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Endoscopic Submucosal Dissection and Endoscopic Mucosal Resection for Early Gastric Cancer Treatment Inchina.

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Abstract:
Earlygastriccancer (EGC)is gastric cancer that limited to the mucosa, submucosa, or both, irrespective of the presence of regional lymph node (LN) metastases and offers an excellent (exceeded 90%) chance of cure based on surgical resection. Various treatment methods have been performed in the treatment of early gastric cancer. Endoscopic resection (EMR) and Endoscopic submucosal dissection (ESD), are established treatmentmethods that allow curative treatment. Endoscopic therapy (EMR or ESD) is definitely indicated in microscopically intramucosal (cT1a) distinguished carcinomas measuring less than 2 cm in diameter. Recently, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have become alternatives to surgery in early gastric cancer,in many country instance, in China,japan, and other countries.

Key Words: *Early gastric cancer; Endoscopic submucosaldissection; Endoscopic mucosal resection; Microscopically intramucosal (cT1a); Gastrectomy.*

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I. Introduction

Gastric cancer is the fourth most common cancer and the third leading cause of cancer mortality in China [1]. Earlygastriccancer (EGC) is stomach cancer that restricted to the mucosa or submucosa irrespective of lymph node involvement. The term "early" is correlated with primary lesion features and not to "early" detection. This histological entity, in 1962 as defined early gastric cancer by the Japanese Society of Gastroenterological Endoscopy, was based on the observation that gastric cancer of this type had a favorable prognosis, with a five-year survival higher than 90% [2-3]. The prognosis of gastric cancer significantly depends on the time of diagnosis. With the development and broad implementation of endoscopic techniques, such as chromoendoscopy, narrow-band imaging, magnifying endoscopy, and confocal microscopy, the diagnosis rates of patients with early gastric cancer (EGC) have been rising [4]. The Early Gastric Cancer relates to the lesion restricted to the mucosa and submucosa, regardless of lymph node metastasis (LNM) [5]. There are many treatment choices for Early Gastric Cancer, such as the endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and gastrectomy plus D1 or D2 lymphadenectomy through the laparoscopic or open operation. Among these treatment methods, radical surgery can obtain adequate oncological clearance with wide resection margins, nodal dissection, and a low rate of recurrence. However, the perioperative mortality compromised long-term gastrointestinal function, long operation time, and lower quality of life after surgical resection could not be ignored [6]. In recent years, with the development of endoscopic technology, the ESD gradually becomes the main choice for EGC. However, the technology of ESD is so complex that the complications were accompanied [7]. In addition, the impossibility of regional lymph nodes removed during the ESD procedure is another major limitation, which may probably happen in tumor recurrence and the invasive radical gastrectomy. EMR is a method used for the staging and treatment of superficial neoplasms of the gastrointestinal (GI) tract. This method was first developed in Japan for the treatment of early gastric cancer (EGC) and has since spread in use throughout the world for numerous indications, including dysplastic Barrett mucosa and sessile colonic neoplasms. Endoscopic mucosal resection was first introduced for endoscopic therapy in 1984 by using the strip biopsy method (two-channel method) [8, 9]. The operation process included submucosal injection under the lesion, snaring, and removing the lesion. This injection-snaring method is simple and convenient. However, it is hard to trap flat type lesions. Furthermore, the steel wire slips easily, which may lead to incomplete resection and local recurrence [10].

EGCclassification basing upon the macroscopic appearance:

Early gastric cancer is described as remaining restrained to the mucosa or submucosa, regardless of lymph node metastasis [11]. The most broadly used classification of EGC is based upon the macroscopic appearance of the tumor EGC is divided into three that are protruded (Type I), superficial (Type II), and excavated (Type III). Type II is additionally subdivided into elevated (IIa), flat (IIb), and depressed (IIc). Commonly, the elevation of type IIa is fewer than twice the thickness of the adjoining mucosa, whereas in type IIb no elevation or depression can be observed, and in type IIc the depression is only erosion.[12]Combinations of the five lesions are common, (for example, a shallow depression (IIc) with a central excavation (III) is classified as type (IIc + III). On the whole, the majority of EGC comprises a depressed or ulcerated component with types IIc or III, or both of, present in higher than 60 %. type II (IIa),(IIb),(IIc) are commonly seen in China.

Treatment of early gastric cancer:

Techniques of endoscopic treatment for early gastriccancer include endoscopic mucosal resection (EMR) andendoscopic submucosal dissection (ESD)which have been broadly accepted as the regular treatment for EGC patients[13,14]. to gastrectomy.Theresults of EMRin treating EGC arecomparable to that of surgery in selectedcases. ESD has been shown to increase en bloc resectionof lesions regardless of their size, location, or presence ofscarring [15, 16, 17]. As a class of minimally invasive endoscopictechniques, ESD is characterized by fewer traumas andcomplications and better therapeutic effects.

Endoscopic therapy :

Endoscopic therapeutic methods, including EMR and ESD, are minimally invasive therapy that permits the patient to conserve the entire stomach and maintain a good quality of life. Furthermore, the cost is usually less thansurgery while the efficacy is comparable.

(1)Endoscopic mucosal resection(EMR):

Endoscopic mucosal resection (EMR) is a method used for the staging and treatment of superficial neoplasms of the gastrointestinal (GI) tract. This method was first developed in Japan for the treatment of early gastric cancer (EGC) and has since spread in use throughout the world for different indications, including dysplastic Barrett mucosa and sessile colonic neoplasms.EMR was first preceded forendoscopic therapy in 1984 by utilizing the strip biopsy method (two-channel mode)[18,19]. The operation process included submucosal injection beneath the lesion, snaring, and removing the lesion. This injection-snaring method is simple and comfortable. However, it is difficult to trap flat type lesions. Furthermore, the steel wire slips easily, which may lead to incomplete resection and local recurrence [20]. The injection-precutting-snaring (EMR-P) method refers to the submucosal injection of hypertonic saline combined with diluted epinephrine, cut around the lesion with a needle knife, and removal of the lesion by a snare. In summary, the injection-snaring and injection-precutting snaring techniques are non-inhalation methods of EMR. The inhalation methods of EMR include EMR with a cap (EMR-C) and EMR with ligation (EMR-L). EMR-C in 1992 was developed [21]. This technique can safely remove intramucosal cancers those are 2 cm or less in diameter by using a transparent plastic cap that is connected to the tip of an endoscope. The procedure includes submucosal injection, suction into the cap, and snare and resection [22, 23]. The operation process of EMR with ligation (EMR-L) is comparable to that of EMR-C. The apparatus of EMR-L is a standard variceal ligation device. After sucking lesion into the cap, the lodged band is deployed underneath the lesion, and then the banded lesion is snared and removed [24, 25]. The outcomes of EMR showed 56%–75.7% en bloc rates and 66.1%–77.5% complete resection rates in various countries [26-27]. A multi-center study on EMR in the treatment of early gastric cancer from Japan indicated that the complete resection rate is related to the lesion size; the complete resection rate of lesions less than 1 cm was 84.5%, while only 16.2% of those larger than 2 cm were resected entirely. Another Japanese literature reported that both 5-year and 10-year survival rates of patients with mucosal EGC less than2 cm that was completely removed by EMR were 99% [28, 29]. the limitations of EMR resection of lesions, EMR is considered a definitive cure for cancer if the lesion is well-differentiated to moderately differentiated, is confined to the mucosal layer, is 2 cm or smaller, and has no lymphovascular invasion. For the limitation of EMR may be considered for definitive treatment of superficial premalignant and well-differentiated to moderately differentiated malignant lesions of the GI tract in the absence of lymph node or distant metastases (T1mN0M0). It also plays an essential role in the staging algorithm of early GI cancers by providing a larger resection specimen than standard forceps biopsy, allowing accurate T staging and establishing the presence of lymphovascular involvement [30].

(2)Endoscopic submucosal dissection(ESD):

ESD is an innovative Japanese method that involves en-bloc resection of the complete lesion irrespective of size, allowing for a detailed analysis of the resected margins and depth of invasion and producing a lower local recurrence when compared to EMR techniques. (ESD) allows en bloc resection of larger lesions [31].In the late of 1990s, ESD was developed for entire removal of EGC despite its size and location by cutting the submucosal layer via the use of through the scope of endoscopic knives[32]. ESD is better to compare to EMR because it permits en-bloc resection and accurate pathologic staging for large EGCs. Momentarily, it has become one of the standard therapies and is being used to obtain en bloc resection for EGCs that would otherwise need piecemeal or surgical resection[33,34,35]. The levels of this endoscopic method consist of marking, submucosal injection, circumferential mucosal precutting, dissection, and dealing with the wound. The marking surrounding the lesion is done and circumferential mucosal pre-cutting is shown after submucosal injection. To differentiate clearly between the muscle layer and the submucosal layer and enable better hemostasis, normal saline infused with diluted epinephrine and indigo-carmine is oftentimes used as a submucosal injection solution. The injection is done again a few times until the mucosa is sufficiently raised. After raising the lesion, the submucosal layer below the lesion is dissected with lateral movement using various knives. Numerous knives have been developed and used for ESD, which including, insulation-tipped diathermic knife (IT knife), needle knife, hook knife, flex knife, triangle tip knife, flush knife, splash knife, IT-2 knife and dual knife[36,37-38]. After resection of the lesion, visible vessels in the artificial ulcer is managed with hemostatic devices to prevent delayed bleeding. The current indications for ESD are based on the criteria reported by Gotoda and colleagues, which include an ulcerative mucosal EGC < 3 cm in diameter or a submucosal invasion depth of the EGC ≤3 cm[39]. For ESD indications, according to the recent Japanese Gastric Cancer guidelines in 2015 [40]. in addition to EMR's indications, the ESD's indications include the following:

(a) UL(–) cT1a differentiated carcinomas greater than 2 cm in diameter.
(b) UL(+) cT1a differentiated carcinomas less than 3 cm in diameter.
(c) UL(–) cT1a undifferentiated carcinomas less than 2 cm in diameter.
(d) The extremely low risk of lymph node metastasis and the possibility of it becoming reasonable to expand the indications when vascular infiltration (ly, v) is absent together with the above-mentioned criteria. (d) The possibility of dealing with subsequent locally recurrent intramucosal cancers under expanded indications (evidence level V, grade of recommendation C1) if a lesion falls within the indication criteria at the initial ESD or EMR. Endoscopic submucosal dissection is the most common early gastric cancer resection uses in China. According to the research, the en bloc resection rate of ESD for early gastric cancer was 94.8%–97.7% and the 5-year survival rate was 83.2%–97.5 %.

A multicenter retrospective study comparing EMR and ESD with resection in early gastric cancer stated that the one-piece resection rate with ESD was significantly higher than that with EMR (92.8% versus 56%) [41]. The rate of perforation was 3.6% with ESD and 1.2% with EMR, although the complications were managed endoscopically. See Figure1for endoscopic submucosal dissection procedure.

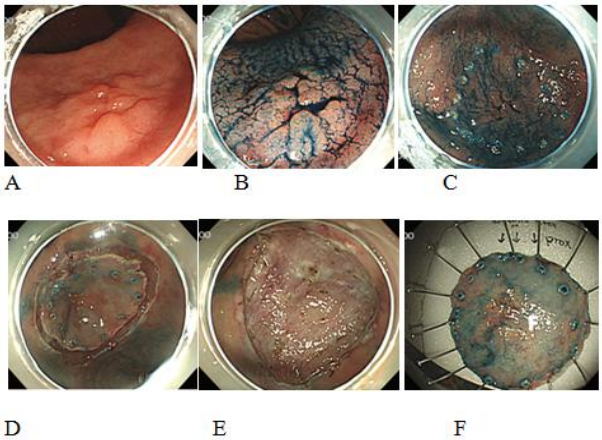

Figure 1 Endoscopic submucosal dissection procedure. A: On the lesser curvature side of the antrum, a: 1.2-cm type Ⅱa + Ⅱc early gastric cancer is observed; B: Indigo-carmine is sprinkled along the area of tumor to aid visualization. C: Marking outside the lesion; D: After giving injection of saline mixed with diluted epinephrine(1:100000) and indigo-carmine into the submucosal layer, circumferential mucosal pre-cutting is performed using a knife; E: After dissection of the submucosal layer, an artificial ulcer is seen; F: Fixation of the tissue specimen.

Indications:

Defining an indication for endoscopic treatment looks to be the most important step in managing patients with EGC. To choose appropriate patients with EGC and to obtain a complete resection, the precise margin and depth of the tumor could be determined through endoscopic evaluations. The horizontal extent area of the tumor can be determined with standard endoscopy and chromoendoscopy
(CE). In some cases with unclear margins even with CE, magnifying endoscopy with narrow-band imaging could be beneficial to recognize the accurate margin[42]. The depth of tumor invasion can also be evaluated with standard endoscopy and CE. In addition, EUS could be utilized to further ascertain the depth. Nevertheless, the precise of EUS in evaluating the depth of invasion in EGC was documented to range from 71% to 78%[43,44].

(1)Conventional indication :

The conventional standard criteria[45] for choosing of patients with EGC who are fitting for the endoscopic therapy are following: (1) well or moderately differentiated adenocarcinoma and/or papillary carcinoma; (2) restricted to the mucosa; (3) less than 2 cm for superficially elevated type lesions; (4) less than 1 cm for the flat and depressed type lesions; (5) without ulcer or ulcer scar; and (6) without venous or lymphatic involvement[46]. The reason for this guideline is based on the knowledge that patientsmeeting the criteria are excluded from the lymph node (LN) metastasis[47].

Expansion of the criteria for the choice of patients with EGC who are suitable for the endoscopic treatment has been introduced in Japan from clinical observations that the extremely strict definite indication leads to undesirable surgery[48]. involving 5265 patients who experienced gastrectomy for EGC[49] were able to further determine the risk of LN metastasis in certain groups of patients with EGC and showed four groups with a low risk of LN metastasis: (1) differentiated intramucosal adenocarcinoma without lymphovascular invasion and ulcer findings, irrespective of tumor size; (2) differentiated intramucosal adenocarcinoma without lymphovascular invasion less than 3 cm in diameter, irrespective of ulcer findings; (3) undifferentiated intramucosal cancer without lymphovascular invasion and ulcer findings less than 2 cm in diameter; and (4) differentiated adenocarcinoma with little submucosal penetration (SM1, cancer intrusion into the upper third of the submucosa) but without lymphovascular intrusion less than 3 cm in diameter. These results have enabled the development of expanded criteria for endoscopic treatment for EGC[50].Expansion of the criteria for the choice of patients with EGC who are suitable for the endoscopic treatment has been introduced in Japan from clinical observations that the extremely strict definite indication leads to undesirable surgery[48]. involving 5265 patients who experienced gastrectomy for EGC[49] were able to further determine the risk of LN metastasis in certain groups of patients with EGC and showed four groups with a low risk of LN metastasis: (1) differentiated intramucosal adenocarcinoma without lymphovascular invasion and ulcer findings, irrespective of tumor size; (2) differentiated intramucosal adenocarcinoma without lymphovascular invasion less than 3 cm in diameter, irrespective of ulcer findings; (3) undifferentiated intramucosal cancer without lymphovascular invasion and ulcer findings less than 2 cm in diameter; and (4) differentiated adenocarcinoma with little submucosal penetration (SM1, cancer intrusion into the upper third of the submucosa) but without lymphovascular intrusion less than 3 cm in diameter. These results have enabled the development of expanded criteria for endoscopic treatment for EGC[50].

(2)Expanded indication :

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Endoscopic Complications:

The main complications of endoscopic resection for EGC are Delayed bleeding and perforation. Delayed bleeding occurs in 2.5-3.9% of EMR patients and 1.8-16% of ESD patients. ESD has a higher rate of delayed bleeding than EMR and delayed bleeding is more common for expanded indication lesions correlated to guideline-indication lesions. Routine coagulation of visible vessels and application of clips at the post-ESD

mucosal defect reduces the rate of delayed hemorrhage [51] and is done as a standard practice. Administration of proton pump inhibitors decreases the incidence of delayed bleeding compared to administration of histamine 2-receptor antagonists [52]. rates of perforation during ESD are moderately higher (1.2-9.7%) than those in EMR (0.5-3.2%) .perforation during EMR only occurs in lesions with fibrosis in the submucosa caused by ulceration, scarring or tumor invasion, whereas perforation during ESD has been seen in 2-5% of cases in all indication categories. Significant risk factors for perforation during gastric ESD are tumor location (upper third), tumor size (>2 cm) and experience of an institution (lesions treated in the early period) [53]. Most intraoperative perforations can be controlled conservatively with endoscopic clipping [54], but surgical intervention is needed for delayed perforation [55]. Stricture or stenosis can happen after >75% resection of antral, prepyloric or cardiac lesions [56,57]. Endoscopic balloon dilation is sufficient for stricture, but one should be careful not to cause perforation and surgical intervention is required in an ineffective case.Aspiration pneumonia is very rare (0.7%-1.5%).Nevertheless, the risk of aspiration pneumonia appears to increase in sedation with consecutive propofol infusion with intermittent or continuous administration of an opioid. and is linked with prolonged procedures that longer than (> 2 h), male gender and old age(> 75 years) are associated with an event of aspiration pneumonia after ESD. Pain after endoscopic resection is often mild and dull in nature and can be managed by PPI's and opioids.

Surgical Treatment:

although endoscopic resection is a choice for patients with EGC who meet"standard" criteria of endoscopic resection, surgical treatment remains a choice with survival rates at 5 years of 97%[58]. Currently, there are no parallel studies between endoscopic treatment and gastrectomy. However, several studies advised the clinical prognosis were similar although patients with endoscopic therapy benefit from a short duration of hospital stay and lower cost[59-60]. Patients who do not meet the guidelines for endoscopic resection have a higher risk of lymph node metastases which needs a gastrectomy with perigastric lymph node excision. Another indication for gastrectomy is the detection during the staging of lymph nodes or a high doubt of their presence. The type of gastrectomy (subtotal gastrectomy or total) is defined by the area of the lesion, reserving the subtotal gastrectomy for EGC located in the lower two-thirds of the stomach. Another option is laparoscopic gastrectomy. EGC (T1N0 or T2N0) is deemed as the only indication for laparoscopic gastrectomy.

Follow-Up After Endoscopicresection:

Early gastric cancer (EGC) patients used by endoscopic resection with curative purpose, need monitoring to recognize local recurrence and metachronous gastric cancer. In patients with EGC who meet criteria for endoscopic resection, it is desirable to do an upper gastrointestinal endoscopy yearly. Patients who meet "expanded" criteria, in addition to the yearly endoscopy, monitoring can be given alternating abdominal CT scan and EUS every 6 months for 3 years. The intent of this additional monitoring is to identify lymph node and distant metastases[61]. Post-ESD ulcers require approximately 6–8 weeks to close completely, during which time antacids are administered [62]. Proton pump inhibitors (PPIs) are said to be more effective for preventing delayed bleeding than H2-receptor antagonists [63], and, recently, the combined use of mucosal protective anti-ulcer drugs with PPIs was listed to further promote ulcer healing [64, 65].

Prognosis Of Ealry Gastric Cance:

The prognosis for EGC after gastric EMR and ESD (5-year survival rate >90%)have an excellent prognosis and with high survival rates in comparison with stage Ⅱ gastric cancer(advanced gastric cancer). overall survival and rates of recurrences are very excellence. However, it is to accentuate that the fewer cases of recurrence deaths happened in patients with a follow-up longer than 15 years (up to 20 years), advising that patients with EGC should be observed for longer periods than patients with advanced(metastasized) gastric cancer, because they should not be deemed fully recovered after 5-10 years of surveillance. EGC has a long natural history [66] and the rate of disease-related death is low, therefore, long-term survival should be studied with a high follow-up rate. Moreover, an intent-to-treat analysis in a prospective cohort study is good. The Japan Clinical Oncology Group is currently conducting a multicenter prospective cohort study investigating the 5-year survival rate of all ESD patients who had EGC that fulfilled the expanded indication criteria, and the result is pending.

II. Conclusion

aim an endoscopic therapy for EGC that is restricted to the mucosa, size ≤ 2 cm, differentiated and regardless of lymph node involvement. EMR had been chosen as a treatment option for small intramucosal carcinoma but ESD allowed high en bloc resection rates for small and large lesions, as well as those with scarring. Consequently, endoscopic resection has been set as a standard treatment for the management of EGC in China. Development in ESD method for tumor elimination is crucial for management of EGC but there are

other important steps to obtain excellent long-term outcome such as the precision of endoscopic diagnosis which defines the optimal treatment; accurate histological assessment of the resected specimen for curability; and surveillance endoscopy for early detection of metachronous multiple cancer. The EGC is a tumor with a very favorable prognosis, with high survival rates in comparison with advanced gastric cancer and there is a wide consent on lymph nodes invasion as a main independent prognostic factor. However, death among these patients' remains a concern and long-term follow up appears to be necessary even for patients successfully treated for EGC, as recommended by recent studies.

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