



Endoscopic treatment of early gastric neoplasia

Gabriela Guirelli Lombardi¹, Maria Clara Monzani Gonçalves da Silva¹, Jarbas Faraco Maldonado Loureiro¹

¹Universidade Santo Amaro, São Paulo - SP, Brasil.

ABSTRACT

OBJECTIVE

Early gastric cancer (EGC) is defined as gastric carcinoma, which invades up to the submucosal layer, with or without lymph node metastasis, regardless of the size of the lesion. The 5-year survival rate for tumors restricted to the mucosa is between 92 and 99%, and when they reach the submucosa, it varies from 85 to 93%. The objective is to gather information about EGC and possible endoscopic therapeutic approaches.

METHODS

In this review, articles were selected through the PubMed and Google Scholar databases, between the years 2017 and 2021, in English and Portuguese.

CONCLUSIONS

Although the gold standard treatment for EGC is gastrectomy with lymphadenectomy, endoscopic resection has become the approach of choice as it presents results comparable to conventional surgery, in reducing morbidity and mortality, with low complication rates and low cost, as well as preserving the quality of life of the patient. There are two possible techniques: endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). When comparing the two techniques, EMR is not indicated for resecting lesions larger than 2 cm, as it increases the risk of local recurrence. In turn, ESD has higher rates of en bloc resection of larger lesions, however, it is associated with higher perforation rates and a longer procedure time. Follow-up is defined based on the classification of the lesion according to the endoscopic curability index (eCure) A, B, or C. Endoscopic treatment for EGC has replaced conventional surgery as it is a minimally invasive method and has several advantages.

DESCRIPTORS

Gastric Neoplasms, Endoscopic Mucosal Resection, Endoscopic Submucosal Resection, Endoscopy.

Corresponding author:

Jarbas Faraco Maldonado Loureiro.

Docente do curso de Medicina da Universidade Santo Amaro, São Paulo - SP, Brasil. Rua Barata Ribeiro, 237, conjunto 66 - Bela Vista, São Paulo, SP, Brasil.

Email: contatodrjarbasfaraco@gmail.com

ORCID ID: <https://orcid.org/0000-0002-8147-1431>

Copyright: This is an open-access article distributed under the terms of the Creative Commons

Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided that the original author and source are credited.

DOI: <https://doi.org/10.56242/globalhealth;2022;2;6;51-55>

INTRODUCTION

Gastric cancer (GC) represents the fifth most common neoplasm in the world. In Brazil, it is the third most frequent type among men and the fifth among women. According to data from the National Cancer Institute (INCA), it is estimated that in 2020, 21,230 new cases of GC were diagnosed, with 13,360 among men and 7,870 among women¹.

The incidence of stomach cancer has reduced in the last 50 years due to the increase in the consumption of fresh fruits and vegetables, decrease in salt intake, eradication of *Helicobacter pylori*, and intensification of screening in several countries, such as Japan. Despite this, the mortality rate remains high. In 2018, GC regained second place in cancer deaths worldwide, surpassing liver cancer and second only to lung cancer².

Early gastric cancer (EGC) is defined as gastric carcinoma, which invades up to the submucosal layer, with or without lymph node metastasis, regardless of the size of the lesion. Survival is closely related to the depth of tumor invasion and lymph node metastasis. In general, the prognosis of early gastric cancer has been shown to be higher when compared to advanced gastric cancer. The 5-year survival rate for tumors restricted to the mucosa is between 92 and 99%, when restricted to the submucosa, 85 to 93%, and those that reach the subserosa range from 15 to 20%³.

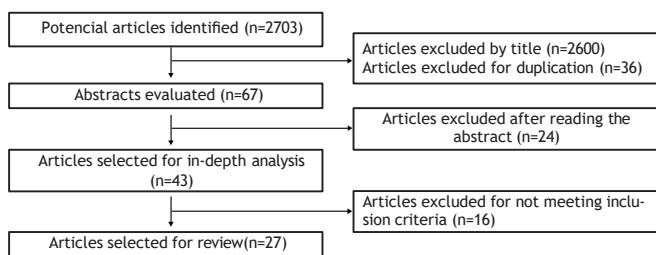
The gold standard treatment is performed by gastrectomy surgery. However, this approach has been replaced by endoscopic resection (ER), as it is a minimally invasive method, with low complication rates, and reduced cost, among other advantages that will be discussed later⁴. The aim is to characterize EGC and possible endoscopic therapeutic approaches.

METHODS

The study consists of a literature review. The search for scientific articles was carried out in the PubMed and Google Scholar databases, in English and Portuguese, with publication dates between the years 2017 and 2021. The descriptors used for the search were: “early gastric cancer”, “endoscopic resection”, “endoscopic submucosal dissection”, “endoscopic mucosal resection”, “câncer gástrico precoce”, “neoplasia precoce de estômago”, and “ressecação endoscópica”.

A total of 27 articles were selected, considering that the inclusion criteria were articles written in English or Portuguese, published between 2017 and 2021, which addressed information about early gastric cancer and endoscopic treatment for this type of neoplasm; including its indications, characteristics of the techniques used, advantages when compared to conventional surgery, follow-up after the procedure and possible complications of the method in question. Duplicate articles, those written in another language, published after the stipulated date, and/or that addressed therapeutic endoscopy applied to another type of tumor were excluded.

Figure 1. Flowchart of the article selection process after applying the inclusion and exclusion criteria.



DISCUSSION

Gastric tumors found during endoscopic inspection are classified according to macroscopic appearance, using the Japanese Gastric Cancer Association (JGCA) classification scheme. Early gastric cancer belongs to class zero, which is subdivided into other subtypes: protruding (0-I), elevated superficial (0-IIa), flat superficial (0-IIb), depressed superficial (0-IIc), and excavated. (0-III)⁵.

In addition to the macroscopic classification, there is also the Lauren histological classification, in which gastric cancer is divided into: (i) intestinal cancer, comprising papillary adenocarcinoma (well or moderately differentiated) and mucinous adenocarcinoma without signet ring cells; (ii) diffuse, which includes signet ring cell adenocarcinoma and undifferentiated adenocarcinoma; and (iii) mixed, defined by characteristics of both intestinal and diffuse types⁶.

Superficial gastric lesions can also be classified according to tumor invasion. In the first group, the tumor is confined to the mucosa (M); in the second, the tumor extends to the submucosa, but does not exceed 500µm (SM1); and in the third, there is invasion of more than 500µm of the submucosa (SM2)⁵.

Once EGC is diagnosed, TNM staging is performed. Imaging tests, preferably computed tomography of the chest and tomography or magnetic resonance imaging of the abdomen and pelvis with contrast, should be requested. The size of the neoplasm can vary from pT1, when the tumor invades the lamina propria, mucosal or submucosal muscle; pT1a for tumors that invade the mucosal lamina propria or muscularis; and pT1b when there is submucosal invasion. Lymph node involvement ranges from the classification N0 in which there is no lymph node metastasis to N3b when there is metastasis in more than 15 regional lymph nodes. The presence or absence of distant metastases is defined by M1 and M0, respectively⁷.

As lymph node metastasis (LNM) is the most important prognostic factor in GC, gastrectomy with lymphadenectomy is the gold standard approach for the treatment of this type of tumor, including for patients with EGC⁸. However, endoscopic resection has become the approach of choice for these cases because it is minimally invasive, shows results comparable to surgical resection, reduces morbidity and mortality, has low complication rates and low cost, and preserves the patient's quality of life^{3,8}.

Since endoscopic resection is a method of local approach, indications should be limited to lesions with a low probability of LNM, assessed using the predicted depth of the tumor, histological type, presence of ulceration (UL), and size of the lesion. The lesions are classified into three categories⁹:

1. Absolute indication: are lesions at risk of <1% of LNM and long-term outcomes similar to those with surgical gastrectomy¹⁰.

- For EMR/ESD techniques, the indication encompasses differentiated intramucosal adenocarcinoma, with depth of invasion clinically diagnosed as pT1a, diameter less than or equal to 2 cm, and no ulceration findings (ULO)¹¹.
- For ESD exclusively, there are two possible situations: (i) differentiated-type adenocarcinomas without ulcerative findings (UL0), in which the depth of invasion is classified as pT1a and the diameter is greater than 2 cm; and (ii) differentiated-type adenocarcinomas with ulcerative findings (UL1), in which the depth of invasion is diagnosed as pT1a and the diameter is less than or equal to 3 cm¹¹.

2. Expanded indication: are lesions that are presumed to have a <1% risk of LNM, but which still lack sufficient evidence for a long-term outcome after endoscopic resection.¹⁰ Covers undifferentiated adenocarcinomas without ulcerative findings (ULO) in which the depth of invasion is diagnosed as pT1a and

the lesion diameter is less than or equal to 2 cm¹¹.

3. Relative indication: covers tumors that do not fit the absolute or expanded indications and should undergo surgical resection. However, these are older patients or patients with severe comorbidities, at high operative risk. Thus, they can undergo endoscopic resection, provided that the patient's consent is obtained after explaining the risk of residual injury, usually in the form of lymph node metastasis¹¹.

The optimal endoscopic treatment method should be selected after analyzing the patient's condition, lesion characteristics, and the experience of the endoscopist¹⁰. There are two main techniques that can be used: endoscopic mucosal resection (EMR) or mucosectomy and endoscopic submucosal dissection (ESD)¹².

By means of the EMR technique, initially, an injection of ten percent glycerin or hyaluronic acid solution is performed in the submucosal layer, to induce its elevation and maintain the "bubble" effect for a prolonged period. After injection of sufficient volume into the submucosa, the target lesion is elevated and can be grasped by the diathermic loop and resected with a safety margin and without excessive thermal damage to muscle tissues^{13,14}.

In ESD, after a thorough inspection of the lesion, the resection limits are marked using cautery, with minimum margins of 5mm. Then, a liquid injection with colloid is performed in the submucosa, usually starting at the proximal margin in antrum lesions and at the distal margin in lesions in the proximal body or cardia, and satisfactory elevation of the lesion should be observed⁴.

A partial or total circumferential incision is performed, with partial being preferable, since the presence of residual mucosa prevents fluid leakage. Throughout the procedure, repeated injections are given into the submucosa to maintain good elevation of the edges. Subsequently, the resection of the deep submucosal layer is performed, in the anal-oral or oral-anal direction, according to the location of the lesion, always preventing or containing the possible hemorrhages that may arise. The en bloc dissection of the submucosal layer is completed using the flap previously created in the mucosa to expose the submucosal space^{3,13}.

EMR was first described in 1984 and has been widely accepted as an effective and minimally invasive treatment for EGC. However, lesions larger than 2 cm in diameter cannot be completely resected at once, prompting a high risk of local recurrence. In 1999, the ESD technique was published for the first time, and it can be performed on larger lesions and using en bloc resection^{15,16}.

When comparing the two techniques in a meta-analysis study, ESD was associated with higher rates of: en bloc resection, complete resection, and curative resection, as well as a reduced risk of local recurrence. On the other hand, it is correlated with higher perforation rates and a longer procedure time. It is also noted that there was no significant difference in post-treatment bleeding in the two approaches¹⁷.

When compared to conventional surgery, endoscopic resection was presented as a method with a lower hospital cost, lower mortality rates during the procedure, less surgical trauma, and faster recovery¹⁸. Nevertheless, the overall and disease-specific survival rates are comparable to surgical resection¹⁹.

Despite presenting low rates, the main complications of EMR are: acute bleeding and late symptomatic bleeding, that can occur from 24 hours to 8 weeks after the procedure, and perforation²⁰. There are other less frequent adverse events, such as transient bacteremia, aspiration pneumonia, pre-pyloric stenosis, and deep vein thrombosis²¹.

The JGCA guidelines for evaluating the curability of endoscopic resection are based on two factors: complete removal

of the primary tumor and the possibility of lymph node metastasis. Thus, resection can be classified into endoscopic curability A (eCureA), B (eCureB), and C (eCureC) according to the conditions foreseen in each group¹¹:

1. eCureA - resection is classified as eCureA when the lesion has no ulcerative findings (UL0) and all conditions are met: en bloc resection, dominant differentiated histological type, pT1a, negative horizontal margin (HM0), negative vertical margin (VM0) and no lymphovascular infiltration (Ly0, V0). However, if the undifferentiated component of the lesion exceeds 2 cm in diameter, the resection is classified as eCureC-2¹¹.

When the cancer has ulcerative findings (UL1), the resection is classified as eCureA when all of the following conditions are met: en bloc resection, tumor size ≤ 3 cm, dominant differentiated histological type, pT1a, HM0, VM0, Ly0, V0¹¹.

2. eCureB - resection is classified as eCureB for dominant undifferentiated histological type when all conditions are met: UL0, en bloc resection, pT1a, HM0, VM0, Ly0, V0, tumor size ≤ 2 cm¹¹.

Resection is also classified as eCureB in cases of pT1b tumors when all of the following conditions are met: en bloc resection, dominant differentiated histological type, pT1b1 (SM1), HM0, VM0, Ly0, V0, tumor size ≤ 3 cm. However, if the undifferentiated component is positive in the submucosal invasion portion, endoscopic curability is classified as eCureC-2¹¹.

3. eCureC - resection can be defined as C-1 (eCureC-1) when it has a differentiated dominant histological type and meets the criteria to be eCureA or eCureB but was not resected en bloc or had a positive horizontal margin (HM1), or as C-2 (eCureC-2), contemplating all other eCureC resections¹¹.

Any sample that does not meet the criteria for curative resection proposed by the JGCA is categorized as a non-curative resection. In this case, gastrectomy with lymphadenectomy is indicated. Nevertheless, as LNM occurs in only 5-10% of patients undergoing radical surgery, the recommendation for all patients who fall into this situation may be considered overestimated and excessive^{22,23}.

Some risk factors may be associated with the recurrence of EGC and LNM after ESD: incomplete resection, tumor size (greater than 3 cm), positive vertical margin, lymphovascular invasion, tumor location in the upper third of the stomach, male sex, older adults over 60 years of age, other previous tumors, undifferentiated dominant histological type, submucosal invasion, and infection by *Helicobacter Pylori*^{24,25,26}.

Follow-up should be planned after assessment of curability based on histopathological examination of dissected samples. For cases of eCureA, follow-up with annual or biannual endoscopy is recommended. For patients classified as eCureB, in addition to the biannual or annual follow-up with endoscopy, ultrasound, or abdominal tomography should be performed for surveillance of metastases. For both classifications, investigation and eradication of *Helicobacter Pylori* is recommended¹¹.

For patients classified in eCureC-1, the options indicated are: repeat ESD, perform surgical resection, wait for the initial effects of the ESD performed and endoscopic coagulation using laser or argon plasma coagulator. As for the eCureC-2 classification, gastrectomy with lymphadenectomy should be considered as the standard treatment¹¹.

Before indicating an invasive procedure to a patient, factors such as: previous comorbidities, adverse events associated with general anesthesia and surgery, quality of life after total/partial gastrectomy, benefits of surgery in terms of clinical follow-up, patient willingness, and prognostic factors related to low overall survival (such as smoking, history of previous

cancer, and presence of lymphovascular invasion (LVI))²⁷.

CONCLUSION

Endoscopic treatment for EGC, using both techniques, has replaced conventional surgery as it is a minimally invasive method; has low cost; presents lower rates of complications; preserves the patient's quality of life; has a quick recovery; minor surgical trauma; virtually zero mortality during the procedure; and has general and disease-specific survival rates comparable to gastrectomy.

REFERENCES

- Instituto Nacional de Câncer (INCA). Câncer de estômago [Internet]. 2021. [Acesso em 12 jul. 2021]. Disponível em: <https://www.inca.gov.br/tipos-de-cancer/cancer-de-estomago>.
- Barchi LC, Ramos MFKP, Dias AR, Andreollo NA, Weston AC, Lourenço LG, et al. II CONSENSO BRASILEIRO DE CÂNCER GÁSTRICO REALIZADO PELA ASSOCIAÇÃO BRASILEIRA DE CÂNCER GÁSTRICO [internet]. 2020. [Acesso em: 12 jul. 2021]. Disponível em: <https://www.scielo.br/j/abcd/a/z5jzkVsqPY4YnGfByzBMk6P/?lang=pt&format=html#>.
- Santos CEOdos, Lopes CV, Lima JCP, Alves AV, Leão ABHS. Manual de Endoscopia Digestiva - Diagnóstico e Tratamento [Internet]. Rio de Janeiro: Revinter; 2017. 25, Câncer Gástrico Precoce; [Acesso em: 12 jul. 2021]; Disponível em: https://books.google.com.br/books?hl=pt-BR&lr=&id=heJDDwAAQBAJ&oi=fnd&pg=PT364&dq=manual+de+endoscopia+digestiva-SOBED+RS&ots=JcHS-a5lNr&sig=m-WLUam_Hx7LhCZguwWpUn383dM#v=onepage&q&f=false.
- Santos CEOdos, Lopes CV, Lima JCP, Alves AV, Leão ABHS. Manual de Endoscopia Digestiva - Diagnóstico e Tratamento [Internet]. Rio de Janeiro: Revinter; 2017. 27, Ressecção Endoscópica das Neoplasias Precoce de Estômago; [Acesso em: 12 jul. 2021]; Disponível em: https://books.google.com.br/books?hl=pt-BR&lr=&id=heJDDwAAQBAJ&oi=fnd&pg=PT364&dq=manual+de+endoscopia+digestiva-SOBED+RS&ots=JcHS-a5lNr&sig=m-WLUam_Hx7LhCZguwWpUn383dM#v=onepage&q&f=false.
- Embaye KS, Zhang C, Ghebrehiwet MA, Wang Z, Zhang F, Liu L, et al. Clinico-pathologic determinants of non-e-curative outcome following en-bloc endoscopic submucosal dissection in patients with early gastric neoplasia [internet]. 2021. [Acesso em: 12 jul. 2021]. Disponível em: <https://bmccancer.biomedcentral.com/articles/10.1186/s12885-020-07762-9#cites>.
- Machlowska J, Baj J, Sitarz M, Maciejewski R, Sitarz R. Gastric Cancer: Epidemiology, Risk Factors, Classification, Genomic Characteristics and Treatment Strategies [internet]. 2020. [Acesso em: 12 jul. 2021]. Disponível em: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7312039/#B10-ijms-21-04012>.
- Teixeira MCA, Araujo TP, Picanço Junior OM, Pinheiro RN, Santos M. CÂNCER DE ESTÔMAGO [Internet]. 2018 [Acesso em: 12 jul. 2021]. Disponível em: https://diretrizesoncológicas.com.br/wp-content/uploads/2018/10/Diretrizes-oncológicas-2_Parte11.pdf.
- Hatta W, Gotoda T, Koike T, Masamune A. History and future perspectives in Japanese guidelines for endoscopic resection of early gastric cancer [internet]. 2019. [Acesso em: 12 jul. 2021]. Disponível em: <https://onlinelibrary.wiley.com/doi/full/10.1111/den.13531>.
- Takizawa K, Ono H, Muto M. Current indications of endoscopic submucosal dissection for early gastric cancer in Japan [internet]. 2019. [Acesso em: 12 jul. 2021]. Disponível em: <https://academic.oup.com/jjco/article/49/9/797/5536104>.
- Ono H, Yao K, Fujishiro M, Oda I, Uedo N, Nimura S, et al. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer (second edition) [internet]. 2020. [Acesso em: 12 jul. 2021]. Disponível em: <https://onlinelibrary.wiley.com/doi/10.1111/den.13883>.
- Association JGC. Japanese gastric cancer treatment guidelines 2018 (5th edition) [internet]. 2020. [Acesso em: 12 jul. 2021]. Disponível em: https://sobedgo.org.br/wp-content/uploads/2021/04/Japanese_Gastric_Cancer_Treatment_Guidelines_5_edition.pdf.
- Choe WH, Kim JH, Park JH, Kim HU, Cho DH, Lee SP, et al. Endoscopic Submucosal Dissection of Early Gastric Cancer in Patients with Liver Cirrhosis [internet]. 2017. [Acesso em: 12 jul. 2021]. Disponível em: <https://link.springer.com/article/10.1007/s10620-017-4814-5>.
- Nishizawa T, Yahagi N. Endoscopic mucosal resection and endoscopic submucosal dissection technique and new directions [internet]. 2017. [Acesso em: 12 jul. 2021]. Disponível em: https://journals.lww.com/co-gastroenterology/Abstract/2017/09000/Endoscopic_mucosal_resection_and_endoscopic.2.aspx.
- Landin MD, Guerrón AD. Endoscopic Mucosal Resection and Endoscopic Submucosal Dissection [internet]. 2020. [Acesso em: 12 jul. 2021]. Disponível em: <https://pubmed.ncbi.nlm.nih.gov/33128880/>.
- Zhao Y, Wang C. Long-Term Clinical Efficacy and Perioperative Safety of Endoscopic Submucosal Dissection versus Endoscopic Mucosal Resection for Early Gastric Cancer: An Updated Meta-Analysis [internet]. 2018. [Acesso em: 12 jul. 2021]. Disponível em: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5820679/>.
- Dumoulin FL, Hildenbrand R. Endoscopic resection techniques for colorectal neoplasia: Current developments [internet]. 2019. [Acesso em: 12 jul. 2021]. Disponível em: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6343101/>.
- Tao M, Zhou X, Hu M, Pan J. Endoscopic submucosal dissection versus endoscopic mucosal resection for patients with early gastric cancer: a meta-analysis [internet]. 2019. [Acesso em: 12 jul. 2021]. Disponível em: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7008428/>.
- Liu Q, Ding L, Qiu X, Meng F. Updated evaluation of endoscopic submucosal dissection versus surgery for early gastric cancer: A systematic review and meta-analysis [internet]. 2020. [Acesso em: 12 jul. 2021]. Disponível em: <https://www.sciencedirect.com/science/article/abs/pii/S1743919119303504?via%3Dihub>.
- Tan Y, Lu J, Lv L, Le M, Liu D. Current status of endoscopic submucosal tunnel dissection for treatment of superficial gastrointestinal neoplastic lesions [internet]. 2020. [Acesso em: 12 jul. 2021]. Disponível em: <https://www.tandfonline.com/doi/abs/10.1080/17474124.2020.1766967?journalCode=ierh20>.
- Manta R, Galloro G, Pugliese F, Angeletti S, Caruso A, Zito FP, et al. Endoscopic Submucosal Dissection of Gastric Neoplastic Lesions: An Italian, Multicenter Study [internet]. 2020. [Acesso em: 12 jul. 2021]. Disponível em: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7141243/>.
- Ahmed Y, Othman M. EMR/ESD: Techniques, Complications, and Evidence [Internet]. 2020 [Acesso em: 12 jul. 2021]. Disponível em: <https://pubmed.ncbi.nlm.nih.gov/32542462/>.
- Kinoshita T. Minimally invasive approaches for early gastric cancer in East Asia: current status and future perspective [internet]. 2020. [Acesso em: 12 jul. 2021]. Dis-

- ponível em: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7063522/>.
23. Hatta W, Gotoda T, Oyama T, Kawata N, Takahashi A, Yoshifuku Y, et al. A Scoring System to Stratify Curability after Endoscopic Submucosal Dissection for Early Gastric Cancer: “eCura system” [internet]. 2017. [Acesso em: 12 jul. 2021]. Disponível em: https://journals.lww.com/ajg/Abstract/2017/06000/A_Scoring_System_to_Stratify_Curability_after.17.aspx.
 24. Zhang QW, Zhang XT, Gao YJ, Ge ZZ. Endoscopic management of patients with early gastric cancer before and after endoscopic resection: A review [internet]. 2019. [Acesso em: 12 jul. 2021]. Disponível em: <https://onlinelibrary.wiley.com/doi/abs/10.1111/1751-2980.12715>.
 25. Barreiro P, Bispo M. Abordagem Clínica Após Dissecção Endoscópica da Submucosa no Cancro Gástrico Precoce: Manter Seguimento pelo Gastrenterologista Poderá Ser a Melhor Opção [internet]. 2017. [Acesso em: 12 jul. 2021]. Disponível em: http://www.scielo.mec.pt/scielo.php?script=sci_arttext&pid=S2341-45452017000100003&lang=pt.
 26. Hatta W, Gotoda T, Kanno T, Yuan Y, Koike T, Moayyedi P, et al. Prevalence and risk factors for lymph node metastasis after noncurative endoscopic resection for early gastric cancer: a systematic review and meta-analysis [Internet]. 2020 [Acesso em: 12 jul. 2021]. Disponível em: <https://pubmed.ncbi.nlm.nih.gov/32277297/>.
 27. Chang JW, Jung DH, Park JC, Shin SK, Lee SK, Lee YC. Long-Term Outcomes and Prognostic Factors of Endoscopic Submucosal Dissection for Early Gastric Cancer in Patients Aged ≥ 75 Years [internet]. 2020. [Acesso em: 12 jul. 2021]. Disponível em: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7692251/>.