of the lesion. (d) Submucosal dissection is assisted by a distal attachment cap. (e) A large ulcer is seen after the completion of the procedure. (f) The lesion is resected en bloc and fixed.

resected en bloc, the precise assessment of the depth of the invasion and the lateral resection margins can be made by the examining pathologist. However, ESD requires a longer procedural time than EMR, is associated with a higher risk of bleeding and perforation, and is technically demanding, with a steep learning curve.

ESD is performed using a standard single channel gastroscope with a variety of special endoscopic knives (Fig. 3). In our practice, we use a combination of needle knife and 2nd generation insulation tip (IT-2) knife (Olympus, Tokyo, Japan). The margin of the lesion is first outlined by spraying it with 0.2% indigo carmine solution. The periphery of the lesion (Fig. 4a) is marked using a standard needle knife with a forced 20W coagulation current (ICC200, ERBE, Tubingen, Germany). Saline mixed with diluted epinephrine (1:100,000) and indigo carmine is injected to raise and expand the submucosal layer. Indigo carmine identifies the submucosa by staining

it blue. A small incision (Fig. 4b) is then made by a standard needle knife with the 80W ENDO-CUT mode with effect 3 (ICC200, ERBE, Tubingen, Germany) so that the tip of the IT-2 knife can be inserted into the submucosal layer. Circumferential mucosal pre-cutting (Fig. 4c) is then performed using the IT-2 knife with the 80W ENDO-CUT mode. The ceramic ball at the tip of the IT-2 knife guards against perforation of the muscle layer. After completing the circumferential cut, submucosal injection is repeated to expand the submucosa, and using the IT-2 knife, the submucosal layer under the lesion is dissected with a lateral movement. It is important to cut tangentially at the submucosal layer so as to avoid perforation. A transparent cap fixed to the distal end of the endoscope (Olympus, Tokyo, Japan) is frequently used to create countertraction and to help exfoliate the submucosal tissue (Fig. 4d). Finally, the resected specimen is retrieved using a pair of grasping forceps. An en bloc resection without size limitation can be achieved (Fig. 4e & f).

The resected specimen is then stretched out and pinned to a mounting board with the oral and anal orientations clearly marked, before a routine formalin fixation is performed. Sections of the specimen are taken at every 2 mm. The pathological reports of the resected specimens should include the macroscopic appearance, size, histological type and extent of the tumour depth. The presence of ulceration and lymphovascular involvement, as well as the status of the resection margin should be reported in detail. If all the criteria detailed in Table II are met, the procedure is considered curative.

COMPLICATIONS OF ESD

Delayed bleeding is the most common complication, with an incidence rate of up to 7%.[5] Prior to ESD, antiplatelet and anticoagulation therapies should be stopped. Immediate bleeding is part and parcel of the procedure and is controlled by meticulous endoscopic haemostasis during ESD. Visible vessels should be coagulated before dissection in order to minimise bleeding, which can obscure the field of vision. The risk of delayed bleeding can be reduced by using proton pump inhibitors and by the prophylactic endoscopic coagulation of all non-bleeding visible vessels at the ulcer base after ESD. In a prospective randomised study, rabeprazole significantly reduced delayed bleeding rates when compared to cimetidine (6% vs. 17%).[33] In another study, the prophylactic coagulation of all visible non-bleeding vessels in the ulcer base after ESD was found to reduce the rate of delayed bleeding from 7.1% to 3.1%.[34]

Perforation is uncommon during EMR (< 1%) but may occur in about 4% of cases during ESD.[5] In most instances, endoscopic closure without a need for surgery is possible, and the patients may even be commenced on feeds the following day. In an analysis of 2,460 cases of endoscopic resection at the National Cancer Centre Hospital, Tokyo, Japan, during the period 1987–2004, gastric perforation occurred in 121 (4.9%) cases. An initial four patients underwent surgery, but as experience accrued, subsequent patients were treated endoscopically with endoclips, and this was successful in 115 (98.3%) patients.[35]

FOLLOW-UP AFTER ESD

During ESD, care must be taken to ensure that the margins of the tumour are clearly demarcated, so that at the end of the ESD, one can be certain that macroscopically, the entire lesion has been resected. If histology shows that the initial resection is incomplete, ESD can be repeated immediately within the same admission. Patients are typically hospitalised for about five days, and oral feeding is gradually reintroduced while awaiting the histology report. Thereafter, the first follow-up gastroscopy should be performed at three months. Subsequently, gastroscopy should be repeated yearly in order to screen for metachronous lesions, and this should be done for an indefinite period of time, depending on the patient's overall health status. In addition, one should perform a yearly computed tomography (CT) of the abdomen to screen for tumour recurrence in the form of distant metastases for a period of three to five years, similar to EGC patients who undergo surgery. For EGC patients who do not fulfil the histopathological criteria for curative resection (e.g. patients with submucosal invasion exceeding 500 micrometres) but yet refuse salvage surgery, close follow-up is needed, including the possibility of performing 3–6-monthly EUS to detect perigastric nodal metastasis and CT scans to detect distant metastasis.

DRAWBACKS AND ADVANTAGES OF ESD

While ESD is an extremely promising technique, it can be technically challenging to resect large lesions or lesions associated with healed ulceration due to underlying fibrosis. Lesions located in certain locations, such as the mid-body greater curvature and the lower body lesser curvature, are also more difficult to remove. Therefore, procedure times may be long, and general anaesthesia may be required for selected cases. In addition, training opportunities in ESD are also limited. The learning curve for ESD is generally accepted to be quite steep, but this may be mitigated by experience in other aspects of

therapeutic endoscopy. The advantages of ESD include en bloc resection in more than 95% of cases, the removal of eccentrically-shaped lesions, and the preservation of gastric anatomy due to the avoidance of surgery.

RESULTS OF ENDOSCOPIC TREATMENT

The five-year relative survival rate after a gastrectomy for EGC has been reported to be 89%.[36] For endoscopic resection to be a viable alternative to surgery, the long-term outcome must match that of surgery. No randomised controlled studies have been, or will likely be conducted. However, on the basis of large series with a long-term follow-up, it is clear that outcomes similar to surgery can be achieved, as long as strict inclusion criteria are met. Patients are thus able to have a curative procedure with a lower morbidity than surgery, without the adverse effects that may follow a gastrectomy. In a large series from a single institution, 124 patients with differentiated mucosal EGC of less than 2 cm in size (without ulceration) underwent conventional EMR from 1978 to 1996. During a mean follow-up of 58 months, two (1.5%) patients died of GC, while the remaining patients remained disease-free. In one of the patients who died of GC 22 months after EMR, a review of the stored pathological specimen revealed a lymphatic invasion, although the initial report had shown a complete resection. In the other case, after two years of negative surveillance endoscopy, the patient was lost to follow-up, and subsequently died of metachronous GC 135 months later. The disease-specific five- and ten-year survival rates were both 99%.[37] In a multicentre study involving 11 Japanese institutions, 714 EGC in 655 consecutive patients were treated endoscopically (EMR: 411; ESD: 303) over a one-year period. The inclusion criteria were differentiated adenocarcinoma, the depth of invasion limited to the mucosa or less than 500 um of submucosal penetration, lesions without ulceration regardless of size, or 30 mm or less in size when the ulceration was present. The rate of curative resection with ESD (73.6%) was significantly higher compared to that for EMR (61.1%). In the context of curative resection, the three-year cumulative residual-free/recurrence-free rate and the three-year overall survival rate were 94.4% and 99.2%, respectively. The three-year cumulative residual-free/recurrence-free rate in the ESD group (97.6%) was significantly higher than in the EMR group (92.5%).[38] The results of these studies confirm that once the histological criteria for curative endoscopic resection are met, the long-term outcome is similar to surgery. However, if these histological criteria are not met, endoscopic resection is non-curative, and the patients should be referred for surgery.

CONCLUSION

The detection of EGC remains a clinical challenge, but it is very important for improving the prognosis. Endoscopic resection, and in particular ESD, is now increasingly recognised as a standard treatment for EGC. Compared to surgery, it has a lower morbidity, and is organ-preserving. The long-term results are comparable to surgery. When the technical expertise is available, it should be a first-line treatment strategy.

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