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Endoscopic Submucosal Dissection for Early Gastric Cancer: Current Standard Indication and Management

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Endoscopic submucosal dissection (ESD) has been established as the standard treatment for early gastric cancer, enabling en bloc resection regardless of lesion size and offering high curability with organ preservation. The indications for ESD have expanded with the accumulation of long-term data, and recent guidelines from Korea, Japan, and Western countries share similar criteria, although subtle differences regarding the undifferentiated-type histology remain. Despite its efficacy, ESD remains technically demanding, particularly for lesions with severe fibrosis or those located at difficult anatomical sites. Furthermore, as the population ages, perioperative management with antithrombotic agents has become a critical safety issue. This review provides a comprehensive overview of the current indications and clinical outcomes of ESD based on large-scale global data. It also offers practical strategies for overcoming technical difficulties and managing adverse events, with a specific focus on updated guidelines for antithrombotic agents and perforation management.

Keywords Stomach neoplasms; Endoscopic submucosal dissection; Guideline; Postoperative complications.

INTRODUCTION

The detection rate of early gastric cancer (EGC) has increased significantly owing to the widespread implementation of national endoscopy screening programs, particularly in East Asia. Therefore, the treatment paradigm for these lesions has shifted from surgical gastrectomy to endoscopic resection. Endoscopic submucosal dissection (ESD) has replaced conventional endoscopic mucosal resection (EMR) as the preferred treatment modality for early stage lesions with a negligible risk of lymph node metastasis (LNM). ESD offers the distinct advantage of achieving en bloc resection regardless of lesion size, which allows for precise histological assessment and significantly reduces the risk of local recurrence compared to EMR.[1]

However, ESD is a technically demanding procedure associated with a longer procedure time and a higher risk of adverse events such as bleeding and perforation. Moreover, endoscopists increasingly encounter elderly patients with multiple comorbidities, necessitating a careful balance between the risk of thromboembolism and procedural hemorrhage. This review discusses the latest global guidelines concerning the indications and clinical outcomes of ESD for EGC, with particular

emphasis on expanded indications, including undifferentiated-type histology and submucosal invasion. It summarizes practical strategies for overcoming technical challenges using various traction methods and details the management of complications, including delayed adverse events, with a focus on recent updates in antithrombotic guidelines. While standard indications ensure safety, the expansion to "beyond standard" criteria allows for organ preservation in a wider patient group, provided that strict risk stratification is applied.

COMPARISON OF GLOBAL GUIDELINES AND INDICATIONS

The indications for ESD have evolved from classic "absolute indications" to "expanded indications" based on accumulating evidence that the risk of LNM is negligible under specific conditions. Table 1 compares the current indications across guidelines from the Korean Gastric Cancer Association (KGCA 2024),[1] Japan Gastroenterological Endoscopy Society (JGES 2021),[2] and European Society of Gastrointestinal Endoscopy especially the Management of Precancerous Conditions and Lesions in the Stomach (MAPS III 2025).[3]

STANDARD INDICATIONS

All three guidelines agree that differentiated intramucosal cancer without ulceration is an absolute or recommended indication for ESD, regardless of tumor size. Similarly, differentiated intramucosal cancer with ulceration is considered an absolute indication if the tumor size is ≤3 cm. The Korean guidelines specifically use the term "standard indications" for well or moderately differentiated tubular or papillary EGCs measuring ≤2 cm without ulceration and confined to the mucosa.[1]

EXPANDED INDICATIONS (BEYOND STANDARD)

Because the definition of "standard indication" differs among regional guidelines, the term "beyond standard indication" in this review refers to lesions that are outside the Korean standard indication, but are still considered appropriate for ESD under the expanded or conditional criteria in the Japanese and European guidelines. These lesions correspond to what has traditionally been termed "expanded indications" in the Japanese and Western literature. These expanded criteria have been validated through large-scale prospective studies, particularly the Japanese JCOG0607 trial, which demonstrated that selected lesions meeting expanded criteria have excellent long-term outcomes comparable to surgery.[1,2]

For differentiated-type EGC, the Korean and Japanese guidelines classify the following expanded indications: 1) differentiated intramucosal cancer >2 cm without ulceration (any size in Japanese guidelines); 2) differentiated intramucosal cancer ≤3 cm with ulceration.

However, an important distinction exists for larger ulcerated lesions: the Japanese guidelines classify differentiated intramucosal cancer >3 cm with ulceration as a "relative indication" rather than an expanded indication, reflecting the need for more cautious patient selection in these cases.[2] The European MAPS III guidelines recommend ESD for differentiated dysplastic or intramucosal lesions of any size if not ulcerated, and ≤30 mm if ulcerated.[3]

UNDIFFERENTIATED-TYPE HISTOLOGY: A CRITICAL CONSIDERATION

Undifferentiated-type EGC, including poorly differentiated adenocarcinoma and signet ring cell carcinoma, represents a

Table 1. Comparison of indications for endoscopic submucosal dissection across international guidelines

Tumor characteristics	Korea (KGCA 2024)	Japan (JGES 2021)	Europe (MAPS III 2025)
Differentiated-type, mucosal			
No ulcer, ≤2 cm	Standard indication	Absolute indication	Recommended
No ulcer, >2 cm	Meets curative resection criteria	Absolute indication	Recommended
With ulcer, ≤3 cm	Meets curative resection criteria	Absolute indication	Recommended
With ulcer, >3 cm	Not recommended	Relative indication	Not recommended
Undifferentiated-type, mucosal			
No ulcer, ≤2 cm	Cautiously considered for ESD	Absolute indication	Can be considered
Submucosal invasion (SM1, ≤500 μm)			
Differentiated, ≤3 cm	Curative resection possible after pathological assessment	Relative indication	Can be considered

KGCA, Korean Gastric Cancer Association; JGES, Japan Gastroenterological Endoscopy Society; MAPS, management of epithelial precancerous conditions and lesions in the stomach; SM1, submucosal invasion ≤500 μm from muscularis mucosae.

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particularly challenging subset of endoscopic management because of the historically higher rates of LNM. However, recent evidence from the Japanese JCOG1009/1010 trials has demonstrated that highly selected undifferentiated-type lesions (≤2 cm, intramucosal, without ulceration) can be safely treated with ESD.[4]

Guideline differences on undifferentiated histology

Based on the JCOG trial evidence, the Japanese guidelines now classify undifferentiated intramucosal cancer ≤2 cm without ulceration as an absolute indication.[2] In contrast, the Korean guidelines remain more cautious, stating that "ESD could be cautiously considered for poorly differentiated tubular or poorly cohesive (including signet-ring cell) EGCs after sufficient discussion when all criteria are met."[1] The European MAPS III guidelines state that such lesions should be considered for ESD and require a multidisciplinary discussion.[3]

Clinical outcomes in undifferentiated-type EGC

While the JCOG trials demonstrated technical feasibility and favorable 5-year overall survival for selected undifferentiated cases, retrospective surgical cohorts have revealed measurable LNM rates, even in lesions meeting the expanded criteria. Studies report LNM rates ranging from 1.1% to 4.1% in undifferentiated EGCs meeting expanded indications.[5,6] Signet ring cell carcinoma, in particular, demonstrates unpredictable biological behavior, and specific outcome data (en bloc and curative resection rates) for pure signet ring cell histology remain limited.

Therefore, for undifferentiated-type lesions, post-resection risk stratification using the eCura or eCuraU scoring systems is essential to guide decisions regarding additional surgical treatment (discussed further in the post-resection surveillance section).

SUBMUCOSAL INVASION: THE SM1 CATEGORY

The Korean guideline states that after pathological review, differentiated-type cancer with minute submucosal invasion (≤500 μm) measuring ≤3 cm may be considered for curative resection if en bloc R0 resection is achieved with no lymphovascular invasion and negative vertical margin.[1] The Japanese guidelines classify this as an expanded indication,[2] whereas MAPS III states that it "can be considered" for differentiated lesions ≤30 mm.[3]

This difference reflects the need for rigorous pathological evaluation to ensure curative resection, particularly in undifferentiated cases. Additionally, while the Japanese guidelines explicitly include local recurrence after EMR/ESD or ESD as an indication, the Korean guidelines generally treat it as a relative indication because of the technical difficulties associated with severe fibrosis.

TECHNICAL STRATEGIES FOR DIFFICULT LESIONS

Successful ESD requires overcoming technical challenges, primarily severe fibrosis and difficult anatomical locations such as the cardia or pylorus. In cases of ulcer scars, the submucosal layer is often thin and fibrotic, making dissection hazardous. The use of high-viscosity injection solutions such as sodium hyaluronate is essential in these scenarios to maintain adequate submucosal elevation.

Table 2. Comparison of traction methods for endoscopic submucosal dissection

Method	Technique	Advantages	Disadvantages	Best indication
Clip-with-line	Clip attached to lesion edge with thread pulled externally	Widely available Effective elevation Reduces procedure time Lower perforation risk	Requires assistant Limited maneuverability Thread interference	Large lesions Difficult locations Severe fibrosis
Double-clip traction	Two clips connected by thread/rubber band	No external traction Stable counter-traction Better visualization	Technically demanding Precise placement needed Limited adjustability	Sustained traction needed Solo operator
Pocket-creation	Creating submucosal pocket, dissecting from inside	Excellent visualization Reduced perforation risk Useful for fibrosis	Steep learning curve Limited applicability Longer initial time	Severe fibrosis Post-ESD recurrence Ulcer scars
S-O clip	Specialized clip with thread	Designed for ESD Stable traction Easier than conventional	Specialized equipment Higher cost Limited availability	Similar to clip-with-line

ESD, endoscopic submucosal dissection.

TRACTION METHODS: A COMPREHENSIVE APPROACH

Gravity often hinders visualization of the dissection plane and increases the risk of perforation. To address this problem, various traction techniques have been developed. Table 2 summarizes the available traction methods and their advantages, disadvantages, and optimal indications.

The clip-with-line method

The most widely studied technique involves attaching a clip with dental floss to the edge of a lesion and pulling it externally. This method is strongly recommended in the current guidelines[7] and has been shown to significantly reduce procedure time and risk of perforation by effectively elevating the lesion and exposing the submucosal layer.

Double-clip traction

This technique uses two clips connected by a thread or rubber band to create internal traction without external assistance. It provides stable countertraction and better visualization, but is technically more demanding.

Pocket-creation method

This new approach involves creating a submucosal pocket and dissecting it from the inside, offering excellent visualization of the submucosal layer. It is particularly useful for severely fibrotic lesions or post-ESD recurrence, but involves a steep learning curve.

Other methods include the Osada clip (S-O clip, Sakamoto-Osada clip), magnetic traction devices, and simple gravity-assisted positioning techniques. While comparative effectiveness data remain limited in the current literature, the choice of traction method should be individualized based on lesion characteristics (size, location, degree of fibrosis), operator experience, and equipment availability.[7,8]

CLINICAL OUTCOMES: A GLOBAL PERSPECTIVE

The safety and efficacy of ESD have been validated globally in numerous large-scale studies. Table 3 summarizes the key findings from both Eastern and Western centers.

In Korea, a prospective multicenter cohort study by Kim et al.[9] reported an en bloc resection rate of 97.4% and a 5-year overall survival rate of 96.6%, confirming the long-term safety of the procedure. In an aging society, outcomes for the elderly are of particular concern. Kim et al.[10] analyzed outcomes in elderly patients aged 75 years and older, finding that while the rate of adverse events was slightly more frequent in older patients, the curative resection rate remained high, justifying the application of ESD in this population.

Although ESD originated in East Asia, it has since been successfully adopted in Western countries. Recent studies from the USA by Yang et al.[11] demonstrated that ESD is feasible in Western practice, with high technical success rates. Studies from Germany by Probst et al.[12] demonstrated that ESD is feasible in Western practice, with en bloc rates exceeding 94%. Recent analyses have also suggested that ESD achieves overall survival comparable to surgery, with significantly fewer ad-

Table 3. Clinical outcomes of ESD for early gastric cancer: a global perspective

Study	Country	Design (n)	En bloc resection	Curative resection	Complications (perforation/bleeding)	Key finding
Kim et al.[9] (2018)	Korea	Prospective multicenter (2422)	97.4%	90.6%	0.9%/2.6%	High long-term survival (96.6% at 5 yr)
Kim et al.[10] (2023)	Korea	Cohort study (442)	98.4%	85.3%	2.7%/4.5%	ESD is safe in elderly (≥75 yr) with acceptable outcomes
Probst et al.[12] (2017)	Germany	Retrospective (107)	94.5%	83.5%	2.8%/3.7%	Expanded criteria safe in Western patients
Abdelfatah et al.[13] (2019)	International	Meta-analysis (2158)	N/A	N/A	N/A	ESD vs. surgery: similar 5-yr survival (approximately 96%), lower morbidity
Zullo et al.[14] (2021)	Western countries	Meta-analysis (1152)	96.0%	84.0%	9.5 (overall)	Western outcomes are improving compared to East
Ortigão et al.[21] (2022)	International	Meta-analysis (17582)	N/A	N/A	N/A	Metachronous lesions: approximately 9.5% at 5 yr after ER
Hatta et al.[4] (2017)	Japan	Multicenter (3842)	N/A	N/A	N/A	Developed eCura system for risk stratification

ESD, endoscopic submucosal dissection; ER, endoscopic resection; N/A, not available.

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verse events.[13,14]

MANAGEMENT OF ADVERSE EVENTS

Perforation

Perforation is a major complication of ESD, with an incidence ranging from 1.2% to 5.2%. Immediate recognition and endoscopic closure are crucial for the prevention of panperitonitis and emergency surgery. Small perforations can usually be managed with through-the-scope clips using a "zipper" technique, starting from the edges of the defect. For larger defects that are difficult to close with simple clips, the over-the-scope clip system provides full-thickness closure and has shown high success rates.[15]

Delayed perforation

Delayed perforation, which occurs >24 h after the procedure, is a recognized but less common complication. While specific incidence data in the recent literature remain limited, delayed perforation is thought to result from transmural thermal injury or delayed necrosis of the muscularis propria. The management principles include the following: 1) high index of suspicion in patients presenting with abdominal pain post-ESD; 2) urgent CT imaging to confirm diagnosis and assess extent of contamination; 3) endoscopic closure may be attempted if diagnosed early with minimal contamination; 4) surgical intervention is often required if peritonitis develops or endoscopic closure fails; and 5) prophylactic measures include meticulous hemostasis, minimization of coagulation injury to the muscle layer, and prophylactic clipping of high-risk areas.[16]

BLEEDING AND ANTITHROMBOTIC MANAGEMENT

Bleeding is the most common adverse event associated with ESD. Although intraprocedural bleeding is managed with electrocoagulation, delayed bleeding requires preventive strategies, particularly the management of antithrombotic agents.

Table 4. Antithrombotic management before gastric endoscopic submucosal dissection

Drug category	Specific agent	Withdrawal period	Heparin bridging	Key management considerations
Antiplatelet				
Aspirin	Aspirin	Generally continue may withhold 5–7 days for ultra-high-risk	NO	High CV risk: continue aspirin Low risk: individualized decision Cardiology consultation if withholding considered
P2Y12 inhibitors	Clopidogrel	Stop 5 days before	NO	On DAPT: withhold P2Y12 inhibitor, continue aspirin Do not stop both agents in coronary stent patients
	Ticagrelor	Stop 5 days before	NO	Same as clopidogrel
	Prasugrel	Stop 7 days before	NO	Longer washout due to irreversible binding
Anticoagulant				
DOACs	Apixaban	Stop 2 days before	NO	Standard for normal renal function Resume 24–48 h post-procedure if hemostasis achieved
	Rivaroxaban	Stop 2 days before	NO	Same as apixaban
	Edoxaban	Stop 2 days before (consider 3 days if renal impairment)	NO	50% renal excretion-monitor renal function
	Dabigatran (CrCl ≥50 mL/min)	Stop 2 days before	NO	80% renal elimination-monitor closely
	Dabigatran (CrCl <50 mL/min)	Stop 5 days before	NO	Extended washout required due to renal impairment
Warfarin	Warfarin	Stop 3–5 days before target INR <1.5	Case-by-case	Bridge only if: mechanical valve or very high-risk AF Most patients do not need bridging

DOAC, direct oral anticoagulant; DAPT, dual antiplatelet therapy; CV, cardiovascular; CrCl, creatinine clearance (mL/min); INR, international normalized ratio; AF, atrial fibrillation.

Table 4 outlines practical strategies based on the latest consensus from gastroenterology and cardiology societies. For patients taking aspirin, monotherapy may be continued even for high-risk procedures such as ESD, as bleeding risk must be balanced against cardiovascular risk. For ultrahigh-risk cases, withholding aspirin for 5–7 days may be considered during cardiology consultations.[17,18] In patients with coronary stents undergoing dual antiplatelet therapy, discontinuation of both agents is contraindicated because of the risk of stent thrombosis. The standard approach is to withhold the P2Y12 inhibitor (clopidogrel for 5 days, prasugrel for 7 days) perioperatively while continuing aspirin monotherapy.[17-19] A significant paradigm shift occurred with the use of direct oral anticoagulants (DOACs). Recent guidelines, including the 2022 American College of Gastroenterology–Canadian Association of Gastroenterology guidelines and the 2024 International Digestive Endoscopy Network consensus, emphasize that heparin bridging is no longer recommended for DOACs because it increases bleeding risk without providing a significant thromboembolic benefit.[17,18]

Drug-specific DOAC management before ESD (based on the Korean IDEN 2024 consensus)[18]: 1) apixaban, rivaroxaban, edoxaban: discontinue 2 days before procedure (D-2); 2) dabigatran with normal renal function (creatinine clearance ≥50 mL/min): discontinue 2 days before procedure; 3) dabigatran in patients with renal impairment (creatinine clearance <50 mL/min) is discontinued 5 days before the procedure due to 80% renal elimination; and 4) edoxaban: extended discontinuation (3 days) may be required if renal function deteriorates, as 50% of patients undergo renal excretion.

All DOACs should be withheld for at least 48 h before high-risk procedures such as ESD based on their approximate 12-hour half-life. DOACs can be resumed 24–48 hours post-procedure if adequate hemostasis is achieved.[18]

Delayed bleeding

Delayed bleeding, defined as bleeding occurring >24 h after ESD, is reported more frequently than delayed perforation, with incidence rates varying by study. Risk factors and management: 1) risk factors include large resection size (>40 mm), lesion location (upper third of the stomach), continuation of antithrombotic agents, and the presence of exposed vessels in the ulcer bed; 2) prevention: meticulous coagulation of visible vessels, prophylactic coagulation of the ulcer bed, consideration of second-look endoscopy in high-risk patients, and proton pump inhibitor therapy; and 3) management: most cases can be managed endoscopically using hemoclipping, thermocoagulation, or hemostatic powder application. Angiographic embolization is reserved for refractory cases.[16,20]

POST-RESECTION SURVEILLANCE

The management pathway after ESD is determined based on the curability of the resection. Patients who achieve curative resection should undergo annual surveillance endoscopy to detect metachronous gastric cancer, the incidence of which is approximately 9.5% at 5 years following endoscopic resection.[21] Furthermore, *Helicobacter pylori* eradication should be performed in *H. pylori*-positive patients because it significantly reduces the risk of metachronous recurrence.[1]

If resection is noncurative, the management strategy depends on the specific reason for non-cure and the risk of LNM (Fig. 1). In cases in which non-curativity is solely due to a positive horizontal margin in a differentiated lesion, the risk of LNM is minimal. Therefore, additional endoscopic treatments, such as re-ESD, argon plasma coagulation, or close observation, may be considered. Conversely, for patients with risk factors for LNM, such as deep submucosal or lymphovascular invasion, additional surgical resection is the standard for care.

THE eCura SYSTEM: RISK STRATIFICATION FOR NONCURATIVE RESECTION

However, for elderly patients or those who represent poor surgical candidates, the eCura system can be utilized to stratify patients and determine a potential observation strategy.[22] It is important to note that the eCura system is a Japanese-derived risk stratification tool and is not explicitly adopted as the standard algorithm in the KGCA guidelines (2022/2024) or European MAPS III guidelines.[1,3]

The eCura system assigns points based on: 1) tumor size >30 mm (1 point); 2) positive vertical margin (1 point); 3) submucosal invasion ≥500 μm (SM2) (1 points); and 4) lymphovascular invasion (3 points).

Risk categories: 1) low risk (eCura 0–1): LNM rate <3%, observation may be considered; 2) intermediate risk (eCura 2–4): LNM rate 5%–10%, multidisciplinary discussion required; and 3) high risk (eCura ≥5): LNM rate >15%, strong recommendation for surgery.

For undifferentiated-type EGC, the modified eCuraU system has been validated, showing LNM rates of 1.1% (low), 5.4% (intermediate), and 13.3% (high) in surgical cohorts.[4,22]

In Korean practice, the decision for additional surgery after noncurative ESD is based on a comprehensive evaluation of pathological risk factors (depth of invasion, lymphovascular invasion, and margin status) and patient factors (age, comorbidities, and patient preference) through a multidisciplinary discussion rather than strict adherence to the eCura score.[1] Eu-

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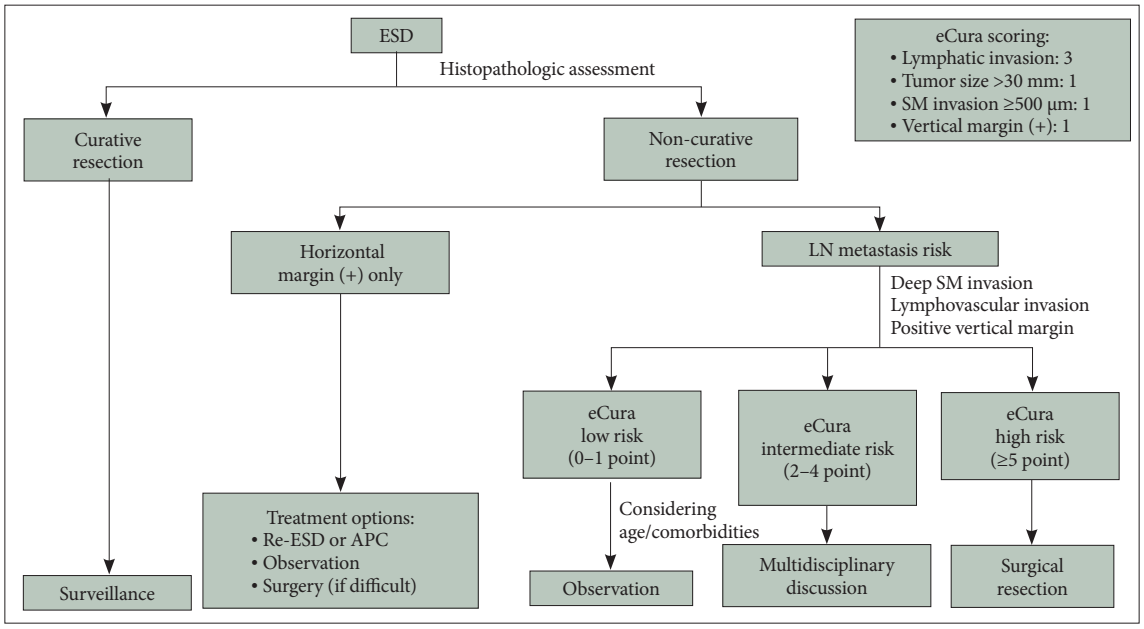

Fig. 1. Management algorithm after ESD for early gastric cancer. After curative resection, the patients underwent surveillance. For noncurative resections, management depends on the estimated risk of lymph node metastasis. Isolated horizontal margin positivity (HM+) can be managed with additional endoscopic treatment or observation. When lymph node risk factors were present, patients were stratified into low-, intermediate-, or high-risk categories using the eCura system. High-risk patients are generally considered for additional surgery, intermediate-risk patients require multidisciplinary discussion, and low-risk patients may be managed with careful observation, considering age, comorbidities, and patient preferences. ESD, endoscopic submucosal dissection; SM, submucosal; LN, lymph node; APC, argon plasma coagulation.

ropean guidelines similarly emphasize multidisciplinary team discussions for high-risk resections.[3] The eCura system serves as a useful tool for counseling patients and guiding clinical decision-making but should not be interpreted as the sole determinant of management.

CONCLUSION

Globally, ESD has been established as the standard treatment for early gastric neoplasms, achieving excellent long-term survival comparable to that of surgery. The indications for ESD have expanded beyond classical absolute criteria to include larger differentiated lesions and, with caution, selected undifferentiated-type lesions including signet ring cell carcinoma in highly selected cases (≤2 cm, mucosal, no ulceration). However, there exist significant differences among international guidelines regarding terminology and risk stratification, particularly for undifferentiated histology and minimal submucosal invasion.

While technical difficulties remain, the use of various traction methods (clip-with-line, double-clip, pocket-creation) and appropriate accessories can enhance success rates, although comparative effectiveness data remain limited, and method selection should be individualized.

Clinicians must be vigilant of adverse events, including immediate and delayed complications. Recent updates in antithrombotic management emphasize drug-specific DOAC withdrawal periods based on renal function, continuation of aspirin for most cases, and a strong recommendation against heparin bridging for DOACs.[17,18]

Finally, a comprehensive post-resection surveillance based on pathological curability is essential. For noncurative resections, risk stratification tools such as the eCura system provide valuable guidance, but management decisions should be made through multidisciplinary discussions considering patient-specific factors, particularly in elderly or high-risk surgical candidates.[1,3,4]

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