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Oncologic Outcomes of Endoscopic Resection for Early Gastric Cancer

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Abstract

Gastric cancer is the fifth most common cancer in the world, and about one million new cases develop globally each year. Early Gastric Cancer (EGC) is a stage that tumor invades gastric mucosa or submucosa with or without involvement of the lymph nodes (LN). Endoscopic resection techniques are endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), latter of which is more popular now. Gastrectomy is the standard choice of treatment but, is highly invasive that requires longer stay at hospital, with higher costs and complication rates, especially at the anastomotic site. EMR was used more frequently before the development of ESD but, now give its popularity to ESD and EMR depends on the region and experience of the center. EMR is more convenient method for smaller lesions, associated with lower bleeding risk and shorter duration of operation compared to ESD. On the other hand, ESD has lower en-block resection rates and recurrence rates compared to EMR. In this review, we analyzed over than 10.000 patients' oncologic outcomes including overall survival, disease free survival and recurrence rates. In conclusion, many newly diagnosed gastric cancer patients are seeking micro-invasive treatment modalities around the World for their early stage cancers. Endoscopic submucosal resection and endoscopic mucosal resection are safe and convenient procedures and had comparable oncologic outcomes with surgery. Additionally, these techniques can easily be used in patients who are not surgical candidates.

Keywords: Early gastric cancer, endoscopic resection, oncologic outcomes.

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Introduction

Gastric cancer is the fifth most common cancer in the world, and about one million new cases develop globally each year[1]. Early gastric cancer (EGC) is the stage in which the tumor invades the gastric mucosa or submucosa, with or without the involvement of the lymph nodes (LN). The probability of metastasis to the LN is known to be around 10%-15% in patients with EGC; this stage is one of the strongest prognostic factors for gastric cancer (GC)[2]. Surgery is the main treatment for EGC with lymph node metastasis, providing 5-year overall survival (OS) rates of more than 90%[3]. However, surgery necessitates a longer hospital stay, has operator- or center-dependent morbidity and mortality rates, and costs more than other treatment modalities. Pathologic reports have shown that only a small percentage of EGC specimens present lymphovascular invasion[4], hence the search for early definitive treatment options. Endoscopic resection (ER) of gastric cancer can be done by either endoscopic submucosal dissection (ESD) or endoscopic mucosal resection (EMR). These methods might be good alternatives to surgery in selected populations. The advantages of ER methods are that they are minimally invasive and require a shorter hospital stay, with probably lower costs and acceptable improvement of quality of life[5]. Nevertheless, the lack of long-term follow-up results and comparative oncologic outcomes are the main concerns about ER methods. Therefore, the present review aimed to determine the oncologic outcomes of ER, such as OS, recurrence rate (RR), and disease-free survival (DFS), and to compare them with surgical results.

Endoscopic Resection: Endoscopic Submucosal Dissection and Endoscopic Mucosal Resection

The protocols for gastric cancer screening in the general population, especially in Asia, have enabled the early diagnosis of gastric cancers and decreased the mortality rates. Additionally, the early diagnosis of GC has been enabled to endoscopic resection. The ESD technique has been particularly used in Japan and Korea, where intensive screening programs allow the early detection of EGC. In industrialized western countries, screening for GC has not yet gained ground. ESD is an exacting technique that involves creating a large submucosal cushion with multiple submucosal injections and necessitates the use of many cautery knives to achieve an en bloc resection[5,6]. The bleeding and complication rates can be decreased with experience in this technique. In the EMR procedure, mucosal areas with clear margins are marked circumferentially with electrocautery, and band ligation is carried out by removing the tissue as whole body or in piecemeal fashion[8]. Lesions smaller than 10-20mm have the highest rates of en bloc resection[9]. The advantages of EMR are that it is relatively safe, allows obtaining bigger samples than in biopsies, and provides more diagnostic information by the prediction of lymphatic and blood vessel invasion[10]. Nevertheless, although ESD and EMR have become more practical, the requirement of experience, the higher recurrence rates, and the lack of evidence of long-term results are major issues of debate.

Early Gastric Cancer

Gastric carcinoma is the second most common cause of cancer-related mortality, and nearly one million new cases develop yearly worldwide. Depending on the region, 15-57% of gastric cancers have been diagnosed in the early stage[1]. Although the gastric cancer distribution shows variation, Eastern Asia, European countries, and Latin America are emerging as regions of higher incidence, probably due to their strict screening programs[11]. These broadly enforced programs allow the detection of early stage gastric carcinoma; thus, western countries have a 20% rate of EGC, whereas Japan and Korea in particular have detected over 50% of gastric carcinomas in the early stages[12,13]. One of the most common reasons for this higher detection rate is the implementation of screening programs. In addition, there are some disagreements between pathologists in the East and the West regarding the interpretation of pathologic specimens. Western pathologists consider lamina propria invasion in the diagnosis of cancer, whereas Eastern pathologists do not. In a study in which EMR specimens were reexamined by different pathologists, a concordance rate of only 31% was found between Eastern and Western pathologists[14]. There are several classification systems for EGC; however, these have mainly been used in East Asia[15]. Molecular classification is a newer topic in EGC studies, and the emerging investigations include evidence about miRNAs and different genetic patterns of diffuse versus intestinal type GC[16,17].

Unfortunately, EGC does not have any specific symptoms, and only active screening programs and upper endoscopy can aid its early detection[18]. After the diagnosis of EGC, all patients should undergo Helicobacter pylori testing and, if the results are positive, the corresponding treatment[19]. Early gastric cancer is defined as all T1 lesions (gastric mucosal and submucosal) regardless of

nodal status and an overall incidence of nodal invasion lower than 15% for all T1 stages[4]. Roviello et al., who investigated 652 EGC patients retrospectively, found lymph node metastases in 14.1% of cases and a significant correlation between nodal metastasis and lesion diameter. Also, the submucosal lesions had a higher nodal metastasis rate than the mucosal lesions[2]. A Japanese study that evaluated 5,265 patients found that lesions smaller than 3 cm did not have nodal metastasis[4]. In the staging of EGC, endoscopic ultrasonography (EUS) provides the most accurate results for predicting the lesion depth. Additionally, mini-probe EUS has higher accuracy than radial EUS (80 vs 60 percent, respectively)[20].

Treatment of Early Gastric Cancer

There are several treatment options for early gastric cancer, including surgery, H. pylori eradication, ER, and adjuvant therapies. Gastrectomy is the standard therapy when there is lymph node invasion. In patients without lymph node invasion, ER is an option; however, this procedure requires the following specific criteria: lesions smaller than 2 cm without ulceration, high possibility of en bloc resection, T1 lesions, intestinal type tumor histology, and absence of lymphatic or venous invasion [5,21]. There is no chance of curing GC without invasive treatment modalities, especially surgery. The 5-year OS rate is still below 30% for all stages, and only 10% of patients are in stage 1 at the time of diagnosis[22,23].

Surgery

Surgeons generally prefer gastrectomy as treatment for EGC, and different surgical methods have comparable results. Two meta-analyses have shown that laparoscopy-assisted gastrectomy has similar results to open gastrectomy; however, these analyses included studies with no satisfactory prospective design[24,25]. In a Japanese trial with 305 patients who underwent pylorus-preserving gastrectomy to treat EGC, with a median follow-up period of about 5 years, 7 patients died. The 5-year OS rate was 98%, the gastrectomy-related mortality and recurrence rates were 0%, and the accuracy of EUS for T1 stage was 95.7%[26]. A larger Japanese trial with 611 EGC patients who underwent the same procedure reported an accuracy rate of 94.3% for EGC and a lymph node invasion rate of 10%; 16.7% of patients had complications without mortality, and the 5-year OS rate was 96.3%[27].

Total gastrectomy is usually recommended for upper third stomach tumors, and subtotal gastrectomy for lower two-third tumors[28]. Most experienced centers also prefer laparoscopic surgery. Laparoscopy-assisted distal gastrectomy (LADG) has been carried out by Japanese and Korean surgeons as a common treatment for EGC, with safe and long-term outcomes and a DFS rate of >98% in patients with stage 1 GC[29]. These retrospective data were obtained over a short follow-up period for early stage gastric cancer, with 6 recurrences reported within 36 months of the median follow-up period. The postoperative complication rate was 12.7%, mostly related to anastomotic sites, whereas the intraoperative complication rate was 1.7%. More recently, a Korean group carried out a randomized trial that included 1,416 patients, in which LADG was compared with open distal gastrectomy (ODG)[30]. In that study, 6 patients (0.9%) in the LADG group needed open surgery. The rates of complications, including wound complications, were significantly lower in the LADG group (13.0%) than in the ODG group (19.9%). Another Korean study compared open and laparoscopic total gastrectomy in 753 patients with EGC[31]. The patterns of the complications were different, with wound site complications being higher in the open group (502 patients), and anastomosis and intra-abdominal complications being higher in the laparoscopy-assisted group (251 patients). There were 4 deaths related to the operation in the laparoscopy-assisted group, and one death in the open group. The median follow-up periods were 55 and 58 months, respectively, in the open and the laparoscopy-assisted group, and there were no significant differences in RR and OS between the groups. The 5-year OS rates were 99.7% and 99% after open and laparoscopy-assisted gastrectomy, respectively.

EMR

In Eastern Asia, ER is widely used to treat GC because it enables to prevent stomach with a high quality of life. This procedure gained popularity before the development of ESD[32]. EMR is not appropriate if lesions have invaded the submucosa; however, it is a practical and safe method when done by expert hands. In selected lesions, the operation time is shorter compared with ESD[33]. The perforation rates are acceptable, with lower intraoperative bleeding rates compared with ESD[34]. A meta-analysis found lower en bloc resection rates and higher RRs with EMR than with ESD[35]. Oka et al., in a study of 711 patients with 825 lesions treated with EMR, reported RRs of 2.9% and 4.4% after en bloc and piecemeal resection, respectively. The average follow-up period was 83 months; however, the authors did not report the OS rates. In a second trial done in the same year, Oda et al. treated 411 EGC pa-

tients with EMR, with a median follow-up of 3.2 years. They found a residual/recurrent tumor rate of 6.6%, a DFS rate of 92.5%, and an OS rate of 99.7%[36]. Another work treated 328 EGC patients with EMR and found an RR of 4%[37]; the OS and DFS rates were not reported. A fourth study included 103 patients treated with EMR; the R0 resection rate was 92% and the RR was 0% within 29 months of follow-up; the OS rate was not reported[38].

Watanabe et al. carried out 245 EMR procedures in 229 patients; they did not observe any mortality related to gastric cancer within a median 38-month follow-up period[33]. In this study, 63% of lesions were diagnosed as adenocarcinoma, whereas the remaining 37% were diagnosed as adenoma; however, the oncologic outcomes were not reported. In a more recent work, Tanabe et al. treated 359 lesions with EMR and found an RR of 4.2% over a median follow-up period of 73 months[39]. The median time to recurrence was 14 months, and the 3- and 5-year DFS rates were 98.2% and 96.6%, respectively. The authors did not observe any mortality related to gastric cancer in the EMR patients. Choi et al. compared surgery with EMR in 379 and 172 patients, respectively[40]. The complete resection rate was 71.2% in the EMR group and 87.7% in the surgery group. The patients who underwent EMR had more comorbidities and were older than those in the surgery group; the follow-up period was more than 80 months. The 5- and 10-year OS rates were, respectively, 93.6% and 81.9% in the EMR group and 94.2% and 84.5% in the surgery group, with no significant differences; the RRs were 1.2% and 1.1%, respectively. Etoh et al. compared EMR and gastrectomy in 93 elderly patients[41]. Surgery was done in 44 patients, and EMR in 49 patients. No significant differences were found in the 3- and 5-year OS rates between the surgery and the EMR group (73.5% vs 82.5% and 55.0% vs. 62.5%, respectively).

EMR versus ESD

Min et al. compared the results of EMR and ESD in 103 and 243 patients, respectively. The en bloc resection rate was significantly higher in the ESD than in the EMR group; however, the R0 resection and complication rates were similar. In this study, the patients who underwent R0 resection in both groups did not have local recurrence[39]. Oka et al. compared EMR with ESD in 711 and 185 patients, respectively. The en bloc and R0 resection rates were significantly higher in the ESD than in the EMR group regardless of the lesion size; however, the complication rates were the opposite. The overall local RR was 3.1%, and all local recurrences could have been treated with EMR[34]. Another large trial included 714 EGC cases in 655 patients; 411 and 303 lesions were treated with EMR and ESD, respectively. The curative resection rate was significantly higher for ESD than for EMR. The 3-year residual-free survival rate was significantly higher in the ESD than in the EMR group (97.6% vs 92.5%, respectively), whereas the 3-year OS rate was similar between the two groups (98.5% vs 99.7%, respectively)[37]. In another study, 71 patients were treated with EMR, and 106 patients with ESD; the en bloc and R0 resection rates were significantly lower in the EMR than in the ESD group (54% vs 94% and 37.5% vs 92.6%, respectively). The median follow-up periods were 54 months and 34 months for EMR and ESD patients, respectively. The 5-year OS rates (82.5% vs 100%, respectively) and the recurrence-free rates (74% vs 100%, respectively) were significantly lower in the EMR than in the ESD group[42]. A more recent study included 780 EGC lesions, 359 of which were treated with EMR, and the remaining 421 with ESD. The median follow-up period was longer than 5 years in both groups; the local RR was significantly higher in the EMR than in the ESD group (2.9% vs 0%, respectively), and the recurrence-free survival at the 5th year was significantly lower (97% vs 100%, respectively). The 5-year OS rates were higher than 99% in both groups, with no significant difference[39].

ESD

In a study of 167 patients diagnosed with EGC who had been treated with ESD, with a median follow-up period of 45 months, only 2 cases (1.2%) had local recurrence, which was treated with repeat ESD. The 5-year OS was 90.7%, and no significant difference was found between ESD and surgery[43]. In a similar report, 74 patients were treated with ESD, and 40 patients with surgery[44]. The three-year OS rates were 94.6% and 89.7%, respectively, and no significant difference was reported. In a large study, Zhou et al. treated 1687 EGC patients with ESD; a 3-year OS rate of over 99% was obtained, which was similar to that in the surgery group consisting of 124 patients[45]. Another study compared ESD with surgery in 76 and 149 patients, respectively[46]. The total RR was found to be significantly higher in the ESD that in the surgery group (14% vs 0.7%, respectively) over a median follow-up period of 42 months. Tanabe et al. compared EMR with ESD in a study of 421 patients who underwent ESD; these patients were found to have significantly higher DFS rates than those treated with EMR (100

vs 97%, respectively)[39]. Kim et al. treated 142 patients with ESD and 71 patients with surgery; the local RRs were nonsignificantly higher for ESD compared with surgery (4.7% vs 0%, respectively). The OS rates of the ESD and surgery groups were 93.4±3.2 and 85.8±5.5 months, respectively, and the DFS rates were 89.7±3.6 and 90.4±3.5 months, with no significant differences; the 5-year OS rates were higher than 95% in both groups[47]. A small study with 96 patients who were treated with ESD and 56 patients who underwent surgery, with a median follow-up period of 71 months in the ESD group, found that the OS rates did not differ significantly between the two groups. However, this study was published only as an abstract presentation[48]. In another abstract, published by Kim et al. in 2015, 106 patients were treated with surgery, and 41 patients with ESD. The 5-year OS rate was 100% in both groups, whereas the DFS was higher in the surgery than in the ESD group (97.6% vs 87.6%, respectively)[49]. Kang et al. treated 60 EGC patients with ESD. They found an R0 resection rate of 94.4% and an RR of 0% within a 13-month median follow-up period; the OS rates were not reported[50]. Another study included 101 patients treated with ESD; the R0 resection rate was found to be 82.5%, the 5-year OS rate was 97.7%, and the overall mortality was 3.9% within a 40-month median follow-up period[51]. In a more recent study, 569 non-curative ESD patients were divided into two groups: the first group (356 patients) was treated with additional gastrectomy, and the second group (212 patients) underwent basic follow-up[52]. Based on the general characteristics of the patients, those who underwent surgery had a higher rate of local invasion, whereas those who underwent basic follow-up had higher comorbidity. Lymph node metastasis was observed in 18 (5.3%) patients in the surgery group. A positive vertical margin with submucosal and lymphovascular invasion was found to be significantly associated with LN metastasis. During the median 70-month follow-up, LN and/or distant metastases were observed in 4.2% of the observation arm. The 5-year DFS rate was 98.8 in the surgery group and 96.8% in the observation arm; the 5-year OS rate was significantly higher in the former than in the latter group (94.7% and 83.8%, respectively).

Elderly and/or comorbid patients: Park et al. reported on their experience with 518 elderly EGC patients, 318 of whom were treated with ESD, and the remaining 218 with surgery[53]. The mean age of the study population was 74.5. The follow-up period was shorter than in previous studies; nevertheless, significantly higher RRs and more metachronous lesions were found in the ESD group compared with the surgery group. The 3-year cancer-free survival was significantly longer in the surgery than in the ESD group (100% vs 80%, respectively). In contrast, the 5-year OS did not differ significantly between the two groups (97.4% for ESD and 96.1% for surgery). Three additional trials investigated the ESD efficacy in elderly patients. The first trial, which included 440 patients older than 80 years, found complication rates similar to those in younger patients, including bleeding and perforation rates of 3.2% and 2.8%, respectively. Additional surgery was carried out in 11.5% of ESD patients due to non-curative resection. The median follow-up period was 41 months, during which no tumor recurrence was observed. The 5-year OS rates were 80.3% in the group that underwent curative ESD, 100% in the group that had surgery after non-curative ESD, and 66.7% in the group without surgical follow-up after non-curative ESD; only the last group was found to have a significantly lower OS[54]. In the second trial, 69 EGC patients were treated with ESD, and a 5-year OS rate of 60% was obtained; however, the patients also had liver cirrhosis concomitant to EGC[55]. The third study included 144 patients who had chronic kidney disease along with EGC; they were treated with ESD. In 19 of 144 patients who were undergoing hemodialysis, the en bloc resection rate was 95.8%; during the 26 months of follow-up, the 3-year OS rate was 92.5%[56].

The data from Western countries are very limited. Najmeh et al. carried out a study in the Western world, in which 37 patients diagnosed with EGC were treated with laparoscopic gastrectomy, and 30 patients with the same diagnosis were treated with ESD[57]. The LN positivity was 48.6% in the surgery group; the R0 resection rate was 89.2% for surgery compared with 86.7% for ESD, with no significant difference between the groups. The OS and DFS rates at 4 years were 90.3% versus 100% and 82.6% versus 84.6% for the surgery and the ESD group, respectively, with no significant differences.

ER versus Surgery

In a more recent study, Kim et al. compared surgery with ER in 457 patients; however, only 18 of the patients underwent EMR, whereas 147 patients were treated with ESD, and 292 patients had surgery[58]. In the ER group, the en bloc resection rate was 78%, and the 5-year OS rate was 97.5%, with 0% mortality. Another study compared the long-term results of surgery and ER in 375

patients[59]. The median follow-up period was about 75 months, and 86 of 261 patients were treated with EMR. The comparison of the EMR and ESD results showed higher en bloc and R0 resection rates for ESD; however, there were no significant differences in OS and DFS between the groups. The 5-year OS, DFS, and RFS rates in the ER and surgery groups were 95.7% versus 93.6%, 90.7% versus 92.8%, and 94.8% versus 99.1%, respectively, with no significant differences between the groups. The mortality rates were 0.3% in the surgery group and 0% in the ER group; the 5-year OS rates did not differ significantly (97% vs 97.5%, respectively) between groups. The gastric cancer RR was significantly higher in the ER than in the surgery group (4.7% vs 0.3%, respectively)[49]. In a small study, Yamashina et al., who compared ER with surgery in patients with gastric cancer who had remnant stomach after gastrectomy, found that the 5-year OS rates did not differ significantly between the ER and the surgery group (81.8% vs 75%, respectively)[60]. A more recent meta-analysis included 1466 patients, of whom 848 underwent surgery, and 618 had ER[61]. The 5-year OS rates were found to be similar between the two groups. According to this meta-analysis, ER required a shorter hospital stay and decreased the postoperative morbidity but had more bleeding complications. Additionally, ESD showed higher en bloc and complete resection rates compared with EMR.

Prospective data: Almost all of the data were obtained from retrospective studies on EGC treatment modalities. In a prospective study started in 2012, cT1a (intramucosal) undifferentiated early gastric carcinoma smaller than 2 cm and without ulceration was treated. The said study intended to include 325 patients, with 5-year OS rates as the primary outcome[62]; however, the results are yet to be published. Prospective studies on ER, especially including oncologic outcomes, thus seem to be needed urgently.

References

1. Engin H, Bilir C, Ustündağ Y. MELD-sodium score and its prognostic value in malignancy-related ascites of pancreatic and gastric cancer. Support Care Cancer. 2013 Apr;21(4):1153-6.
2. Roviello F, Rossi S, Marrelli D, Pedrazzani C, Corso G, VindigniC, Morgagni P, Saragoni L, de Manzoni G, Tomezzoli A. Numberof lymphnodemetastasesanditsprognosticsignif icance in earlygastriccancer: a multicenterItalianstudy. J SurgOncol 2006; 94: 275-280
3. Sun K, Chen S, Ye J, Wu H, Peng J, He Y, Xu J. Endoscopic resection versus surgery for early gastric cancer: a systematic review and meta-analysis. Dig Endosc 2016;28: 513-25
4. Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, Kato Y. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer 2000; 3: 219–25
5. Soetikno R, Kaltenbach T, Yeh R, Gotoda T. Endoscopic mucosal resection for early cancers of the upper gastrointestinal tract. J ClinOncol. 2005; 23: 4490–4498
6. Deprez PH, Bergman JJ, Meisner S, Ponchon T, Repici A, Dinis-Ribeiro M, Haringsma J. Current practice with endoscopic submucosal dissection in Europe: position statement from a panel of experts. Endoscopy 2010;42:853–858
7. Cao Y, Liao C, Tan A, Gao Y, Mo Z, Gao F. Meta-analysis of endoscopic submucosal dissection vs. endoscopic mucosal resection for tumors of the gastrointestinal tract. Endoscopy 2009;41:751–757
8. Balmadrid B and Hwang J.H. Endoscopic resection of gastric and esophageal cancer. Gastroenterol Rep (Oxf). 2015; 3: 330–338
9. Yamashita T, Zeniya A, Ishii H, Tsuji T, Tsuda S, Nakane K, Komatsu M. Endoscopic mucosal resection using a cap-fitted panendoscope and endoscopic submucosal dissection as optimal endoscopic procedures for superficial esophageal carcinoma. SurgEndosc 2011;25:2541–2546
10. Yamasaki M, Kume K, Yoshikawa I et al. A novel method of endoscopic submucosal dissection with blunt abrasion by submucosal injection of sodium carboxymethylcellulose: an animal preliminary study. GastrointestEndo sc2006;64:958–965.
11. Noguchi Y, Yoshikawa T, Tsuburaya A, Motohashi H, Karpeh MS, Brennan MF.Is gastric carcinoma different between Japan and the United States? Cancer 2000; 89: 2237.
12. Lee HJ, Yang HK, Ahn YO. Gastric cancer in Korea.Gastric Cancer 2002;5:177
13. Maehara Y, Orita H, Okuyama T, Moriguchi S, Tsujitani S, Korenaga D, Sugimachi K. Predictors of lymph node metastasis in early gastric cancer. Br J Surg 1992; 79: 245.
14. Schlemper RJ, Itabashi M, Kato Y, Iwashita A, Kato Y, Koike M, Lewin KJ, Riddell RH, Shimoda T, Sipponen P, Stolte M, Watanabe H. Differences in diagnostic criteria for gastric carcinoma between Japanese and western pathologists. Lancet 1997; 349: 1725.
15. Japanese Classification of Gastric Carcinoma - 2nd English Edition. Gastric Cancer 1998; 1:10.
16. Hasuo T, Semba S, Li D, Shirasaka D, Aoyama N, Yokozaki H. Assessment of microsatellite instability status for the prediction of metachronous recurrence after initial endoscopic submucosal dissection for early gastric cancer. Br J Cancer 2007; 96:89.
17. Zhu C, Ren C, Han J, Ding Y, Du J, Dai N, Dai J, Ma H, Hu Z, Shen H, Xu Y, Jin G. A five-microRNA panel in plasma was identified as potential biomarker for early detection of gastric cancer. Br J Cancer 2014; 110:2291.
18. Ballantyne KC, Morris DL, Jones JA, Gregson RH, Hardcastle JD.Accuracy of identification of early gastric cancer.Br J Surg 1987; 74:618
19. Fuccio L, Zagari RM, Eusebi LH, Laterza L, Cennamo V, Ceroni L, Grilli D, Bazzoli F. Meta-analysis: can Helicobacter pylori eradication treatment reduce the risk for gastric cancer? Ann Intern Med 2009; 151:121.
20. Choi J, Kim SG, Im JP, Kim JS, Jung HC, Song IS.Comparison of endoscopic ultrasonography and conventional endoscopy for prediction of depth of tumor invasion in early gastric cancer. Endoscopy 2010; 42:705.
21. Min YW, Min BH, Lee JH, Kim JJ.Endoscopic treatment for early gastric cancer. World J Gastroenterol 2014; 20: 4566.
22. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012; 62: 10
23. Wanebo HJ, Kennedy BJ, Chmiel J, Steele G Jr, Winchester D, Osteen R. Cancer of the stomach. A patient care study by the American College of Surgeons. Ann Surg 1993; 218: 583.
24. Chen K, Xu XW, Zhang RC, PanY,Wu D, Mou YP.Systematicreviewand meta-analysis of laparoscopy-assistedandopen total gastrectomyforgastriccancer. World J Gastroenterol2013; 19: 5365–5376.
25. Shen H, Shan C, Liu S, Qiu M. Laparoscopy-assistedversusopen total gastrectomyforgastriccancer: a meta-analysis.J LaparoendoscAdvSurgTech A2013; 23: 832–840.
26. Hiki N, Sano T, Fukunaga T, Ohyama S, Tokunaga M, Yamaguchi T. Survival benefit of pylorus-preserving gastrectomy in early gastric cancer.J Am CollSurg2009; 209:297-301.
27. Morita S, Katai H, SakaM, Fukagawa T, Sano T, Sasako M. Outcome of pylorus-preserving gastrectomy for early gastric cancer.Br J Surg 2008;95: 1131
28. Folli S, Dente M, Dell'Amore D, Gaudio M, Nanni O, Saragoni L, Vio A. Early gastric cancer: prognostic factors in 223 patients. Br J Surg 1995;82:952.
29. Kitano S, Shiraishi N, Uyama I,Sugihara K, Tanigawa N and the Japanese Laparoscopic Surgery Study Group. A Multicenter Study on Oncologic Outcome of Laparoscopic Gastrectomy for Early Cancer in Japan. Ann Surg 2007; 245: 68–72.
30. Kim W, Kim HH, Han SU, Kim MC, Hyung WJ, Ryu SW, Cho GS, Kim CY, Yang HK, Park DJ, Song KY, Lee SI, Ryu SY, Lee JH, Lee HJ; Korean Laparo-endoscopic Gastrointestinal Surgery Study (KLASS) Group. Decreased Morbidity of Laparoscopic Distal Gastrectomy Compared With Open Distal Gastrectomy for Stage I Gastric Cancer: Short-term Outcomes From a Multicenter Randomized Controlled Trial (KLASS-01). Ann Surg2016;263: 28-35.
31. Lee JH, Nam BH, Ryu KW, Ryu SY, Park YK, Kim S, Kim YW. Comparison of outcomes after laparoscopy-assisted and open total gastrectomy for early gastric cancer. Br J Surg2015;102: 1500-5
32. Tada M, Murakami A, Karita M, Yanai H, Okita K. Endoscopicresection ofearlygastriccancer. Endoscopy 1993;25:445–50.
33. Watanabe K, Ogata S, Kawazoe S, Watanabe K, Koyama T, Kajiwara T, Shimoda Y, Takase Y, Irie K, Mizuguchi M, Tsunada S, Iwakiri R, Fujimoto K. Clinicaloutcomes ofEMR forgastrictumors: historical pilot evaluationbetweenendoscopicsubmucosaldissectiona ndconventionalmucosalresection. GastrointestEndosc 2006;63: 776–82.
34. Oka S, Tanaka S, Kaneko I,Mouri R, Hirata M, Kawamura T, Yoshihara M, Chayama K. Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. GastrointestEndosc 2006;64:877–83.
35. Facciorusso A, Antonino M, Di Maso M, Muscatiello N. Endoscopic submucosal dissection vs endoscopic mucosal resection for early gastric cancer: A meta-analysis. World J GastrointestEndosc2014;6: 555-63.
36. Oda I, Saito D, Tada M, Iishi H, Tanabe S, Oyama T, Doi T, Otani Y, Fujisaki J, Ajioka Y, Hamada T, Inoue H, Gotoda T, Yoshida S.A multicenter retrospective study of

References

endoscopic resection for early gastric cancer. Gastric Cancer2006;9:262-70.

37. Hoteya S, Iizuka T, Kikuchi D, Yahagi N.Benefits of endoscopic submucosal dissection according to size and location of gastric neoplasm, compared with conventional mucosal resection. J Gastroenterol Hepatol 2009;24:1102-1106.
38. Min BH, Lee JH, Kim JJ, Shim SG, Chang DK, Kim YH, Rhee PL, Kim KM, Park CK, Rhee JC. Clinical outcomes of endoscopic submucosal dissection (ESD) for treating early gastric cancer: comparison with endoscopic mucosal resection after circumferential precutting (EMR-P).Dig Liver Dis 2009;41: 201-209
39. Tanabe S, Ishido K, Higuchi K, Sasaki T, Katada C, Azuma M, Naruke A, Kim M, Koizumi W. Long-term outcomes of endoscopic submucosal dissection for early gastric cancer: a retrospective comparison with conventional endoscopic resection in a single center. Gastric Cancer2014; 17:130-136.
40. Choi KS, Jung HY, Choi KD, Lee GH, Song HJ, Kim DH, Lee JH, Kim MY, Kim BS, Oh ST, Yook JH, Jang SJ, Yun SC, Kim SO, Kim JH.EMR versus gastrectomy for intramucosal gastric cancer: comparison of long-term outcomes. Gastrointest Endosc 2011; 73: 942-948
41. Etoh T, Katai H, Fukagawa T, Sano T, Oda I, Gotoda T, Yoshimura K, Sasako M. Treatment of early gastric cancer in the elderly patient: results of EMR and gastrectomy at a national referral center in Japan. Gastrointest Endosc 2005; 62: 868-871.
42. Nakamoto S, Sakai Y, Kasanuki J, Kondo F, Ooka Y, Kato K, Arai M, Suzuki T, Matsumura T, Bekku D, Ito K, Tanaka T, Yokosuka O. Indicationsfortheuse of endoscopicmucosalre sectionforearlygastriccancer in Japan: a comparativestudywithendoscopicsubmucosaldi ssection. Endoscopy 2009; 41: 746-750.
43. Fukunaga S, Machida H, Tominaga K, Tanaka H, Muguruma K, Ohira M, Nagami Y, Sugimori S, Okazaki H, Tanigawa T, Yamagami H, Watanabe K, Watanabe T, Fujiwara Y, Hirakawa K, Arakawa T. Short-and long-term prognosis of patients with early gastric cancer: comparative analysis between endoscopic submucosal dissection and surgical operation Gastrointest Endosc 2012;75:AB234–AB235.
44. Chiu PW, Teoh AY, To KF, Wong SK, Liu SY, Lam CC, Yung MY, Chan FK, Lau JY, Ng EK. Endoscopic submucosal dissection (ESD) compared with gastrectomy for treatment of early gastric neoplasia: a retrospective cohort study. SurgEndosc 2012; 26: 3584-3591.
45. Zhou P, Peng G, Yang S, Dongfeng C, Yanqing L, Haoxiang Z, Dianchun F, LiqingY. Effectiveness of endoscopic submucosal dissection vs gastrectomy for early gastric cancer and precancerous lesions. J Third Military Med Univ 2014;36:1507–1511.
46. Chung MW, Jeong O, Park YK, Lee KH, Lee JH, Lee WS, Joo YE, Choi SK, Cho SB. Comparison on the longterm outcome between endoscopic submucosal dissection and surgical treatment for undifferentiated early gastric cancer. Korean J Gastroenterol2014;63:90–98.
47. Kim DY, Hong SJ, Cho GS, Jeong GA, Kim HK, Han JP, Lee YN, Ko BM, Lee MS. Long-term efficacy of endoscopic submucosal dissection compared with surgery for early gastric cancer: a retrospective cohort study. Gut Liver 2014; 8:519–525.
48. 48 Sim EH, Kim BW, Kim JH, Kim JJ. Long-term outcome of endoscopic submucosal dissection for early gastric cancer compared to surgical resection. J Clin Oncol 2014;32:Suppl 1.
49. Kim BG, Kim BW, Kim JS, Park SM, Lim KJ, Kim JI, Park JM, Oh JH. Comparison of long-term outcome between endoscopic submucosal dissection and surgical resection for early gastric cancer. J Clin Oncol 2015;33:Suppl 1
50. Kang HY, Kim SG, Kim JS, Jung HC, Song IS. Clinical outcomes of endoscopic submucosal dissection for undifferentiated early gastric cancer. Surg Endosc 2010; 24: 509-516
51. Okada K, Fujisaki J, Yoshida T, Ishikawa H, Suganuma T, Kasuga A, Omae M, Kubota M, Ishiyama A, Hirasawa T, Chino A, Inamori M, Yamamoto Y, Yamamoto N, Tsuchida T, Tamegai Y, Nakajima A, Hoshino E, Igarashi M.Long-term outcomes of endoscopic submucosal dissection for undifferentiated-type early gastric cancer. Endoscopy 2012;44: 122-127.
52. Suzuki H, Oda I, Abe S, Sekiguchi M, Nonaka S, Yoshinaga S, Saito Y, Fukagawa T, Katai H. Clinical outcomes of early gastric cancer patients after noncurative endoscopic submucosal dissection in a large consecutive patient series. Gastric Cancer 2016 [Epub ahead of print] [DOI: DOI 10.1007/s10120-016-0651-z]
53. Park CH, Lee H, Kim DW, Chung H, Park JC, Shin SK, Hyung WJ, Lee SK, Lee YC, Noh SH. Clinical safety of endoscopic submucosal dissection compared with surgery in elderly patients with early gastric cancer: a propensity-matched analysis. Gastrointest Endosc 2014;80: 599-609.
54. Abe N, Gotoda T, Hirasawa T, Hoteya S, Ishido K, Ida Y, Imaeda H, Ishii E, Kokawa A, Kusano C, Maehata T, Ono S, Takeuchi H, Sugiyama M, Takahashi S.Multicenter study of the long-term outcomes of endoscopic submucosal dissection for early gastric cancer in patients 80 years of age or older. Gastric Cancer2012; 15:70-75.
55. Kato M, Nishida T, Hamasaki T, Kawai N, Yoshio T, Egawa S, Yamamoto K, Ogiyama H, Komori M, Nakahara M, Yabuta T, Nishihara A, Hayashi Y, Yamada T, Takehara T.Outcomes of ESD for patients with early gastric cancer and comorbid liver cirrhosis: a propensity scoreanalysis. SurgEndosc 2015; 29: 1560-1566.
56. Yoshioka T, Nishida T, Tsujii M, Kato M, Hayashi Y, Komori M, Yoshihara H, Nakamura T, Egawa S, Yoshio T, Yamada T, Yabuta T, Yamamoto K, Kinoshita K, Kawai N, Ogiyama H, Nishihara A, Michida T, Iijima H, Shintani A, Takehara T.Renal dysfunction is an independent risk factor for bleeding after gastric ESD.EndoscInt Open 2015;3: 39-45.
57. Najmeh S, Cools-Lartigue J, Mueller C, Ferri LE. Comparing Laparoscopic to Endoscopic Resections for Early Gastric Cancer in a High Volume North American Center. J Gastrointest Surg 2016;20:1547-1553.
58. Kim YI, Kim YW, Choi IJ, Kim CG, Lee JY, Cho SJ, Eom BW, Yoon HM, Ryu KW, Kook MC. Long-term survival after endoscopic resection versus surgery in early gastric cancers. Endoscopy 2015;47: 293-301.
59. Choi IJ, Lee JH, Kim YI, Kim CG, Cho SJ, Lee JY, Ryu KW, Nam BH, Kook MC, Kim YW. Long-term outcome comparison of endoscopic resection and surgery in early gastric cancer meeting the absolute indication for endoscopic resection. Gastrointest Endosc 2015; 81:333-341.
60. Yamashina T, Uedo N, Dainaka K, Aoi K, Matsuura N, Ito T, Fujii M, Kanesaka T, Yamamoto S, Akasaka T, Hanaoka N, Takeuchi Y, Higashino K, Ishihara R, Kishi K, Fujiwara Y, Iishi H.Long-term survival after endoscopic resection for early gastric cancer in the remnant stomach: comparison with radical surgery. Ann Gastroenterol2015;28:66-71.
61. Wang S, Zhang Z, Liu M, Li S, Jiang C. Endoscopic Resection Compared with Gastrectomy to Treat Early Gastric Cancer: A Systematic Review and Meta-Analysis. PLoS One 2015;10:e0144774.
62. Takizawa K, Takashima A, Kimura A, Mizusawa J, Hasuike N, Ono H, Terashima M, Muto M, Boku N, Sasako M, Fukuda H; Gastrointestinal Endoscopy Study Group (GIESG) of Japan Clinical Oncology Group (JCOG); Stomach Cancer Study Group (SCSG) of Japan Clinical Oncology Group (JCOG).A phase II clinical trial of endoscopic submucosal dissection for early gastric cancer of undifferentiated type: Japan Clinical Oncology Group study JCOG1009/1010.Jpn J Clin Oncol 2013;43:87-91.