

Non-Curative Resection in Patients with Early Gastric Cancer Treated with Endoscopic Resection

Short title: Non-curative resection of endoscopic treatment in EGC

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ABSTRACT

EGC, also known as early gastric cancer is known to be restricted to the mucosa or submucosa of the stomach, regardless of the presence or absence of lymph node metastasis, which can be treated through an endoscopic resection procedure that includes endoscopic submucosal dissection and endoscopic mucosal resection. However, some cases underwent residual disease, recurrence, or additional gastrectomy because of non-curative resection. Therefore, we aimed to systematically review the available literature to present the research progress of non-curative resection of endoscopic treatments in early gastric cancer.

Keywords: Early gastric cancer, Non-curative resection, Endoscopy, Literature review

INTRODUCTION

Gastric cancer is one of the leading types of cancer in the world. According to the 2020 International Agency for Research on Cancer statistics, ^[1] it is the fifth most common cancer and the fourth leading cause of cancer death worldwide. and the number of new cases and deaths of gastric cancer in China is about 480,000 and 370,000 per year respectively.

Endoscopic treatment has now become the main therapeutic method for early gastric cancer (EGC) due to its minimally invasive and good prognosis. However, compared with curative resection, endoscopic non-curative resection (NCR) has a greater risk of residual cancer, recurrence, and lymph node metastasis (LNM), which is an important factor leading to poor prognosis of endoscopic treatment of EGC. Combined with the

recent results of domestic and international studies, we aim to present a review of the research progress of NCR in patients with EGC treated with endoscopic resection.

Definitions

According to the first edition of Japanese guidelines for endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR) for EGC, ^[2] when a lesion meets none of absolute or expanded indications for curative resection, it is considered non-curative resection (NCR), and the incidence of it is approximately 11.9%-18.5%. In 2021, the second edition of Japanese guidelines for ESD and EMR for EGC ^[3] have changed the traditional distinction between the concept of the curative endoscopic resection and NCR to endoscopic curability (eCura), with endoscopic curability A (eCuraA) and endoscopic curability B (eCuraB) being curative resections and endoscopic curability C (eCuraC) being NCR.

In accordance with the latest guidelines, eCuraA includes the following conditions: (1) predominantly differentiated type, pT1a, UL0, HM0, VM0, Ly0, V0, regardless of size; (2) long diameter ≤ 2 cm, predominantly undifferentiated type, pT1a, UL0, HM0, VM0, Ly0, V0; or (3) long diameter ≤ 3 cm, predominantly differentiated type, pT1a, UL1, HM0, VM0, Ly0, V0; and simultaneously, the lesion is resected en bloc. eCuraB is defined as en bloc resection, ≤ 3 cm in long diameter, predominantly of the differentiated type, pT1b1(SM1) ($< 500\mu\text{m}$ from the muscularis mucosae), HM0, VM0, Ly0, and V0.

When a lesion meets none of the above-mentioned eCuraA and eCuraB conditions, it is considered eCuraC, which including eCuraC-1 and eCuraC-2. When eCuraC lesions are differentiated type and fulfill other criteria to be classified into either eCuraA or eCuraB, but was either not resected en bloc or had positive HM, they are

considered eCuraC-1. All other eCuraC lesions are considered eCuraC-2. eCuraC corresponds to the concept of NCR described in the first edition of Japanese guidelines for ESD and EMR for EGC.

RISK FACTORS FOR NON-CURATIVE RESECTION

Accurate Preoperative Diagnosis

Endoscopic examination and biopsy is necessary to assess whether the lesion meets the indications for endoscopic resection. The indications assessed by preoperative endoscopic examination are related to the experience of the gastrointestinal endoscopist, it was shown that preoperative misdiagnosis is the most common factor to NCR for undifferentiated EGC.^[4] Usually, endoscopic resection indication is judged by postoperative pathological findings, nonetheless, the preoperative pathological diagnosis of endoscopic therapy is also quite important. Bang *et al* ^[5] noted that the difference between preoperative and postoperative pathology of ESD can be used to estimate the risk of LNM. Therefore both preoperative and postoperative pathology should be evaluated in detail.

Characteristics of the Lesion

Not all lesions are suitable for endoscopic treatment. As EGCs are mostly treated with endoscopic resection, more and more studies are concerned about the prognosis of endoscopic therapy. Previous studies have shown that older age, undifferentiated type, carcinoma of the upper gastric body, tumor diameter ≥ 2 cm, and presence of ulcers are independent risk factors for NCR ^[6]. Risk factors in other studies include flat type or depressed lesions ^[7], mixed tumor types ^[8] and female ^[9].

Accurate Pathological Diagnosis

Study by Huang ^[10] found that the main reason for complete resection (en bloc resection and negative margins) but not curative resection is mainly due to changes in the types of pathological differentiation of the resected lesions or escalation of the depth of infiltration, indicating that preoperative biopsy has certain limitations. Liang *et al* ^[11] showed that the diagnostic coincidence rate of preoperative biopsy pathology and postoperative pathological diagnosis of ESD was 67.50%. Therefore, the resected specimens need to be processed in a standardized manner and evaluated carefully, determining lesion size, macroscopic type, histological type, resection margin, depth of invasion, presence/absence of ulceration, presence/absence of vascular invasion, so as to evaluate the degree of endoscopic radical treatment.

Change of Indications for Endoscopic Treatment

In the past, the indications for EGC endoscopic treatment were limited to non-ulcer and differentiated mucosal carcinoma with a diameter of ≤ 2 cm ^[12]; with the development of gastrointestinal endoscopy techniques and increasing number of well-designed clinical studies, deeper infiltration, ulcerated and undifferentiated EGC have also become the indications for endoscopic treatments ^[13].

PROGNOSTIC RISK FACTORS OF NON-CURATIVE RESECTION AND FOLLOW-UP TREATMENT

Non-curative resection mainly includes two aspects: (1) Incomplete resection,

including non-en bloc resection and/or positive margins; (2) There are risk factors for LNM, such as deep submucosal infiltration of cancer cells (SM2), poor pathological differentiation ^[14], and vascular invasion ^[15].

Incomplete resection

Studies have found that the diameter of tumor ≥ 20 mm, submucosal fibrosis, and submucosal infiltration of cancer cells are independent risk factors for piecemeal resection ^[16]. The fourth edition of the 2014 Japanese gastric cancer treatment guidelines ^[13] pointed out that the risk of LNM for differentiated cancers that are not en bloc resection but meet other curative resection criteria is low, the patient could be closely followed up without immediate additional treatment.

Positive Horizontal Margins

A meta-analysis ^[17] of nine studies including 1720 patients with NCR treated with additional radical surgery found that positive horizontal margins were not a risk factor for LNM. Kim *et al* ^[18] followed up 55 NCR patients with positive horizontal margins for a median time of 23 months (6-87 months), and found that 20 of them (36.4%) had local recurrence, pointing out that the diameter of positive horizontal margin > 6 mm is an independent risk factor for local recurrence of the lesion. The 4th edition of the 2014 Japanese guidelines for the treatment of gastric cancer ^[13] stated that piecemeal resection or resection en bloc with positive horizontal margins had a low risk of LNM, open surgical resection is not the only option.

Positive Vertical Margins

Several studies have shown that positive vertical margins are a risk factor for the development of LNM in patients with NCR, and most vertical margin-positive EGC lesions have infiltrated deeper than SM1^[16, 17]. Open or laparoscopic surgical resection is indicated.

Deep Submucosal Infiltration

The rate of LNM was found to be only 1-3% for mucosal infiltration, whereas it increased to 11-20% for submucosal carcinoma. A meta-analysis of nine relevant studies involving 1720 EGC patients who underwent additional surgery following the NCR by Zhao *et al* ^[17] found that SM2 (submucosal infiltration depth $\geq 500\mu\text{m}$) was a risk factor for LNM. And the Guidelines state that further surgical treatment of deep submucosal infiltration is recommended ^[2].

Poor Pathological Differentiation

Pathologically poorly differentiated gastric cancers include poorly differentiated adenocarcinoma and signet ring cell carcinoma. Lee *et al* ^[19] found that the rate of LNM was significantly higher in patients whose resected lesions contained hypodifferentiated or undifferentiated component than in patients with differentiated carcinoma (51% vs 0.5%, $P < 0.001$), and the presence of hypodifferentiated or undifferentiated component was a risk factor for LNM, which could rise to 10% when coexisting with other risk factors such as lesion diameter >2 cm and combined ulceration.

Vascular Invasion

A Meta-analysis of 1720 patients with NCR from nine studies ^[17] showed that lymphatic invasion ($P < 0.001$, OR = 11.06) and venous invasion ($P < 0.001$, OR = 2.79) were risk factors for LNM. Another study of 200 patients with NCR undergoing additional surgical radical surgery by Sunagawa *et al* ^[20] proposed an index to predict the risk of LNM based on venous invasion, which is "venous invasion + ≥ 1 factor of NCR", and the data showed that the sensitivity of the index was 100%, the specificity was 63.8%, and the negative predictive value was 100%, but the positive predictive value was 18.3%, showing that both lymphatic invasion and venous invasion are independent risk factors for LNM. Therefore, the additional surgery with lymphadenectomy should be strongly recommended when a patient who underwent NCR had two or more risk factors associated with LNM.

eCura Risk Scoring System

Hatta *et al* ^[21] proposed the eCura scoring system to assess the risk of LNM in patients with NCR through combining LNM risk factors. The scoring system included five factors: lymphovascular invasion (3 points), tumor diameter >3 cm (1 point), positive vertical margins (1 point), venous invasion (1 point), and submucosal infiltration depth ≥ 500 μm (1 point). The system was divided into low risk group (0-1 point, 2.5% risk of LNM), medium risk group (2-4 points, 6.7% risk of LNM), and high risk group (5-7 points, 22.7% risk of LNM).

And they demonstrated the validity of the eCura risk scoring system in a subsequent study^[22] of 1969 NCR patients, showing that the recurrence rate of patients with

additional radical surgery in the high-risk group was significantly lower ($P = 0.024$), whereas the recurrence rate in patients with additional radical surgery in the mediate-risk and low-risk groups were not significantly different from those in the follow-up patients, suggesting that patients in the high-risk group of the eCura score system should be treated aggressively with additional radical surgery.

Long-Term Follow-up Post-treatment

A risk of metachronous gastric cancer exists after endoscopic resection. According to the 5th edition of the Japanese gastric cancer guidelines ^[23], patients with eCuraA resection should be followed up with annual or biannual endoscopy; though patients with eCuraB resection should be followed up with annual or biannual endoscopy and abdominal ultrasonography or computed tomography (CT) for the surveillance of metastases.

For those with eCuraC-1, when the lesion is differentiated type of ≤ 3 cm and either UL1 or pT1b1 (SM1), size of the residual mucosal lesion should be reassessed by endoscopy. When the sum of the length of the resected and residual lesions exceeds 3 cm, gastrectomy with lymphadenectomy should be considered as the standard of care. In addition, patients with positive horizontal margin within the portion of submucosal invasion and those who underwent piecemeal resection in which the resection line involved the portion of submucosal invasion should be recommended to undergo gastrectomy with lymphadenectomy, since the histological diagnosis under these circumstances is destined to be uncertain. Gastrectomy with lymphadenectomy should be considered as the standard of care for eCuraC-2. When surgery cannot be recommended because of old age or severe comorbidities, the risk of residual disease in the form of LNM and possibility of the subsequent local recurrence and/or distant

metastasis should be assessed and explained sufficiently to the patients, along with the information that the recurrent disease is usually incurable with dismal prognosis. For both eCuraA, eCuraB and eCuraC resection, it has been recommended that *Helicobacter pylori* be examined and, if positive, be eradicated ^[3].

PROGNOSIS OF ENDOSCOPIC NON-CURATIVE RESECTION OF EARLY GASTRIC CANCER

It was shown that disease-specific survival was significantly lower in NCR patients who did not receive further treatment after ESD than in curatively resected patients ^[6], and similarly, disease-specific survival was significantly lower in all NCR patients including those who did or did not receive further treatment after ESD than in curatively resected patients ^[24].

In addition, more studies have shown that patients with NCR who underwent additional radical surgery had higher survival rates than patients who only followed up. Eom *et al* ^[25] found that the mortality and recurrence rates were not significantly different in NCR patients with additional radical surgery and those with traditional radical surgery, while mortality and recurrence rates were significantly higher in NCR patients without additional radical surgery than in those with traditional radical surgery. This suggests that patients with NCR who underwent additional radical surgery had the similar effect as those who underwent radical surgery as their treatment.

SUMMARY

Endoscopic resection has become the standard treatment for EGC that meets the

indications due to the advantages of equivalent curative rate compared with surgery, minimally invasive, less complications and higher quality of postoperative survival. It can be seen that the absolute indications for endoscopic treatment of EGC are expanding with the maturation of endoscopic treatment techniques.

Patients with NCR have a higher risk of LNM compared to those with curative resection, and it is important to assess the risk of LNM in patients with NCR. Many studies have proposed a predictive score for LNM risk based on risk factors, which is useful to guide further treatment of patients with NCR. The proposed endoscopic radical degree eCura provides a more detailed grading of the degree of endoscopic cure, which is more beneficial to guide further treatment of NCR patients.

NCR patients have a higher rate of tumor recurrence and a lower survival rate than patients with curative resection, additional surgical radical surgery can significantly improve their survival rate, however, not all patients with NCR are suitable for additional radical surgery, the risk of LNM and surgery should be taken into consideration before deciding whether to perform additional radical surgery. It is believed that the incidence of NCR will decrease with the development of endoscopic treatment.

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