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EDITORIAL

Challenges and advancing strategies of endoscopic submucosal dissection for early gastric cancer: The puzzle of eCura C1

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Abstract

In this editorial, we explore the challenges of managing noncurative resections in early gastric cancer after endoscopic submucosal dissection (ESD), starting from the consideration recently made by Zhu *et al*. Specifically, we evaluate the management of eCura C1 lesions, where decisions regarding further interventions are pivotal yet contentious. Collaboration among endoscopists, surgeons, and pathologists is underscored to refine risk assessment and personalize therapeutic management. Recent advancements in ESD techniques and interdisciplinary collaboration offer opportunities for outcome optimization in managing eCura C1

lesions. Moreover, despite needing further clinical validation, molecular biomarkers have emerged as promising tools for enhancing prognostication. This manuscript highlights the ongoing research attempts to define treatment paradigms effectively and evaluates the potential of emerging options, ultimately aiming to improve patient care and outcomes in this complex clinical scenario.

Key Words: Early gastric cancer; Endoscopic submucosal dissection; eCura; Non-curative resection; Multidisciplinary approach

Core Tip: This editorial details the management of early gastric cancer after endoscopic submucosal dissection (ESD), focusing on noncurative resections, especially eCura C1. Collaborative and personalized approaches are advisable in order to position patient treatment correctly. Recent advancements in ESD techniques offer promise for optimizing outcomes, but further validation is still needed. Future research to define effective treatment strategies and enhance patient prognostication through molecular biomarkers is expected to refine treatment protocols and advance strategies for managing eCura C1 lesions in ESD procedures.

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INTRODUCTION

Early gastric cancer (EGC) is defined as gastric cancer limited to the submucosal layer, irrespective of lymph node involvement (T1, NX)[1]. In Eastern countries such as Japan and South Korea, EGC accounts for 50% of cases, given the availability of intense screening programs[2,3], which dramatically impact early diagnosis and treatment. The need for a minimally invasive but curative treatment of this kind of lesion, carrying a low risk of lymph node metastases (LNM)[4], has led to the development and improvement of endoscopic submucosal dissection (ESD). This technique has progressively integrated and, in some cases, substituted gastrectomy with lymph node dissection as EGC treatment[5] due to the similar long-term outcomes and lower procedure time and risks[6,7]. ESD is a challenging technique which requires both high technical skills and diagnostic accuracy for case selection[8]. It has quickly disseminated in Asian countries, given the high incidence of EGC[9].

Conversely, in Western countries, the growth of ESD has occurred more recently, involving a lengthy process of acquiring technical skills and improving outcomes to reach those of Eastern countries[10]. Interestingly, in this issue of the World Journal of Gastroenterology, the authors join the debate regarding the management of noncurative ESD. Together with technical skills, proficiency in the endoscopic evaluation of the lesions is crucial for achieving positive ESD outcomes. Up to 20% of ESD turns out to be noncurative after pathological evaluation[11]. Hence, estimating the depth of submucosal invasion and the risk of LNM is essential for the successful implementation of ESD. To address this specific goal, in 2017, the eCura score was developed and validated in a Japanese cohort[12,13] to stratify lesions as low, intermediate, and high-risk. Given the high reliability of this model, the eCura system has also been adopted in the Japan Gastroenterological Endoscopy Society (JGES) guidelines for ESD in EGC[4] considering the following clinicopathological findings: Histopathological type, pT staging, lesion size, presence of an ulcer, horizontal and vertical margins, and lymph vascular invasion. Based on these features, ESD can be classified as curative (eCura A and B) or noncurative (eCura C). This evaluation guides the physician in tailoring appropriate post-endoscopic resection management and follow-up for each patient. Subsequently, Morais *et al*[14] validated and modified it in Europe as a Western eCura system[14,15]. Despite the widespread adoption of the eCura system, a notable grey area remains in eCura C resections, as highlighted by Zhu *et al*[16]. The authors conclude that research should focus on this topic to address this significant issue. Building on these considerations, in this editorial, we aim to expand the discussion on aspects of eCura C resection and propose a treatment strategy for this specific setting, such as eCura C1.

INSIGHTS ON NONCURATIVE RESECTIONS: DOES EAST MEET WEST

According to the JGES guidelines[4], noncurative resections (NCR) are classified as eCura C. The latter is further classified as eCura C1 when the resection encounters eCura A/B criteria (differentiated lesions of all sizes, ≤ 3 cm with ulcers, ≤ 3 cm with ≤ 500 μm depth invasion; undifferentiated lesions ≤ 2 cm without ulcers), but positive horizontal margins (HM) are present or piecemeal resection is performed. Conversely, the lesion is considered eCura C2 when

positive vertical margins (VM), > 500 μm submucosal invasion (sm²) or lymph vascular invasion are detected. The subsequent treatment of eCura C2 lesions is established and commonly regarded as open or laparoscopic resection due to the high risk of LNM[17,18]. It is indeed suggested by literature data that in the presence of risk factors such as lymph vascular invasion or deep submucosal invasion, the risk of LNM ranges between 10.5 and 22.7%[19,20]. The latter data result in a significant improvement in overall survival for patients who undergo surgery after NCR[21]. Regarding the subsequent treatment of eCura C1 lesions, few data are available in the literature, and guidelines do not provide a clear therapeutic pathway: JGES guidelines consider surgery, diathermy, repeated ESD or close follow-up as a valid option upon a case-by-case evaluation. However, in the case of a predominantly differentiated type, pT1a with ulcers, or a predominantly differentiated type with a long diameter ≤ 3 cm, SM1, if the combined size of the remnant lesion plus the resected specimen is greater than 3 cm, additional surgery is advised. In contrast, the European Society of Gastrointestinal Endoscopy guidelines[22,23] do not incorporate the eCura system. Instead, they classify resections as curative, local-risk, or noncurative. Local risk resections, akin to eCura C1, are curative for all parameters except for HM and piecemeal resection, with the main distinction from eCura C1 being that cancer remains confined to the mucosal layer. Consequently, the suggested treatment consists of complete staging and close endoscopic follow-up to treat the possible local recurrence.

CURRENT CHALLENGES ON eCURA C1

In a low-risk LNM scenario, like eCura C1, unveiling the correct post-ESD management is crucial. The possible indication for surgery carries a high risk of complications and reduced quality of life[24]. Hence, identifying cases where it can be avoided is a focal point to address this specific issue. Moreover, the choice of a partial (either proximal or distal) or total gastrectomy carries different rates of complications: Proximal and total gastrectomy are, indeed, associated with a postoperative complication rate of 21%[24,25], while distal gastrectomy carries a rate of 15.5%[25]. The literature still lacks a comprehensive comparison between surgery and other treatments/observations in eCura C1 settings. However, few studies are available despite being affected by a retrospective design and a small sample size. Kim *et al*[26] retrospectively analyzed 76 NCRs that underwent further treatment, finding a comparable outcome in patients treated with re-ESD or additional surgery. On the other hand, most studies focus on the scenario of NCR globally without acknowledging the presence of different features[21,27] or excluding eCura C1, which is considered a possible bias source[28]. Consequently, the indication for post-NCR surgery is mainly based on the patient's frailty and survival expectancy. According to a study conducted by Hatta *et al*[29], which investigated the prognostic factors in 143 NCRs for EGC in ≥ 85-year-old patients, the overall 5-year survival in patients who underwent gastrectomy and patients who did not was 63.1% and 65.2%, respectively. The prognostic factors associated with poor survival were the high-risk eCura category, Charlson comorbidity index ≥ 3, and male sex. Even though eCura C1 resections were excluded from the analysis, applying the same concept for positive HM or piecemeal resections may be reasonable.

As highlighted by Zhu *et al*[16], endoscopic follow-up is a choice, but it should be reserved for cases where HM positivity is not extensive. According to the data from a study conducted by Yoon *et al*[30], the total length of HM involvement was the sole risk factor for tumor recurrence. In this regard, we report data from a retrospective study conducted by Ryu *et al*[31]: Among the 49 histologically incomplete resections (not explicitly referring to HMs), 11 (22.5%) had endoscopic recurrence at follow-up. Five underwent surgery, one showing LNM, while three underwent ESD and one argon-plasma coagulation without showing further recurrence; two patients were lost to follow-up. Moreover, Madhu *et al*[32] have recently presented a case series showing the effectiveness of nine re-ESD as salvage therapy after positive HMs gastric ESD. Consistently, current data show a trend towards reasonably performing close follow-up with re-ESD in case of recurrence when HMs are not extensively involved. Future research, based on prospective studies, should focus on the specific outcomes of eCura C1 resection, considering factors that could affect the survival rate, such as age and comorbidities, to validate the effectiveness of close follow-up with re-ESD of recurrence site in eCura C1 resections and clearly define treatment strategies, which, nowadays, show low-grade of accordance between endoscopists[33].

Moreover, new diagnostic technologies, like magnification and virtual chromoendoscopy, and more advanced resection techniques, like submucosal tunnelling endoscopic resection, or full-thickness endoscopic resection, offer unprecedented precision and efficacy in lesion eradication. Nevertheless, their utilization must be judiciously tailored to each case's unique anatomical and pathological features, sharing the therapeutic path with the other involved specialists.

FUTURE PERSPECTIVES

Collaboration between specialists assumes paramount significance in the comprehensive evaluation and management of eCura C resections. Based on the experience from other fields[34], a node-sparing surgery has been proposed: According to the study conducted by Roh *et al*[35], an indocyanine fluorescence lymphography on the NCR site can guide a selective lymphadenectomy with high sensitivity and negative predictive value, avoiding a systemic lymphadenectomy. Hence, the collaboration between endoscopists and surgeons can provide valuable results for a less invasive approach.

Nevertheless, close cooperation with the pathologist is also desirable in this multidisciplinary team. First, a correct and adequate histopathological report should be carried out to evaluate all the possible characteristics of invasion, such as tumor site, macroscopic type, size, histological type, distribution of undifferentiated-type carcinoma, depth of invasion, presence or absence of ulceration within the lesion, presence or absence of vascular infiltration, and evaluation of HMs and VMs[4]. In this context, the type of carcinoma seems to represent an impacting factor. Despite ESD being potentially

curative for undifferentiated-type EGC[36], a close endoscopic follow-up might be appropriate even in curative resections [37]. Secondly, the emerging molecular biomarkers represent a promising avenue for refining risk stratification and guiding personalized therapeutic interventions in gastric lesion management. Kang *et al*[38] found that p44/42 ERK and p-Chk1 expression levels exhibited a significant decrease along the lateral axis of the recurrent resection margin to 5.5 mm from the lesion, with no notable changes observed in the normal zone. These findings suggest a potential association of p44/42 ERK and p-Chk1 with the recurrent side: P-Chk1 activity is, indeed, considered required for p53 inactivation in tumor cell growth[39], while p44/42 ERK is overexpressed in gastric precancerous lesions[40]. Based on these assumptions, the authors conclude that a 5.5 mm distance between the lesion and the resection would be advisable for reducing the recurrence rate, even though the literature data is quite heterogeneous on this topic[41,42]. However, the lack of a large dataset makes applying this tool in real-life settings difficult. Large studies are desirable to evaluate further and validate the use of molecular biomarkers for HM evaluation after ESD.

CONCLUSION

In summary, while managing eCuraC1 lesions presents significant challenges due to the lack of clear guidelines and optimal treatment strategies, recent advancements in ESD and other endoscopic techniques, together with molecular imaging technologies, offer promising solutions for addressing these challenges and improving patient outcomes. Continued research and innovation in these areas are essential for refining treatment protocols and advancing strategies for managing eCuraC1 lesions in ESD procedures.

FOOTNOTES

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