Early gastric cancer: detection and endoscopic treatment

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BACKGROUND: *Early Gastric Cancer (EGC) is defined as a neoplasm confined to the mucosa or submucosa regardless of regional lymph node metastasis. The rate of EGC, which varies by country, is up to 40-60% of all gastric cancer cases in Japan, whilst in Western countries, the proportion remains at 5-10%. There is a strong male predominance in EGC. The average 5-year survival rate of patients with EGC reached over 90% in Japanese and European data.*
MATERIALS AND METHODS: *Many EGC patients present with symptoms suggestive of a benign gastric ulcers. The combination of serum pepsinogen and Helicobacter pylori status may provide even more sensitive information for screening. However high-quality endoscopic evaluation with biopsy is the key to diagnosis. To improve the quality of observation several endoscopic imaging modalities have been developed for the diagnosis of early gastric cancer. Endoscopic resection is a viable alternative to surgery for curative treatment of EGC, with similar long term results. Endoscopic mucosal resection (EMR) of EGC without any risk of lymph node metastasis was developed in Japan in the 1980s, and it has been one of the standard treatments of EGC for nearly 20 years. Recently, several EMR techniques developed in Japan have been accepted and done in Western countries. These EMR techniques are safe and efficacious but unsuitable for large lesions.*
DISCUSSION: *Because we could not remove a large lesion in 1 fragment, which was very important for the precise diagnosis of tumor depth, local recurrence increased in large-lesion cases. An innovative procedure using newly developed endoscopic knives, called endoscopic submucosal dissection (ESD), was developed in the late 1990s, which made it possible to remove a large lesion en bloc.*
CONCLUSION: *Theoretically, ESD has no limitation with respect to tumor size; therefore, it is expected to replace the surgical treatment in some situations. Although ESD has spread throughout Japan within a short period, there remain several disadvantages, such as a higher incidence of complications and a requirement of higher endoscopic skills compared to those of conventional EMR methods.*

KEY WORDS: Early gastric cancer, Endoscopy.

Introduction

Early gastric cancer (EGC) was first defined in 1962 by the Japanese Society of Gastroenterological Endoscopy as adenocarcinoma confined to the mucosa or submucosa irrespective of lymph node involvement [1]. The need for such a definition was based on the observation that gastric cancer of this type had a favourable prognosis.
The incidence of EGC varies between countries. EGC accounts for almost 40-60% of all gastric cancers treated in Japan, whilst in Western countries, the proportion remains at 5-10% [2]. A variety of reasons for this discrepancy has been offered, including mass screening of the asymptomatic population introduced in Japan in 1957, population characteristics, the natural history of the disease and differences in operative technique.
The 5-year survival rate of patients with EGC is over 90% after gastrectomy with complete removal of the primary and secondary lymph nodes in Japanese data and recent European series. The incidences of nodal metastases of intramucosal and submucosal EGC are 3 and 20%, respectively [3].

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Histopathology

Macroscopic Apparence

The most widely used classification of EGC is based upon the macroscopic appearance of the tumour (Fig 1). According to the Japanese Research Society for gastric cancer EGC is divided into tumours that are protruded (I), superficial (II), and excavated (III). Type II is further subdivided into elevated (IIa), flat (IIb), and depressed (IIc).[4] The elevation of type IIa is less than twice the thickness of the adjacent mucosa, whereas in type IIb no elevation or depression can be seen, and in type IIc the depression is only erosion. Combinations of the five lesions are common, (for instance, a shallow depression (IIc) with a central excavation (III). The majority of EGC contain a depressed or ulcerated component with types IIc or III, or both. This is true for both Western and Japanese series. The remainder are mainly elevated, with only a very small number of flat lesions (type IIb) being identified. This no doubt reflects not only the fact that ulcerated lesions are easier to detect, but also that a large number of EGC ulcerate as part of their natural history, an observation first made by Sakita et al.[5] When flat lesions are detected, however, they are characterised simply by a reddening or pallor of the mucosa. They are usually of minute or small size, and limited to mucosal invasion, suggesting that they are at an early stage in their natural history.

Size

The size of EGC varies greatly, ranging from less than 0.5 cm to 7.0 cm. Mean size is reported between 1.7 cm and 3.0 cm in Europe and the USA. With advancing diagnostic techniques, the proportion of smaller sized lesions is increasing. This is especially true in Japan. Lesions with a maximum diameter of 5 mm or less are classified as "minute", and those with a diameter of between 6 and 10 mm as "small". These lesions tend to be flat (type IIb) and histologically well differentiated.[6]

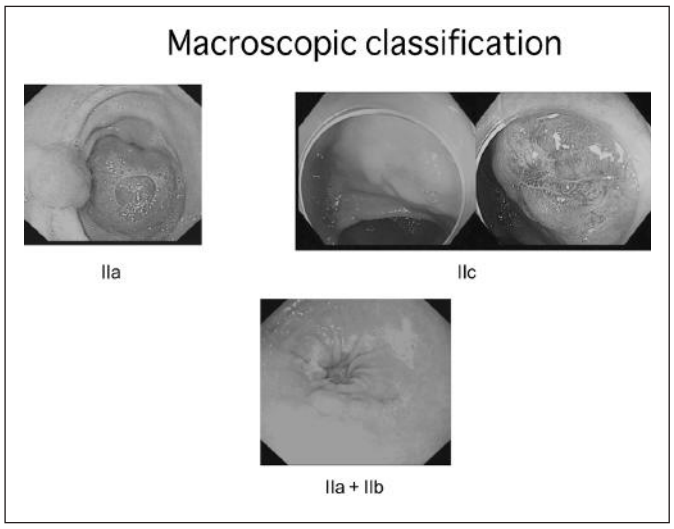

Fig. 1: Macroscopic Classification of Early Gastric Cancer (according to the Japanese Research Society for gastric Cancer).

Depth of invasion

The definition of EGC allows for invasion only as far as the submucosa, without penetration through the muscularis propria. However, EGC can be divided into those that invade the mucosa only, and those that penetrate the muscularis mucosa to the submucosa. Although there is wider variation between the smaller Western series, the proportion between mucosal and submucosal EGC is half and half both in Japan and Europe. Depth of invasion may be predicted by macroscopic type, with polypoid and ulcerated/eroded lesions having deeper invasion than flat lesions.

Microscopic Apparence: histological diagnosis

In 1965 Lauren described two histological subtypes of gastric cancer: intestinal and diffuse.[7] The intestinal type consists of a cohesive group of neoplasic cells that form distinct well-defined tubular structures whereas in the diffuse-type, the cohesion is lost with individual cells infiltrating the gastric wall without a glandular structure. The description closely resembles that of the Japanese classification of differentiated (papillary, well- or moderately differentiated adenocarcinoma) and undifferentiated types (poorly differentiated adenocarcinoma, signet ring cell carcinoma, mucinous carcinoma). The intestinal-type usually arises in the distal part of the stomach, affecting mainly older patients and occurring more commonly in areas of high prevalence. Instead, the diffuse-type has a constant rate worldwide, often occurring in a younger age group. The development of intestinal-type is thought to follow the pathway from chronic atrophic gastritis to cancer, being more influenced by environmental factors unlike the diffuse form, which occurs independently to intestinal metaplasia and is more likely to have a primary genetic predisposition. Both intestinal and diffuse types are almost equally seen in the West and in Japan[8,9], although among EGC the intestinal type is dominant in many reports.[10] There has been considerable controversy between Japanese and Western pathologists regarding the histological reporting of mucosal lesions. Some observers suggested that the reported incidence of EGC in Japan were attributable to over-diagnosis of dysplastic lesions into invasive cancer. Using biopsy specimens and the corresponding endoscopic mucosal resection specimen from patients with a range of diagnoses, Schlemper et al. compared the findings of both Japanese and Western pathologists.[11] The paper concluded that Japanese pathologists often diagnosed gas-

tric cancer when western pathologists would use the term dysplasia to define cancer. Japanese pathologists have traditionally relied on nuclear features such as enlargement, pleomorphism, prominent nucleoli and loss of polarity along with glandular architectural abnormalities, whereas in the West, pathologists require evidence of definite invasion into the lamina propria. It is now recognized that a significant number of discrepancies were due to a reflection in the nomenclature rather than to the concept of cancer. The need for a consensus led in 1998 to the Vienna classification[12], a reporting system that has relevance for the whole gastrointestinal tract, with emphasis on dysplasia. Categories for non-invasive high-grade dysplasia and invasive neoplasia encompassing both intramucosal and submucosal carcinoma were included

Lymphnode invasion

Lymph node invasion is relatively common, with rates varying between 10 and 20%. The presence of nodal metastases is very closely related to the depth of local invasion. With submucosal invasion, lymph nodes are involved between 15 and 30%, whereas in mucosal lesions, lymph node involvement is much less common (0-7%). Furthermore, lymph node invasion is commoner with larger tumours, and possibly with poorly differentiated tumours, although this relation is reported less consistently.

Distant metastases

Liver/haematogenous metastases are rare at the time of diagnosis of EGC, and were reported in only two of the case series reviewed. Although this may be biased owing to the reporting of potentially curative surgery alone, it is consistent with the high postoperative survival rates and the benign nature of this disease.

Synchronous cancers

The concept of multiple synchronous gastric cancers is well recognised. The criteria for diagnosis were first established by Moertel in 1957 [13]:
(a) each lesion must be of pathologically proven malignancy;
(b) all lesions must be distinctly separated by intervals of microscopically normal gastric wall;
(c) the possibility that a lesion represents local extension or metastasis must be ruled out beyond any reasonable doubt.
When reported, the prevalence of synchronous cancers is between 2 and 14% in the European literature. This closely echoes the Japanese experience of 5-13%. In addition to double tumours, triple and quadruple tumours have also been reported. Synchronous EGC, however, do not differ from their solitary counterparts with regard to pathological features. It has been found that the frequency of multiple tumours is commoner in EGC than Advanced Gastric Cancer (AGC) and this has been taken to imply that progressive carcinoma could be result of convergence of multiple primary foci.

Clinical features

As in AGC, there is a strong male predominance in EGC. In the European literature the male:female ratio varies from 1 to 4.75. In the Japanese literature, the male:female ratio was reported in five series with a mean of 1.97. This is only slightly higher than the European mean, but may reflect higher screening rates of the working male population in Japan.
The mean age of patients with EGC in European reports is 59.9 years. This is only marginally older than the mean age in Japan (57.8 years). A surprising finding if one considers their screening programme.
The presenting symptoms of EGC resemble those of benign gastric ulcer. Epigastric pain and dyspepsia are very frequently present (between 60 and 90%). Anaemia is uncommon at presentation, and history of gastrointestinal bleeding is usually present in less than 25%. Weight loss almost always occurs in less than 40% of patients. It is diffcult to interpret the observation that the EGC symptom profile and duration more closely resemble benign gastric ulceration than advanced cancer. It may suggest either that EGC can exist undetected in the stomach, causing mild symptoms only for long periods of time, or that there is a gradual malignant conversion of benign disease over such a period. Nevertheless, this similarity in clinical features, taken with the notion that these ulcers can undergo a healing phase, strengthens the need for aggressive, early investigation of older patients with ulcer-like symptoms [14].

Detection of ECG

Serum pepsinogen analysis is a simple test useful for detection of patients with chronic atrophic gastritis, regarded as a risk factor for carcinogenesis [15]. It is now being evaluated as a screening tool to pick up high risk subjects who should undergo endoscopy. The combination of serum pepsinogen and Helicobacter pylori status may provide even more sensitive information for screening.
High-quality endoscopic evaluation with biopsy is the key to diagnosis. Barium meal studies are alternative options, but they are not as sensitive. Simple measures routinely performed in 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, 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. The appropriate use of topical contrast agents, such as indigo carmine, will help to highlight subtle lesions [16,17,18].

Once the lesion or suspicious areas has been detected, targeted biopsies should be taken. To improve the quality of observation several endoscopic imaging modalities have been developed for the diagnosis of early gastric cancer [19], such as:

Magnification endoscopy: The role of high-magnification endoscopy is to magnify the target area in which conventional endoscopy detects some abnormality in conventional pictures. By using high-magnification endoscopy it's possible to observe the surface mucosal pattern (pits pattern) and the capillary structure. On the basis of the analysis of the surface structure pattern obtained by magnification, histological changes of carcinoma, dysplasia, and adenoma might be suspected. [20,21]

Red flag techniques with "virtual" Chromoendoscopy: "Red flag" methods involve special techniques that are added to standard white-light endoscopy in order to increase the sensitivity for detecting early neoplasia in a broadfield imaging examination [22].

Olympus Narrow Band Imaging (NBI), Fujinon Intelligent Colour Enhancement system (FICE), and Pentax I-Scan are applied to a new generation of high-resolution endoscopes, allowing the endoscopist to easily switch between the "Virtual chromoendoscopy-mode" and the normal "High resolution-mode" with no need for special equipment or dyes.

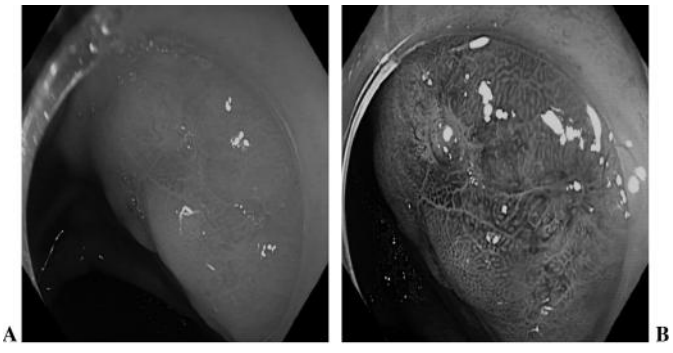

Fig. 2: Early gastric cancer visualized with standard white-light (A) and with NBI (B).

NBI works through the application of a special optical filter to the white light source, enabling to "narrow" the wavelength of the light and to emphasize both the mucosal "pit-pattern" and the vascular network (Fig 2) [23,24].

The FICE system is based on a computed spectral estimation technology that processes the reflected photons to reconstruct virtual images with a choice of different wavelengths. This leads to enhancement of the tissue microvasculature as a result of the differential optical absorption of light by haemoglobin in the mucosa [25].

I-Scan (Pentax, Tokyo, Japan) is an endoscopic postprocessing light filter technology which uses sophisticated software algorithms with online image mapping technology embedded in the high-definition EPKi processor.[26] This technology enables resolution above HDTV standard, which can provide detailed analysis based on vessel (V-mode), pattern (P-mode), or surface architecture (SE-mode).

Functional Imaging: While NBI, FICE, and I-Scan rely on improved anatomic resolution and contrast, other methods focuse on functional imaging. During progression from normal tissue to neoplasia, tissue undergoes both architectural and biochemical changes which lead to alterations in its interaction with light, producing spectral signatures useful to differentiate between various tissues.

Autofluorescence imaging (AFI) detects subtle changes in the concentration of specific chemicals in tissue that have the ability to fluoresce when activated by specific wavelengths of light. As an example, most changes noted in BE with AFI rely on loss of collagen in dysplastic tissue resulting in reduced green and increased red fluorescence [27].

Raman spectroscopy is based on detecting characteristic spectral "fingerprints" of molecules in the tissue based on the molecular vibrations in response to light energy. Reflectance spectroscopy qualifies the colours and the intensity of reflected light, altered by the tissue through absorption of certain wavelengths such as haemoglobin, thus defining vascularity and oxygenation status. Light scattering spectroscopy uses the variation in scattered light across a full spectrum to measure the size and density of nuclei in the epithelial layer. This is a highly accurate method which correlates directly with histologic changes of dysplasia.

Some authors suggest that it may be ideal if AFI and NBI could be used back-to-back in a complimentary fashion with a multi-modal system that incorporate high-resolution videoendoscope (HRE), NBI and AFI: high-resolution imaging should be used for a standard examination, AFI to detect suspicious lesions in selected patients and NBI for a close inspection of these areas.

Virtual histology: In vivo confocal laser endomicroscopy (CLE) is a newly developed diagnostic tool that allows

immediate optical histology of the mucosal layer during ongoing endoscopy. Confocal laser microscope can be integrated into the distal tip of a conventional video endoscope *(Pentax EC-3870CIFK; Pentax, Tokyo, Japan)*, or a miniaturized probe, using a single optical-mode fibre acting as both the illumination point source and the detection pinhole can be used as "baby-scope" *(Optiscan Pty. Ltd., Notting Hill, Victoria, Australia, and Cellvizio, MaunaKea Technologies, Fort Washington, Pennsylvania, USA)*. The grey-scale image created is an optical section representing one focal plane within the examined specimen. Series of confocal images within successive planes can be used to reconstruct three-dimensional structures in a virtual specimen [28,29].

Endocytoscopy (EC) provides, in combination with chromoagents, in vivo histologic images with the use of an ultra high magnification (450–1125 times) catheter which is passed through the working channel of the endoscope. Unlike CLE, EC provides images in colour but is limited to the most superficial cell layer. Endocytoscopy imaging may correlate closely with histopathology in differentiating between neoplastic and non-neoplastic lesions as well as adenomas and invasive cancer, with an estimated sensitivity and specificity of 79 and 90% respectively [30].

Optical coherence tomography (OCT) performs a cross-sectional, high-resolution, tomographic imaging of the microstructure of mucosal tissues by measuring back-scattered or back-reflected infrared light [31]. The microscopic structure of tissues can be observed, but the depth of penetration is limited.

Endoscopic ultrasonography: EUS is capable of diagnosing the depth of cancer invasion, which is an important factor to choose the preferred treatment (e.g.endoscopic resection, laparoscopic surgery, or laparotomy). The diagnostic accuracy of the depth of carcinoma invasion is around 80%, when we divide the lesions into mucosal (m) carcinoma, submucosal (sm) carcinoma, carcinoma invading the muscularis propria, (pm), and deeper than the subserosal layer (ss). Some endoscopists insist that the EUS study before endoscopic treatment is unnecessary, but EUS reveals important information such as the presence of dilated vessels or cystic changes beneath the mucosa and gastrointestinal wall in some cases [32,33].

Treatment of EGC

At present, it is impossible to make a definite non-surgical diagnosis of a neoplasm regarding depth, histological type and lymphatic vessel invasion before treatment. It is often experienced that although a biopsy specimen shows adenoma/dysplasia of a lesion, a diagnosis of cancer is undoubdtely made after its total resection. Therefore, a precise pathological evaluation of the resected specimen is essential to judge the endoscopy as curative (Fig. 3) [34]. In contrast to surgical resection, which also allows for lymph-nodes dissection, endoscopic resection (ER) is limited to the local removal of a lesion. Only patients with a minimal risk of lymph node metastases are, therefore, candidates for curative endoscopic treatment. This implies the optimal selection of patients, and the risk-stratification of each lesions. The best indication for endoscopic treatment are lesions limited to the mucosa (m1–m3) without ulcerative fibrosis reaching the proper muscle, histological findings showing well differentiated adenocarcinoma, less than 30 mm in size. Lesions infiltrating deep into the submucosa, poorly differentiated cancer, or the presence of a well-diagnosed lymphatic/vascular involvement, have a higher probability of lymphonode involvement and must therefore be referred to surgery.

Factors for no risk of lymph node metastasis
- Intestinal-type histology;
- No lymphatic or vascular infiltration;
- Intramucosal cancer regardless of tumour size without ulcer finding;
- or intramucosal cancer less than 30 mm in size with ulcer finding;
- or minute submucosal invasive cancer (sm1) less than 30 mm in size

Factors for resection margin
- Tumour-free horizontal margin
- Tumour-free vertical margin

Fig. 3: Histological Criteria for curative endoscopic resection.

Technique of endoscopic mucosal resection

Endoscopic mucosal resection: EMR techniques are subdivided into those with and those without the use of suction. The former include the "inject and cut" technique, the "strip biopsy" technique and the "simple snare resection" technique using a monofilament stainless steel wire snare. In essence, the lesion is ensnared, with or without prior elevation with submucosal saline injection, before being resected. The latter include cap-assisted EMR (EMRC) and EMR with ligation (EMRL). For these techniques, a pseudopolyp is created by suction in order to facilitate resection. 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%.[35,36]

Endoscopic submucosal dissection: Endoscopic submucosal dissection (ESD), first described by Ono and Hosokawa at the National Cancer Center Hospital of Tokyo in 2001, was developed for direct dissection along

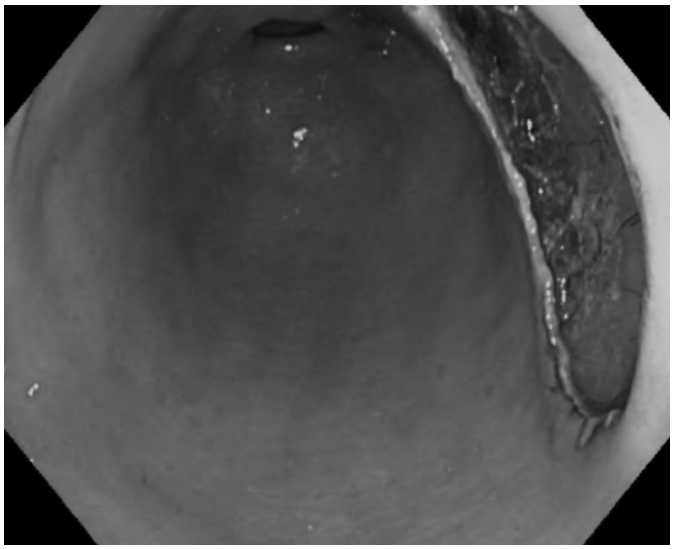

Fig. 4: ESD: final result.

the submucosal layer using specialized devices with a standard single-channel endoscope, and to obtain en bloc radical resection of lesions largest of 2 cm (Fig. 4) [37].
Standard ESD consists of three main steps:
1. after identification of the lesion with the help of chromoendoscopy, its margins are marked approximately 5 mm outside by spotty electrocautery knife. Argon plasma coagulation may also be used for peripheral marking. Then, fluid is injected into the submucosa to elevate the lesion and create a space between the submucosal and muscular layers. To promote elevation, several fluids such as saline, glycerol and hyaluronic acid are usually combined with diluted epinephrine, which is used for the prevention of active bleeding.
2. circumferential cuts are made around the lesion by a standard needle knife.
3. special endoscopic knives are used to dissect the submucosal layer underneath the lesion in order to obtain a large resection specimen with the neoplasia resected en bloc. 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. Specially designed hot grasping forceps can be also useful to control bleeding during the dissection.
To facilitate a complicated standard ESD procedure performed by using a single working-channel gastroscope, the magnetic-anchor–guided ESD (MAG-ESD) controlled by an extracorporeal electromagnet, was developed. The magnetic anchor *(Pentax Co, Tokyo, Japan)* consists of 3 parts: a hand-made magnetic stainless-steel weight, a microforceps, and a connecting thread, controlled by a high-power electromagnet placed outside the body of the patient. It was designed to facilitate gastric ESD by use of an extracorporeal hands-free electromagnet, whereby magnetic forces allow a suitable countertraction for submucosal dissection, achieving ideal mucosal lifting.
There are some disadvantages of ESD with regard to its technical difficulties and complications, such as bleeding and perforation.
Bleeding during the procedure may be managed by direct coagulation with special forceps. Clipping can also be used but usually avoided because it may impair the completion of the procedure. The incidence of delayed bleeding after ESD is as common as in conventional EMR. The frequency of delayed bleeding differs with the tumor location and size, being higher for lesions located in the fundus.
Compared to conventional EMR, perforation with ESD is more frequent (1–4%). Perforation is almost always currently managed conservatively by complete endoscopic closure with endoclips. A nasogastric suction tube is applied for 12– 24 h, and a broad-spectrum antibiotic is given for 48 h. Oral intake is initiated 2–3 days after the procedure. Delayed perforation is thought to occur because of the excessive electrical coagulation of the vessels lying within the submucosal or muscular layers. When these vessels need coagulation, care must be taken not to push the device to the gastric wall and not to coagulate for long intervals. If air leakage from the perforated lesion causes severe abdominal fullness, decompression of the pneumoperitoneum must be performed quickly [38,39].

Treatment Outcomes

Survival Rate of EGC Treated by Endoscopic Resection

The five-year relative survival rate after a gastrectomy for EGC has been reported to be 89%.[40] For endoscopic resection to be a viable alternative to surgery, the longterm outcome must match that of surgery. No randomized 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 diseasefree. 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%.[41] In a multicentre study involving 11 Japanese institutions, 714 EGC in 655 consecutive patients were treated endoscopically (EMR: 411; ESD: 303) over a oneyear 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 residualfree/ 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%) [42]. 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.

Recurrence Rate of EGC Treated by EndoscopicResection

The risk of local recurrence after EMR varies between 2 and 35%, and the recurrence rate correlates with the number of resected specimens. Above all the greatest advantage of ESD compared to conventional EMR is the rate of complete resection, which is defined as the cut margin free from cancer and 1-fragment resection. ESD must be able to reduce the risk of local recurrence. However, if the lateral margin of the tumor is misdiagnosed and resected incompletely, local recurrences cannot be avoided [43,44].

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.

Riassunto

L'early gastric cancer (EGC) è una forma di neoplasia gastrica, diagnosticata precocemente, che è limitata alla mucosa e sottomucosa, ovvero ai 2 strati superficiali della parete gastrica, indipendentemente dalla compromissione linfonodale. L'incidenza dell'EGC varia nei diversi Paesi. L'EGC rappresenta circa il 40-60% di tutte le neoplasie gastriche trattate in Giappone, mentre solo il 5-10% di quelle trattate nei Paesi Occidentali. L'importanza della diagnosi precoce per il cancro gastrico è dimostrata dalla prognosi, con il 90% di sopravvivenza a 5 anni per la neoplasia diagnosticata allo stadio precoce, contro il 10% di sopravvivenza a 5 anni per il cancro avanzato. Non sono ben noti i fattori di rischio dell'ECG. Le principali evidenze riguardano l'infezione cronica da Helicobacter Pylori che l'OMS (l'Organizzazione Mondiale della Sanità) ha classificato come cancerogeno di prima classe, per l'oramai accertato ruolo del microrganismo nell'innesco della progressione da gastrite cronica atrofica verso le lesioni precancerose. Nel processo di cancerogenesi gastrica intervengono, inoltre, fattori correlati alle abitudini alimentari come il consumo eccessivo di cibi salati e/o affumicati, contenenti amine aromatiche policicliche e nitrati, che favoriscono lo sviluppo della gastrite cronica atrofica. Al contrario, tra gli agenti protettivi la refrigerazione riduce la formazione di nitriti e nitrati tramite la riduzione della contaminazione batterica e fungina dei cibi, mentre l'elevato consumo di frutta e verdura ricchi in agenti antiossidanti riducono i radicali liberi e prevengono il danno al DNA. L'endoscopia rappresenta il gold standard per la diagnosi di cancro gastrico. Studi effettuati valutando le curve di crescita della neoplasia gastrica hanno dimostrato che il tempo necessario affinché una lesione early si trasformi in una neoplasia avanzata è di circa 7 anni, per cui è necessario concentrare tutti gli sforzi per fare la diagnosi in questo periodo. A tal fine negli ultimi anni si è assistito allo sviluppo di nuove tecnologie che hanno portato ad un aumento dell'accuratezza diagnostica. Come la prognosi, anche la terapia viene condizionata dalla diagnosi precoce. Il cancro allo stadio precoce è passibile di terapia endoscopica, mentre il cancro avanzato richiede la chirurgia e il trattamento chemioterapico in relazione alla compromissione linfonodale. La terapia endoscopica è rappresentata dalla mucosectomia

(EMR) e dalla dissezione sottomucosa (ESD), tecniche che consentono l'asportazione solo del tessuto interessato dal processo neoplastico, quindi interventi molto meno invasivi rispetto alla chirurgia tradizionale. Requisiti fondamentali per l'effettuazione dell'EMR sono rappresentati dalla possibilità di scollare gli strati superficiali della parete gastrica interessati dalla neoplasia dagli strati profondi e dall'assenza di metastasi linfonodali. L'EMR ha rappresentato un grande progresso nella terapia endoscopica, ma tale tecnica ha il suo limite nelle dimensioni della lesione, che non può superare i 20 mm. L'ESD rappresenta un'evoluzione dell'EMR. L'ESD eseguita con l'impiego di aghi diatermici usati come bisturi per incidere la mucosa sana intorno alla lesione neoplastica. I vantaggi dell'ESD rispetto all'EMR consistono nella possibilità di rimuovere porzioni di tessuto di maggiori dimensioni, riducendo il rischio di non radicalità e di recidive, nonché nella possibilità di fornire al patologo un unico pezzo per l'esame istologico. Il patologo può in questo modo formulare una diagnosi più precisa in termini di estensione laterale della lesione e di invasione degli strati profondi.

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