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OPINION REVIEW

Endoscopic treatment and management of rectal neuroendocrine tumors less than 10 mm in diameter

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Abstract

Rectal neuroendocrine tumors (rNETs) measuring less than 10 mm in diameter are defined as small rNETs. Due to the low risk of distant invasion and metastasis, endoscopic treatments, including modified endoscopic mucosal resection, endoscopic submucosal dissection, and other transanal surgical procedures, are effective. This review article proposes a follow-up plan according to the size and histopathology of the tumor after operation.

Key Words: Rectal neuroendocrine tumors; Endoscopic; Endoscopic submucosal dissection; Endoscopic mucosal resection

Core Tip: Rectal neuroendocrine tumors (rNETs) measuring less than 10 mm in diameter are defined as small rNETs. Due to the low risk of distant invasion and metastasis, endoscopic treatments, including modified endoscopic mucosal resection, endoscopic submucosal dissection, and other transanal surgical procedures, are effective. This review article proposes a follow-up plan according to the size and histopathology of the tumor after operation.

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INTRODUCTION

Among different types of rectal tumors, neuroendocrine tumors (NETs) are relatively rare. However, the incidence of rectal NETs (rNETs) has been on the rise in recent years, accounting for approximately 48% of gastrointestinal NETs[1]. Due to the increasing popularity of colonoscopy, 85% to 95% of rNET cases are diagnosed in the early stage of the disease[2]. rNETs usually occur locally and have a relatively low risk of distant metastasis and a relatively high five-year survival rate[3]. The World Health Organization graded the NETs according to histology features[4]. However, no consensus has been reached on the best diagnostic, treatment, and management approaches. More research is needed to determine how to fully evaluate the rNET stage, select the best surgical approaches, predict the disease prognosis, and formulate the follow-up strategies. Preoperative assessment of the tumor size, depth of invasion, and presence of distance metastasis is extremely important for the diagnosis and treatment of rNETs.

The risk factors for rNET metastasis include the tumor size, invasion of the muscularis propria, pathological classification (Ki-67 index and mitoses), vascular infiltration, and atypical endoscopic findings[5,6]. Tumor size is the most important factor for predicting the risk of rNET metastasis[7]. rNETs measuring less than 10 mm in diameter are defined as small rNETs, which are relatively indolent tumors. Because of their low risk of distant metastasis, most small rNETs are confined to the mucosa and submucosa and rarely infiltrate into the muscularis propria. In addition, small rNETs rarely have distant lymph node metastasis and can be clinically cured by endoscopic treatment[8]. rNETs are usually found in early stage, and pelvic radiotherapy is not required after localized resection of rNETs [9]. To date, common treatments for rNETs include endoscopic treatment and other transanal surgical procedures, both of which completely remove the rNET locally[10,11]. The follow-up strategies are determined according to the disease prognosis and postoperative pathological evaluation.

This review article introduces the characteristics and keys for the preoperative evaluation of rNETs; compares the characteristics of existing treatment methods for rNETs less than 10 mm in diameter; and summarizes the disease prognosis, follow-up strategies, clinical diagnoses, treatments, and management of rNETs.

PREOPERATIVE EVALUATIONS OF RNETS

Pretreatment evaluation of rNETs is very important for the selection of surgical approaches and prognosis prediction. The main content of preoperative evaluation of rNETs includes tumor staging and classification, endoscopic ultrasonography (EUS), imaging examinations such as magnetic resonance imaging (MRI), and histological examinations.

rNET staging and classification

rNETs usually secrete glucagon and enteroglucagon instead of serotonin; thus, rNETs rarely lead to neuroendocrine tumor syndrome and do not arouse early attention[12]. rNETs are usually revealed unintentionally during colonoscopy. Patients with rNETs may have certain symptoms, such as changes in bowel habits, blood in stools, tenesmus, anal pain, and weight loss[12]. The relevant guidelines of the United States and Europe argue that the staging and histological evaluation of rNET are the basic factors for predicting disease prognosis[13,14], with the consensus of dividing NETs into grades 1, 2, and 3 (G1, G2, and G3) based on mitotic figures and Ki67 index[4]. The European Neuroendocrine Tumor Society (ENETS) and the Union for International Cancer Control (IUCC)/American Joint Committee on Cancer (UICC/AJCC) have also proposed the TNM classification of rNETs[15].

Tumor stage and size are important predictors of lymph node metastasis and affect the disease prognosis. A tumor diameter of 10 mm is used as a cutoff value for the assessment of the rNET prognosis. Only 1% of rNETs smaller than 10 mm in diameter have distant metastasis, while the metastasis rate of rNETs larger than 2 cm in diameter is 60%[16]. Thus, tumor size nearly accurately predicts the prognosis of the disease and is strongly correlated with the prognosis and survival rate. Tsang *et al*[9] in a single-center study of 91 rNET cases over 13 years showed that patients with rNETs of less than 10 mm in diameter had a 2% distant metastasis rate, while a study by Soga *et al*[17] of 1271 rNET patients reported a 5.5% metastasis rate among patients with rNETs less than 10 mm in diameter.

The 2016 ENETS guidelines proposed that the size and the depth of invasion of an rNET can be used to predict lymph node metastasis. rNETs smaller than 10 mm in diameter have a 3% chance of lymph node metastasis[16]. Good histological characteristics of rNETs include a low grade (G1) and no evidence of lymphatic, vascular, and perineural or muscularis propria invasion[18,19]. The incidence of lymph node involvement in patients with rNETs smaller than 10 mm in diameter is between 1% and 10%, the incidence of lymph node involvement in patients with rNETs 1 to 2 cm in diameter is increased to 30%, and the incidence of lymph node involvement in patients with rNETs greater than 2 cm in diameter is increased to 60%[19]. The risk factors for lymph node metastasis in rNET patients include tumor size, mitotic figures, and lymphatic vascular invasion (LVI)[20]. In a previous study, a risk scoring system of lymph node metastasis, which included tumor size, LVI, and whether the depth of submucosal invasion was greater than or equal to 2000 μm, was used to score the risk of lymph node metastasis in patients with rNETs[21].

Small rNETs also have a risk of metastasis. Any suspected malignancy should be fully evaluated for infiltration depth and disease stage. The typical rNET is a small and smooth sessile tumor appearing normal or yellow in color with a submucosal bulge, which is usually approximately 5 cm from the anal verge. According to their morphology, rNETs can be divided into the following categories: Type Ia rNETs are protruding lesions with an angle between the tumor and the periphery of less than 90°; type Ib rNETs are protruding lesions with an angle between the tumor and the periphery of 90° to 150°; type II rNETs involve flat or slightly raised lesions with an angle of greater than 150°; and type III rNETs present a collapsed surface or ulcerated lesions. Type I lesions are the most common, especially subtype Ib lesions. Incomplete resection of type II and type III lesions is more likely to occur[22]. A meta-analysis showed that the endoscopic G1-stage of rNETs less than 16 mm in diameter involved no typical endoscopic characteristics (*e.g.*, central depression, ulcer, semi-ulcer, erosion, ulcer, and hyperemia) and were confined to the submucosa without lymphatic vascular infiltration, showing a high complete resection rate and good long-term prognosis in patients[23].

Tumor size, TNM stage, lymph node metastasis, and tumor classification of rNETs are significantly correlated with recurrence and survival outcomes in patients[24]. More and more pathological markers have been used as predictors of rNET prognosis. With the development of new technologies, the extensive application of gene technology and sequencing technology may provide more information and predict the prognosis of patients with rNETs[9].

EUS and imaging examinations

EUS, together with imaging examinations and colonoscopy, provides important information for the selection of rNET treatment options. EUS also judges the size and depth of the tumor. An rNET appears as a smooth, uniform, hypoechoic submucosal mass under EUS that protrudes on the third layer and is covered by the second layer but often blurred above it. The judgment of the size and depth of rNETs by experienced radiologists is usually highly consistent with the final histological evaluation. EUS can well assess rNETs by accurately evaluating the tumor size, depth of invasion, and presence of lymph node metastasis in the perirectal space[5].

EUS and MRI complement the assessment of rNETs. MRI can well identify rNET and assist in the tumor staging[25]. MRI is sensitive to the assessment of lymph nodes. However, it is relatively easy to miss T1-stage rNETs using MRI, while EUS can accurately distinguish T1- and T2-stage rNETs but can hardly evaluate T4-stage rNETs[26]. Computed tomography (CT) can assess the fat, fascia, and lymph nodes around the rectum, supplementing MRI, thereby facilitating the assessment of distant metastases of rNETs. Moreover, MRI is necessary for T2, T3, T4 and nodal-positive tumors[27], especially to assess the involvement of other pelvic structures and liver[5].

Histological examinations

The ENETS guidelines suggest that all endoscopists should conduct at least one biopsy and one EUS before the surgical resection of rNETs and should choose the resection approach for rNETs based on the pathological diagnosis, tumor stage, and tumor classification. However, in clinical practice, pathologists often accidentally discover the NETs after routine polypectomy, and the selection of resection approaches is often affected by the experience of surgeons and the conditions of surgical equipment. By combining the assessment of rNET stage and classification as well as the application of EUS, MRI, pathological examinations, and other examinations, a comprehensive evaluation of rNET before surgery is essential for the selection of surgical approaches and the prediction of disease prognosis.

TREATMENT OPTIONS FOR RNETS LESS THAN 10 MM IN DIAMETER

Decision of rNET resection approaches during the first endoscopy procedure

The only cure for rNETs less than 10 mm in diameter is to completely remove the tumor locally. A localized resection of an rNET refers to clean or complete resection of the local tumor, which is evaluated by histopathological examination when the lateral and vertical margins are negative. Selection of rNET treatment methods should be based on the comprehensive diagnostic evaluation as aforementioned, with the goal of achieving the best tumor resection, *i.e.*, with a clear edge and no residual tumor tissue. Tumor size is the simplest indicator for the prediction of rNET prognosis and is thus often used as an important reference for the selection of treatment approaches for rNETs. Minimally invasive endoscopic treatments for rNETs less than 10 mm in diameter with no vascular invasion and distant metastasis can achieve clinically curative outcomes. The relevant guidelines reported previously also recommend that endoscopic local resection of rNETs be the first choice for rNET treatment[5]. rNETs less than 10 mm in diameter carry a lower risk of metastasis, and the tumors can be completely resected locally by endoscopy or other transanal surgical procedures[10,11,28]. A study has shown that, compared to ordinary polypectomy, advanced endoscopic or surgical procedures better achieve a pathologically complete response[29]. In clinical practice, small rNETs are difficult to distinguish quickly from rectal polyps when they are first discovered. The surgeons thus often choose to adopt ordinary endoscopic rectal polyp resection methods, such as biopsy forceps. However, researchers do not recommend the use of endoscopic biopsy clamps for the removal of rNETs because the histological characteristics of these tumors that affect the complete resection rate of the tumor are not accurately revealed through this approach, increasing the risk of postoperative residual and local recurrence[15]. Some researchers have suggested that any suspicious rNETs that cannot be confirmed for the first time should be marked under endoscopy to facilitate the search for these lesions before the next treatment and should be subjected to further treatment after confirming the results of a full evaluation. In summary, if the tumor size and mucosal and submucosal changes are confusing, further and full evaluation is needed instead of simply resection methods.

Comparison between endoscopic and surgical resection of rNETs

Selection of the best surgical approaches among the endoscopic and surgical resection techniques is still under heated debate even after the full evaluation and assuming the suspicious lesion is an rNET by preoperative EUS. Transanal resection of rNETs removes the tumor within 8 cm from the anal verge and ensures a deep removal in the muscularis mucosa. However, the risk of aggressive surgery, *i.e.*, rectal anterior resection, when treating rNETs less than 10 mm in diameter is greater than the benefit. Transanal endoscopic microsurgery (TEMS) is a localized resection approach of the lesion under a laparoscopic view through the anus, with the advantage of direct and complete removal of the lesion without worrying about perforation, and the resection wound is fully and surgically sutured under direct vision[8]. A previous study has shown that TEMS achieves relatively great short-term and long-term prognoses for rNETs, and this surgical treatment when applied for small rNETs has a greater chance of retaining the anus[30]. However, TEMS needs to be performed in an operating room, thus carrying expensive fees for the operation and anesthesia. Intubation and anesthesia have a relatively large impact on patients. Most importantly, postoperative fecal incontinence may occur if the lesion is close to the anal margin[31], especially for small rNETs less than 10 mm in diameter because TEMS may cause adverse effects in patients. Therefore, the surgical indications of TEMS should be strictly controlled[30]. Endoscopic treatment does not require general anesthesia, and it can be carried out in daytime operating rooms or outpatient clinics to avoid the risks of intubation and anesthesia and can save time and medical costs, rendering it more easily acceptable by patients.

Comparison between endoscopic mucosal resection and endoscopic submucosal dissection

Some scholars have proposed that G1 rNETs revealed under endoscopy are usually less than 16 mm in diameter, without irregular endoscopic findings (*e.g.*, central depression, ulcers, and congestion), and are limited to the submucosa without LVI, suggesting a relatively high rate of complete resection and a good prognosis. Thus, endoscopic treatment is suitable for G1 rNETs and leads to better postoperative life compared to general surgery. Small rNETs less than 10 mm in diameter are limited to the submucosa and have no lymph node or distant metastasis, and, therefore, endoscopic treatment is the first choice for their treatment[32,33]. Since the development of endoscopic technology, the main surgical procedures for lesion resection are endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). Traditional EMR is technically simple, but it seems difficult to guarantee complete resection for rNETs with this approach. Therefore, various device-assisted improved EMR techniques have been derived and may be compared to ESD.

The main challenge of traditional EMR resection of rNETs is that the depth of vertical resection is not fully guaranteed, resulting in a positive vertical resection margin. Therefore, improved EMR is used to assist the device to fully attract and lift the lesion to ensure the depth of vertical resection. Cap-assisted EMR (EMR-C) (Figure 1), a transparent cap-assisted EMR approach, injects a water cushion under the tumor, *i.e.*, placing a crescent snare in the transparent cap. After fully attracting the tumor to the transparent cap, the rNET is endoscopically removed using a snare, followed by clipping the wound with a hemostatic clip. EMR-C is ideal for relatively small rNETs[34]. Considering the effectiveness of treatment, operation duration, and surgical complications, a previous study has suggested that EMR-C may be the best endoscopic treatment for rNETs available[25]. The EMR-C procedure commonly used in our endoscopy center can also achieve a good resection effect for rNETs. However, further studies are needed to confirm whether the depth of the vertical resection margin is fully guaranteed when the water cushion is not injected before the resection.

EMR using a dual-channel endoscope (EMR-D) is a simple, easy-to-learn, and effective technique, but it requires dual-instrument channel endoscopy[35], where one channel delivers the snare and the other channel delivers the forceps to lift the lesion before directly removing the lesion by the snare. The

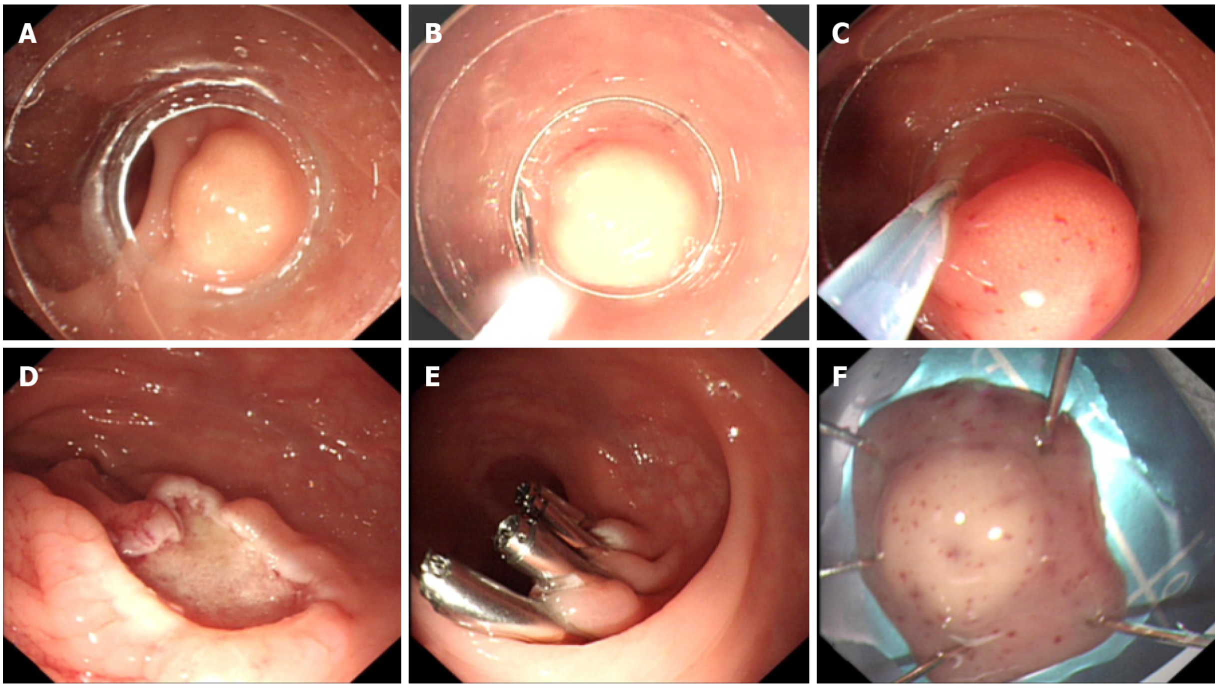

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Figure 1 Cap-assisted endoscopic mucosal resection. A: A pale yellow mass with a diameter of about 9 mm in the rectum; B: Placement of an endoscope with a transparent cap worn at its front end into a crescent snare; C: Resection of the mass with the crescent snare after negative pressure suction; D: Wound surface after the removal of the mass; E: Wound clipping with titanium clips; F: The resected mass for pathological biopsy.

vertical depth of the resection can be fully ensured by the way of lifting[36] (Figure 2). Compared to ESD, EMR-D is technically simple, minimally invasive, and safer for the removal of small rNETs[36].

EMR with a ligation device (EMR-L) (Figure 3) improves the complete resection rate of rNETs[37-39]. Similarly, an injection is performed in the submucosa of the lesion to fully attract the tumor to the transparent cap before releasing the rubber ring from the ligation device to form a pseudo-polyp, which is followed by retracting the snare under the rubber ring, then electro-coagulating and resecting the tumor. Compared to traditional EMR, EMR-L more fully ensures the vertical depth of tumor resection due to the use of a snare and ligation device[40]. Traditional EMR is likely to cause incomplete resection of the lesion and crush the wound, which affects the pathological evaluation[35]. EMR-L improves these shortcomings of traditional EMR, resects without destroying or deforming the tumor, and moves the tumor further away from the lateral and vertical incisal margins[33]. In the treatment of initial lesions, when the tumor diameter is less than 5 mm and known to be an rNET, application of EMR technology, especially with the aid of a transparent cap or a ligature, usually achieves an ideal resection outcome [31].

In addition, some scholars have proposed that underwater EMR (UEMR) (Figure 4) ensures a clean resection margin and safe removal of rNETs[32]. Here, the local intestinal tube is pumped and filled with water under endoscopy and without submucosal injection to float the tumor by the buoyancy of the water before electro-coagulating and resecting the tumor using a snare. However, some scholars have suggested that EMR electrocoagulation damages the edge of the specimen, which is not conducive to the judgment of the margin. Application of traction and magnification *via* underwater ESD may be better than UEMR[41,42].

ESD is commonly used for lesion resection, and it achieves radical treatment of local lesions, even in lesions involving the submucosa, retaining the muscle layer, *i.e.*, preserving the local anatomy and function[43]. Patients with rNETs less than 10 mm in diameter have no lymph node or distant metastases, and a G1 rNET limited to the submucosa is an absolute indication for ESD[44] (Figure 5). The biological characteristics of rNETs are derived from lower crypts by growing deep into the submucosa, showing a subepithelial tumor–like growth pattern[33]. Due to the proximity to the muscularis propria, it is difficult to dissect the submucosa and is easy to result in a positive vertical margin[45]. Linked imaging mode is used to assist in identifying bleeding points during ESD surgery, and white light is used to avoid vascular damage[46]. For rNETs that are too small in size, it is challenging to use ESD to separate the submucosa from the muscularis propria. More approaches should be used, such as submucosal tunneling endoscopic resection, to improve the ESD resection of rNETs[33]. Some scholars have proposed that small rNETs can be removed by ESD using a pocketed-creation method with a hook knife to drill into the precut submucosa pocket of a transparent cap to expand the submucosa and finally complete the tumor resection[47].

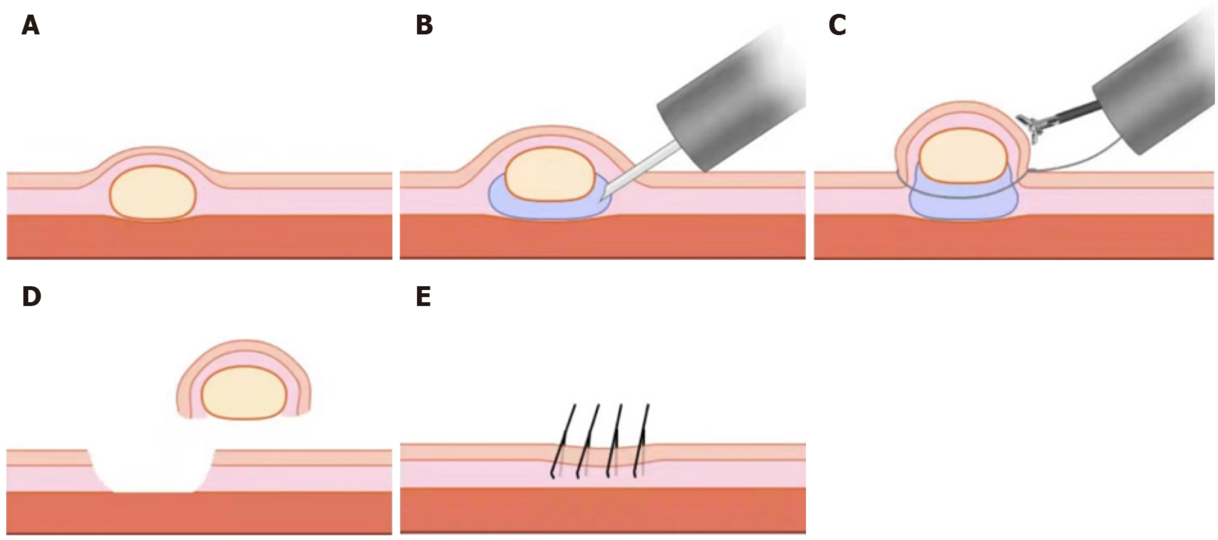

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Figure 2 Endoscopic mucosal resection using a dual-channel endoscope. A: A pale yellow mass in the rectum; B: Submucosal injection of the mass with an injection needle; C: The use of a dual-channel endoscope, with one channel inserted with forceps to lift the lesion, and the other inserted with an electrosurgical snare to resect the mass; D and E: Wound clipping with titanium clips after mass resection.

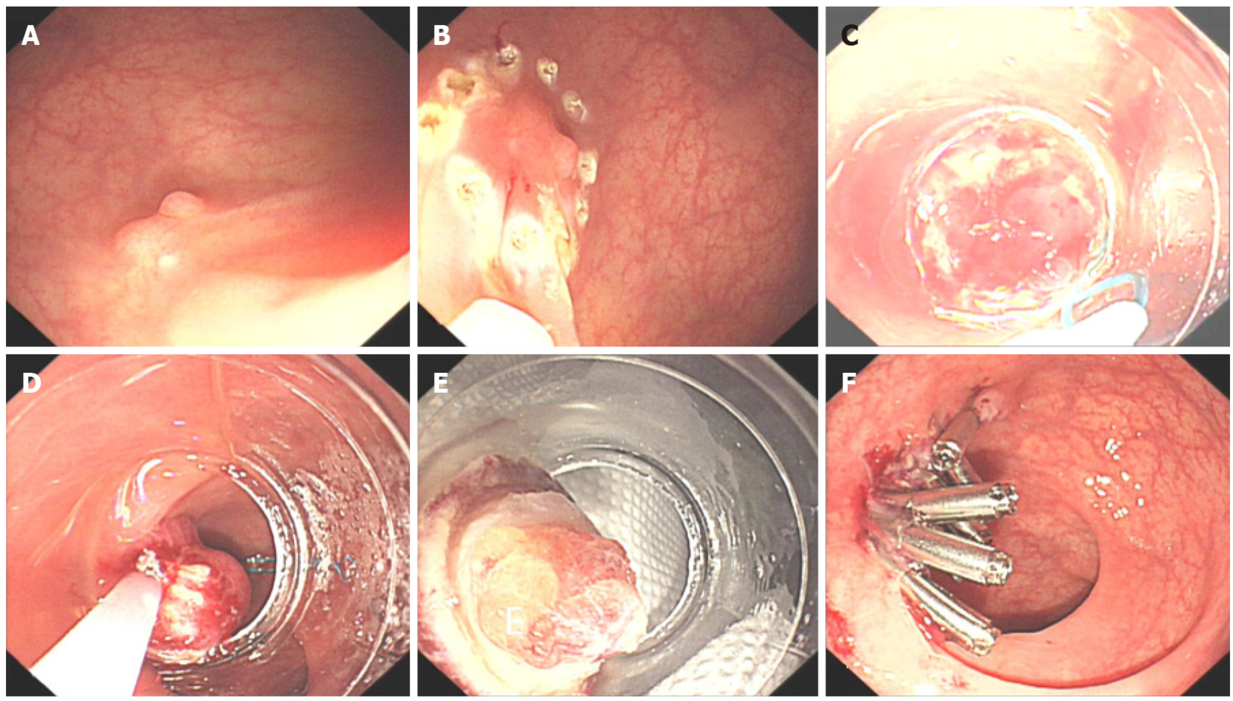

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Figure 3 Endoscopic mucosal resection with a ligation device. A: A pale yellow mass with a diameter of about 6 mm in the rectum, with visible scar after biopsy on the surface; B: Electrocoagulation marking in the peritumoral area by using the front end of the electrosurgical snare; C: Ligation of the root of the mass after negative pressure suction with a single-ring nylon ring; D: Resection of the mass at the root with an electrosurgical snare; E: Resected mass; F: Wound clipping with titanium clips after mass resection.

Many studies have shown that there is no significant difference between modified EMR and ESD in the operation duration, *en bloc* resection, complete resection rate, complications, or recurrence rate[22,48]. ESD usually lasts for a long time and requires highly experienced surgeons for the operation. A meta-analysis suggested that EMR with attraction for the treatment of rNETs less than 10 mm in diameter achieves a higher complete resection rate, shorter operation duration, and similar complete resection and recurrence rates compared to ESD[49]. Compared to EMR, the recurrence rate of rNETs after ESD is lower, while the risk of perforation in rNET patients undergoing ESD is greater, and the requirements for the ESD operator are also higher[15]. Some investigators believe that the complete

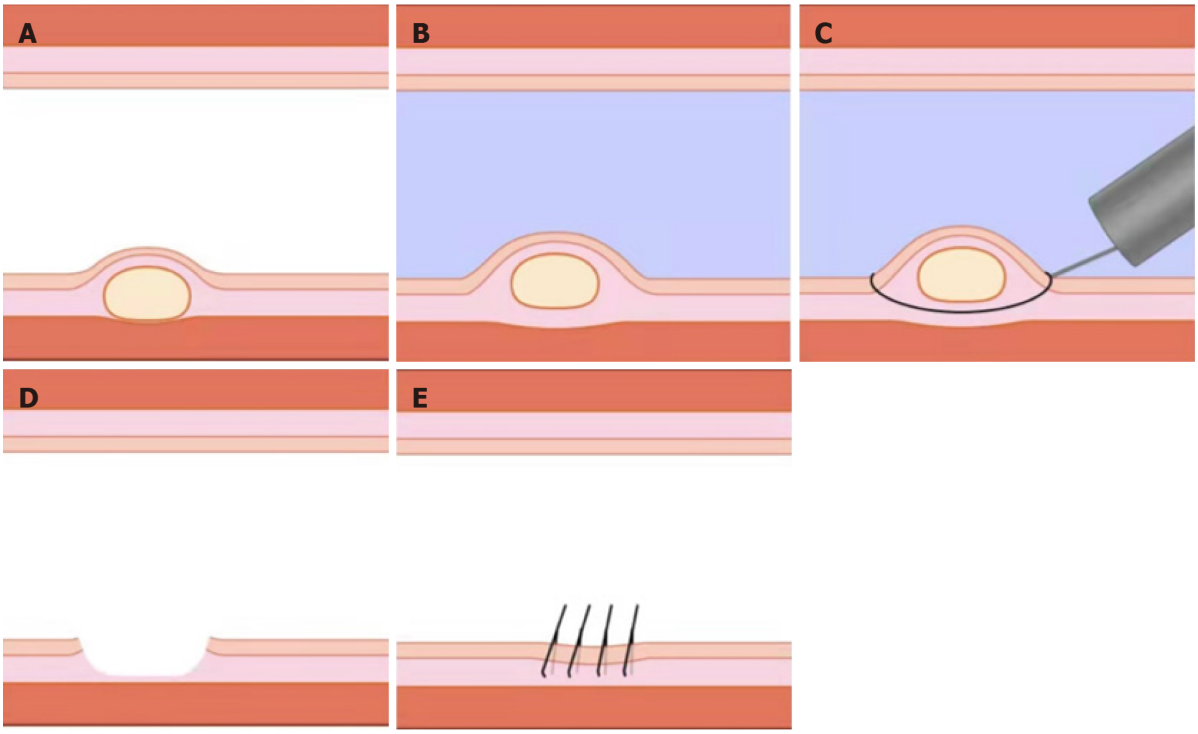

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Figure 4 Underwater endoscopic mucosal resection. A: A pale yellow mass in the rectum; B: Floating of the mass through the buoyancy of water after air extraction and water injection into the rectum; C: Resection of the mass by using electrosurgical snare; D and E: Wound clipping with titanium clips after mass resection.

resection rate of rNETs by EMR-L is as high as that with ESD[45]. Some scholars carried out a retrospective study of rNET cases undergoing EMR-L and ESD resection and showed that these two types of surgery could be used to completely remove whole lesions in all cases, and the complete resection rate of EMR-L was higher than that of ESD, with the lateral and vertical resection margins being farther away from the tumor[33]. EMR-L also obtains a more sufficient distance of the vertical resection margin; further, it is easily performed and less time-consuming[50], and carries a lower risk of adverse events such as bleeding and perforation[45]. In addition, the incidence of low rectal perforation during EMR-L is lower. These findings suggest that EMR-L is more suitable for the treatment of rNETs than ESD. Comparison of different endoscopic and surgical techniques is listed in Table 1.

Combined with preoperative evaluation, some scholars recommend that rNETs less than 5 mm in diameter and without irregular characteristics should be treated with modified EMR or ESD. EUS and MRI should be completed prior to ESD or surgery in cases of rNETs with irregular characteristics or measuring 5 mm to 2 cm in diameter to assess whether the lesion invades the muscularis propria or regional lymph nodes. MRI and CT or functional imaging should be completed to evaluate the presence of distant metastasis in cases with infiltration of the muscularis propria or local lymph node metastasis [51]. Hepatic or systemic treatment should be performed if the lesion has metastasized to a distant location. Surgical treatment should be performed if the lesion has no distant metastasis. The 2016 updated guidelines of ENETS recommended endoscopic resection of T1-stage (G1/G2) rNETs less than 10 mm in diameter. Pathological assessment of G1 Lesions should be re-examined 6 mo after incomplete resection of rNETs. Localized resection should be performed if necessary. A G2-stage tumor identified as such by pathological assessment should be completely resected locally again. For T2-stage (G1/G2) lesions, complete localized resection is recommended; TEMS should be considered if complete resection cannot be achieved. G3 Lesions with a tumor diameter of less than 10 mm are extremely rare and should be accessed by MRI/CT/positron emission tomography (PET) to confirm the presence of distant metastasis; those without metastasis should be subjected to rectal resection or TEMS and those with metastasis complicated by intestinal obstruction or bleeding that is difficult to control should be subjected to TEMS.

The operator can select the treatment method according to the conditions and characteristics of the center under the premise of fully evaluating the rNETs before the operation in accordance with the recommendations of the guidelines. More research and comparisons of different endoscopic treatment methods are necessary to select the best approach and to explore more innovative surgical methods.

Table 1 Comparison of different endoscopic and surgical techniques

Technique	Description	Advantages	Risks	Percentage of R0 resection and complication
Transanal resection	Removes the tumor at a higher position	Ensures a deep removal in the muscularis mucosa	For rNETs less than 10 mm, the risk is greater than the benefit	96.8% R0 resection; urinary tract infection, subcutaneous emphysema, urinary tract infection[56]
Transanal endoscopic microsurgery (TEMS)	A localized resection under a laparoscopic view through the anus	Direct and complete removal of the lesion and the resection wound is fully and surgically sutured under direct vision	Expensive fees for the operation and anesthesia; postoperative fecal incontinence	92.3% R0 resection, no complication[57]
Traditional EMR	Mucosal resection by electro-coagulation	Fast and convenient	Incomplete resection; crushed wound affects the pathological evaluation	50% R0 resection, 7.1% complic-ations[37]
Cap-assisted EMR (EMR-C)	Attracts the tumor to a cap and removes it using a crescent snare	Effective treatment, short operation duration	The depth of the vertical resection margin needs fully guaranteed	94.1% R0 resection 8.8% intraprocedural bleeding[58]
Dual-channel endoscope (EMR-D)	One channel delivers the snare and the other delivers the forceps to lift the lesion	Simple, easy-to-learn, and effective; ensuring the vertical depth of the resection by lifting	Requires dual-instrument channel endoscopy	86.3% R0 resection, minor bleeding (1/44)[36]
EMR with a ligation device (EMR-L)	Injection and rubber ring to form a pseudo-polyp, retracting the snare under it and resect the tumor	More fully ensures the vertical depth of tumor resection; resects without destroying or deforming the tumor	Inadequacy for large tumors	89.5%[37], 99.4%[59], 86.2%[55] R0 resection, 0.6% perforation and 6.1% delayed bleeding[59]
Underwater EMR (UEMR)	To float the tumor by the buoyancy of the water without submucosal injection before electro-coagulating resection	Ensures a clean resection margin and safe removal of rNETs	Electrocoagulation damages the edge of the specimen	83% R0 resection, no complication[60]
ESD	Submucosal dissection	Lower recurrence rate	Perforation and bleeding; lasts for a long time and requires highly experienced surgeons	94.7%[37], 100%[47], 92%[50], 97%[55], 88.4%[36], 86.1%[32], 11.5% minor bleeding[36], 2.5% adverse events[32]

ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; rNETs: Rectal neuroendocrine tumors.

SUBSEQUENT STRATEGIES AFTER INCOMPLETE RESECTION OF RNETS

In clinical practice, pathological examinations accidentally discover NETs in the lesion sometimes after routine polypectomy, and the selection of surgical procedures is often affected by the experience of surgeons and the conditions of surgical equipment[31]. No strong literature support is available for the requirement of a second salvage endoscopic treatment or surgical treatment for unexpectedly discovered rNETs, especially very small rNETs (≤ 5 mm in diameter)[52].

Existing ENETS guidelines propose different management approaches based on three parameters[16]: Tumor size, EUS stage (T and N), and the World Health Organization classification (G1/2 or G3). Eighty to ninety percent of rNETs are less than 10 mm in diameter and confined to the submucosa. Small rNETs are usually difficult to distinguish from hyperplastic polyps or adenomas and are easily removed by cryotherapy, even during a biopsy that may easily cause incomplete resection. In this circumstance, EMR may be a feasible approach for the removal of a single rectal lesion less than 5 mm in diameter and without high-risk manifestation. A previous study observed a residual rate of 22.6% in patients with incidentally removed rectal neuroendocrine neoplasms followed by locally remedial ESD; the residual rate of patients with rectal neuroendocrine neoplasms more than 3 mm in diameter was as high as 60% to 90%[31]. These data indicate that, even for very small rNETs, ordinary polypectomy still carries a higher risk of incomplete resection. It is recommended that patients with incomplete initial resection of rNETs undergo EMR or ESD for complete resection of the scar in the resection site[34].

Patients with postoperative pathology of rNETs showing positive margins should undergo EUS evaluation of the scar area before the second remedial operation, especially those with tumors measuring greater than 5 mm in diameter. EUS assesses the remaining submucosal tissues and lymph nodes, and pelvic MRI can be used as an aid for the evaluation. Remedial operations include EMR-C [53], ESD, or TEMS. However, the therapeutic outcome of ESD is affected by the scar tissue. Scarring changed the normal stratification of the intestinal wall, affecting the accuracy of EUS in evaluating the residual lesions in the operation site[31]. Thus, it has been suggested that remedial ESD should be performed when rNETs are greater than 3 mm in diameter, regardless of the tumor classification or the EUS manifestations on the scar[31]. Patients with incompletely resected rNETs less than 10 mm in diameter and without obvious evidence of residual disease are recommended to undergo monitoring by

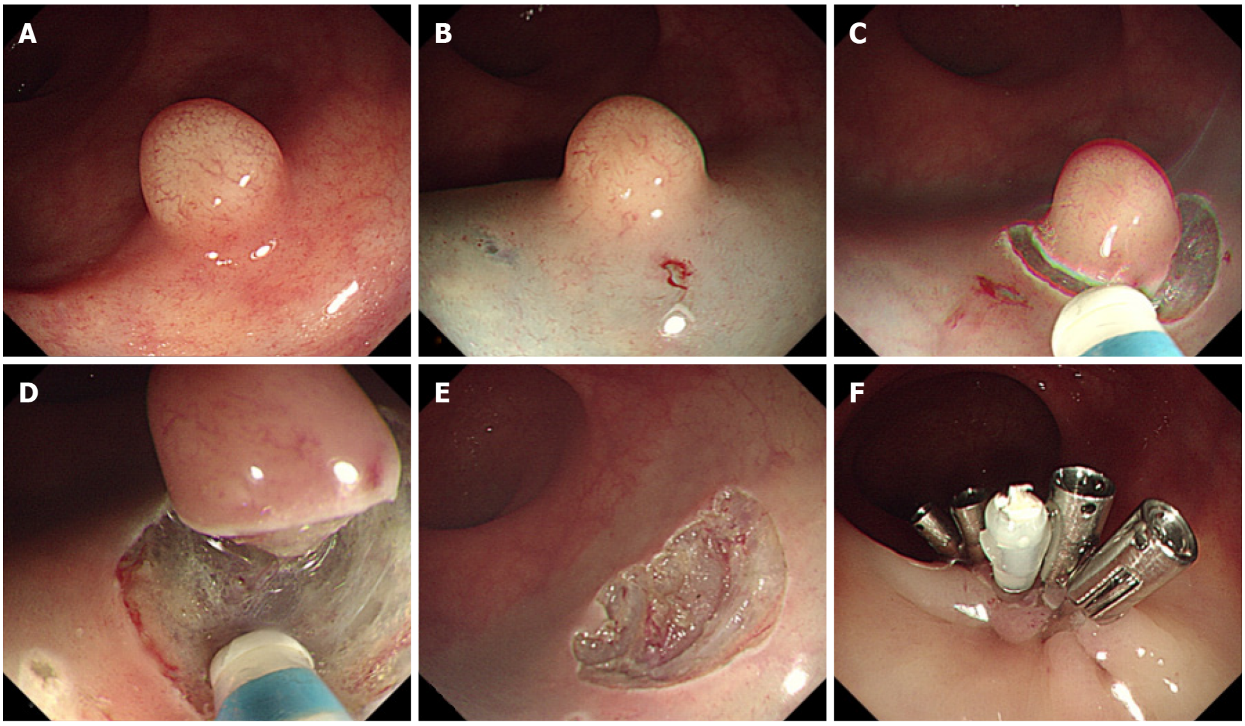

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Figure 5 Endoscopic submucosal dissection. A: A pale yellow mass with a diameter of about 6 mm in the rectum; B: Submucosal injection of the mass with an injection needle; C: Circumferential resection of the submucosa of the mass with a mucosal resection knife; D: Mass dissection with a resection knife; E: Wound surface after the removal of the mass; F: Wound clipping with titanium clips after mass resection.

EUS every 6 mo for two years[15].

In a previous study, pathological evaluations revealed LVI in more than 25% of small rNET specimens, and the evaluation indicator for LVI is required to be more accurate. The incidence of postoperative LVI in rNET cases might be even higher, but it did not affect the short-term prognosis so far[54]. The Guidelines of the North American Neuroendocrine Tumor Society indicate that the rate of lymph node metastasis of rNETs less than 10 mm in diameter is very low, while this review article discussed a certain probability of lymph node metastasis even in these small rNETs. These differences may be linked to the frequent additional remedial operations performed in Japan and the implementation of CT alone for the evaluation of lymph node conditions in Western countries. The latter approach lowers the sensitivity of the evaluation of lymph node metastasis. Another study has shown that patients with rNETs less than 6 mm in diameter have a 0% lymph node metastasis rate[55], which may also be related to the insufficient sample size of the study. Further discussion is needed for the risk assessment and follow-up of postoperative lymph node metastasis in patients with small rNETs. Distant metastasis of rNETs often occurs in the liver and requires systemic assessment and multidisciplinary collaboration. A reduction in local bleeding during rNET resection to improve the symptoms of intestinal obstruction should be performed in the case of distant metastasis.

POSTOPERATIVE FOLLOW-UPS

Postoperative follow-up strategies for patients with rNETs are mainly chosen based on the tumor size, pathological classification, overall tumor stage, and lymphatic metastasis[15]. Patients with complete resection of rNET are still recommended to undergo colonoscopy and CT within one year after surgery. rNET patients with positive lateral or vertical margins are required to undergo additional surgery and local lymph node dissection. For those who refuse to receive additional surgery, colonoscopy, chest imaging, and abdominal CT findings must be reviewed every year. An endoscopic biopsy is required in those patients with residual tumors revealed on the postoperative scar during the colonoscopy.

The guidelines further clarify that patients with complete resection of G1/G2 rNETs less than 10 mm in diameter and without lymph node metastasis or invasion of the muscularis propria should be considered to be at low risk of recurrence and recommend no routine follow-up[5]. Patients with G3 rNETs less than 10 mm in diameter have an increased risk of recurrence and should be reviewed by colonoscopy at least once a year for five years[15] and followed for adenomatous polyps. EUS, colonoscopy, and MRI should also be included in the follow-up plan. Patients with incomplete resection of rNETs less than 10 mm in diameter are subjected to pathological examinations, and those who have no obvious residual lesions should be reviewed and evaluated by EUS every 6 mo for two years. The scar area after EMR-C or ESD is recommended to be resected in an extensive manner, and histological evaluation should be repeated[15].

TREATMENT OPTIONS FOR RNETS LARGER THAN 10 MM IN DIAMETER

Endoscopic resection is recommended for rNETs less than 10 mm with no risk of recurrence. While surgery is suggested for tumors larger than 20 mm or with depression appearing in the tumor center regardless of tumor size. For rNETs with a diameter between 10 mm to 20 mm, options should be made according to the risk of metastasis and the patient's personal choice[7,10].

CONCLUSION

Although rNETs less than 10 mm in diameter have a low risk of metastasis, complete resection and adequate prognostic evaluation are required for the development of follow-up plans. Endoscopic and surgical procedures for these cases can achieve relatively good curative effects. The application of endoscopic treatment for patients with small rNETs also achieves more beneficial outcomes. The curative rate is high by the effort of the experts. With the continuous innovation and development of endoscopic technology, we look forward to more surgical procedures to perfect the treatment. Multicenter, large-sample studies should be carried out to provide sufficient evidence for the selection of the best surgical procedure. The follow-up of patients based on disease prognosis and postoperative evaluation helps to detect disease recurrence in time and improve their quality of life.

FOOTNOTES

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Abstract

Lymphography by radioisotope or dye is a well-known technique for visualizing the lymphatic drainage pattern in a neoplastic lesion and it is in use in gastric cancer. Indocyanine green (ICG) more recently has been validated in fluorescent lymphography studies and is under evaluation as a novel tracer agent in gastric cancer. The amount and dilution of ICG injected as well as the site and the time of the injection are not standardized. In our unit, endoscopic submucosal injections of ICG are made as 0.5 mg in 0.5 mL at four peritumoral sites the day before surgery (for a total of 2.0 mg in 2.0 mL). Detection instruments for ICG fluorescence are evolving. Near-infrared systems integrated into laparoscopic or robotic instruments (near-infrared fluorescence imaging) have shown the most promising results. ICG fluorescence recognizes the node that receives lymphatic flow directly from a primary tumor. This is defined as the sentinel lymph node, and it has a high predictive negative value at the cT1 stage, able to reduce the extent of gastrectomy and lymph node dissection. ICG also enhances the number of lymph nodes detected during extended lymphadenectomy for advanced gastric cancer. Nevertheless, the practical effects of ICG use in a single patient are not yet clear. Standardization of the technique and further studies are needed before fluorescent lymphography can be used extensively worldwide. Until then, current guidelines recommend an extensive lymphadenectomy as the standard approach for gastric cancer with suspected metastasis.

Key Words: Indocyanine green; Fluorescence; Lymphography; Sentinel lymph node; Gastric cancer; Lymphadenectomy

Core Tip: Endoscopic injection of indocyanine green (ICG) the day before surgery is a simple technique that could increase the number of lymph nodes recovered during lymphadenectomy for advanced gastric cancer. In addition, ICG-guided sentinel lymph node detection could reduce unnecessary extensive lymphadenectomy and the amount of gastric resection in early gastric cancer. However, further research is needed to confirm its usefulness in both scenarios. Currently, D1/D2 Lymphadenectomy remains the standard of care for gastric cancer with suspected metastasis. Our review explores this topic in depth and provides practical information for the endoscopic use of ICG.

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INTRODUCTION

Lymphography dates back to the 1950s when the first studies were carried out[1]. The term ‘sentinel lymph node’ (SLN) was originally used in 1960[2]. A sentinel node is defined as the node that receives lymphatic flow directly from a primary tumor. The beneficial effects of SLN detection were first published by Morton *et al*[3] in 1992. They injected isosulfan blue vital dye in a melanoma, with the aim to select and evaluate neoplastic infiltration to the first LN. They demonstrated that if there was no metastasis in the SLN, then metastasis would also be absent in the downstream LNs, thus avoiding unnecessary lymphadenectomy. SLN navigation surgery is a widely accepted technique for malignant melanoma[3] and breast cancer[4]. Several tracer agents have been studied over the past 70 years[1,5-7] and are used for the detection of lymphatic drainage in several digestive surgical settings[8,9]. Studies of lymphatic drainage in gastric cancer have been carried out only relatively recently[10]. The primary outcomes in these studies was an increase in LN harvest[11] and in detection of SLNs[12].

Historically, a radioisotope (RI) technetium-99 tracer combined with a blue dye was injected endoscopically into the gastric submucosa around the tumor the day before surgery. The radioactivity of the LN was measured during surgery using a hand-held gamma probe[5,13]. This technique has a high detection rate and accuracy[14]. A meta-analysis based on 46 reports that included 2684 patients with gastric cancer using RI and/or dye showed sensitivity, detection rate, negative predictive value and positive predictive value of 87.8%, 97.5%, 91.8% and 38.0%, respectively[15]. The disadvantages of RI are expensive cost and the requirement of a radioactivity-controlled area. While this technique is considered the gold standard, it is rarely performed outside of Eastern Countries, currently.

INDOCYANINE GREEN AS A LYMPHATIC TRACER

Indocyanine green (ICG) is gaining status as the most utilized tracer in surgical practice. ICG is a sterile water-soluble tricarbocyanine dye that rapidly binds to plasma proteins and is subsequently drained by the lymphatic system. The visualization of ICG is difficult for the naked eye when observed in human tissue. However, when excited by near-infrared light at 700–900 nm, ICG emits fluorescence at a wavelength of approximately 820 nm and is easily visualized by various devices[16-18].

ICG submucosal (SM) or subserosal (SS) injection is virtually free of adverse effects. Although, rare cases of anaphylactic shock have been reported (0.05%-0.4%)[19]. Several methods of ICG mapping exist; they include, naked eye observation under white light by Hiratsuka *et al*[12] and Ichikura *et al*[10], Infra-Red Electronic Endoscopy (IREE); by Nimura *et al*[18], Infrared Ray Laparoscopic System (IRLS); by Takahashi *et al*[20], and Near-Infrared Fluorescent Imaging (NIFI); by Kusano *et al*[16] and others. Of note, Hiratsuka's method is no longer used, largely due to its poor contrast, while Nimura's IREE and Takahashi’s IRLS have fallen out of use due to the devices being commercially unavailable but they are still generally considered excellent techniques. Only ICG fluorescent mapping NIFI is currently performed.

ICG was evaluated in surgical management of gastric cancer in order to guide selective lymphadenectomy in intraoperative SLN identification as well as comprehensive lymphadenectomy by increasing the number of total and metastatic LNs retrieved during gastric surgery. Feasibility of ICG lymphography by NIFI was demonstrated in open[11], laparoscopic[21] and robotic surgeries[22]. Surgeons are able to switch between white light, near-infrared light and a composite vision. Technical details were published by Zhu *et al*[23].

RATIONALE FOR LN STAINING IN GASTRIC CANCER

According to the European Society for Medical Oncology gastric cancer treatment guidelines 2022[24], D1 Lymphadenectomy limited to perigastric LNs and those along the left gastric artery is recommended for early tumors (cT1) that do not meet the criteria for endoscopic resection. However, only 20% of T1 tumors have lymphatic involvement, and this approach resulted in overtreatment for most patients[24,25]. Furthermore, D2 Lymphadenectomy with removal of additional LNs along the hepatic artery, splenic artery and coeliac axis is frequently performed in cT1 gastric cancer due to the difficulty of excluding micrometastases. This has a negative effect on morbidity and quality of life[26-28]. The number of LNs harvested during surgery for advanced gastric tumors was associated with correct staging and better prognosis[29-31]. However, extensive lymphadenectomy is a demanding procedure that carries a high risk of tissue or vascular injury. Therefore, detecting SLN draining in early (cT1) gastric tumors and facilitating the detection of LN in advanced gastric cancer would be beneficial and accepted in the clinical setting[11,29,32,33].

ICG FLUORESCENCE FOR SLN DETECTION IN GASTRIC CANCER

A pioneer study was conducted by Hiratsuka *et al*[12] and demonstrated that after peritumoral ICG injection SLN status was able to be visually defined with 100% sensitivity in a T1 group (44 patients) and 88% sensitivity in a T2 group (29 patients). The authors concluded that SLN status could predict the presence of lymphatic metastasis with a high degree of accuracy, especially in patients with T1 gastric cancer.

Two meta-analyses regarding the diagnostic value of ICG for SLN detection in gastric cancer were published in 2018. In the first, Skubleny *et al*[34] included 643 patients from 10 studies conducted with IREE or NIFI detection devices; among them, 513 (79%) were cT1 patients. Pooled sensitivity and specificity of ICG fluorescence for SLN detection was 87% and 100%, respectively. Metastatic SLNs were retrieved in 18.7% of the enrolled patients. IREE demonstrated a higher diagnostic odds ratio, sensitivity and identification rate than NIFI. In the second meta-analysis, He *et al*[35] included 13 studies conducted with IREE, IRLS or NIFI devices. Significant heterogeneity among the included studies was found for sensitivity (from 50% to 100%) and for specificity (from 60% to 100%). There was also significant publication bias. An interesting subgroup analysis demonstrated that sensitivity for T1 was much higher than T2-T3. Intraoperative IGC injection was compared with preoperative injection. The sensitivity of the intraoperative injection subgroup was slightly lower than the preoperative injection subgroup (98% *vs* 99%). SM injections were compared to SS injections. The pooled sensitivity of the SM injection subgroup was considerably higher than that of the SS injection subgroup (98% *vs* 40%). NIFI also showed a lower sensitivity rate than either IREE or IRLS. Finally, when the ICG concentration of 5.0 mg/mL was compared to a diluted ICG concentration of 0.5 mg/mL or 0.05 mg/mL, the sensitivity of the former was lower than that of the latter (83% *vs* 98%); this was explained as due to a reduction of ICG fluorescence intensity with the higher concentration (*i.e.*, the "quenching effect"). A comprehensive evaluation of effects of various ICG concentrations for SLN detection was conducted by Kinami *et al*[36].

The clinical application of sentinel node biopsy for gastric cancer must still overcome the problem of rapid intraoperative diagnosis of micrometastasis in the SNL. To reduce the rate of false negative findings, Miwa *et al*[37] suggested "en bloc" dissection of blue dye-stained perigastric SLN according to defined basins in their pilot study. The subsequently identified the SLN at the back table in the surgical suite (*ex vivo*). This method was termed "lymphatic basin dissection" and is now regarded as the standard method for SLN navigation surgery. A decade after that study, a landmark multicenter research project by Kitagawa *et al*[14] demonstrated that lymphatic basin dissection with RI+ dye was able to detect the SLN in 97.5% of patients (n = 387/397). The accuracy of nodal evaluation for metastasis was 99% (n = 383/387). There were only four false-negative SLN biopsies, and in all patients with a false-negative intraoperative pathologic diagnosis the metastatic spread was limited to either the SLNs or within the SLN basins. To further limit false negative SLNs, it was suggested that only < 4-5 cm diameter T1 neoplasms be focused on. Another suggestion was to perform nucleic acid amplification, reverse transcription-polymerase chain reaction or immunohistochemistry in association with the intraoperative rapid (hematoxylin and eosin) pathology examination.

Kinami *et al*[38] described the algorithm for SLN navigation surgery conducted with ICG fluorescence detected by NIFI. The SLN detection is performed first, followed by lymphatic basin dissection, *ex vivo* identification and biopsy of the SLN(s), and intraoperative rapid pathology. If a metastatic SLN is detected, then a standard gastrectomy with nodal dissection up to D2 is performed; if the SLNs are diagnosed negative, then the extent of gastrectomy is reduced and function-preserving curative gastrectomy is applied (Figure 1).

Oncological effectiveness of the lymphatic basin dissection method for SLN detection has been demonstrated, along with its ability to prolong survival better than total gastrectomy and extensive LN dissection[38]. Importantly, function-preserving curative gastrectomy is safe and well tolerated[39,40] (Figure 2).

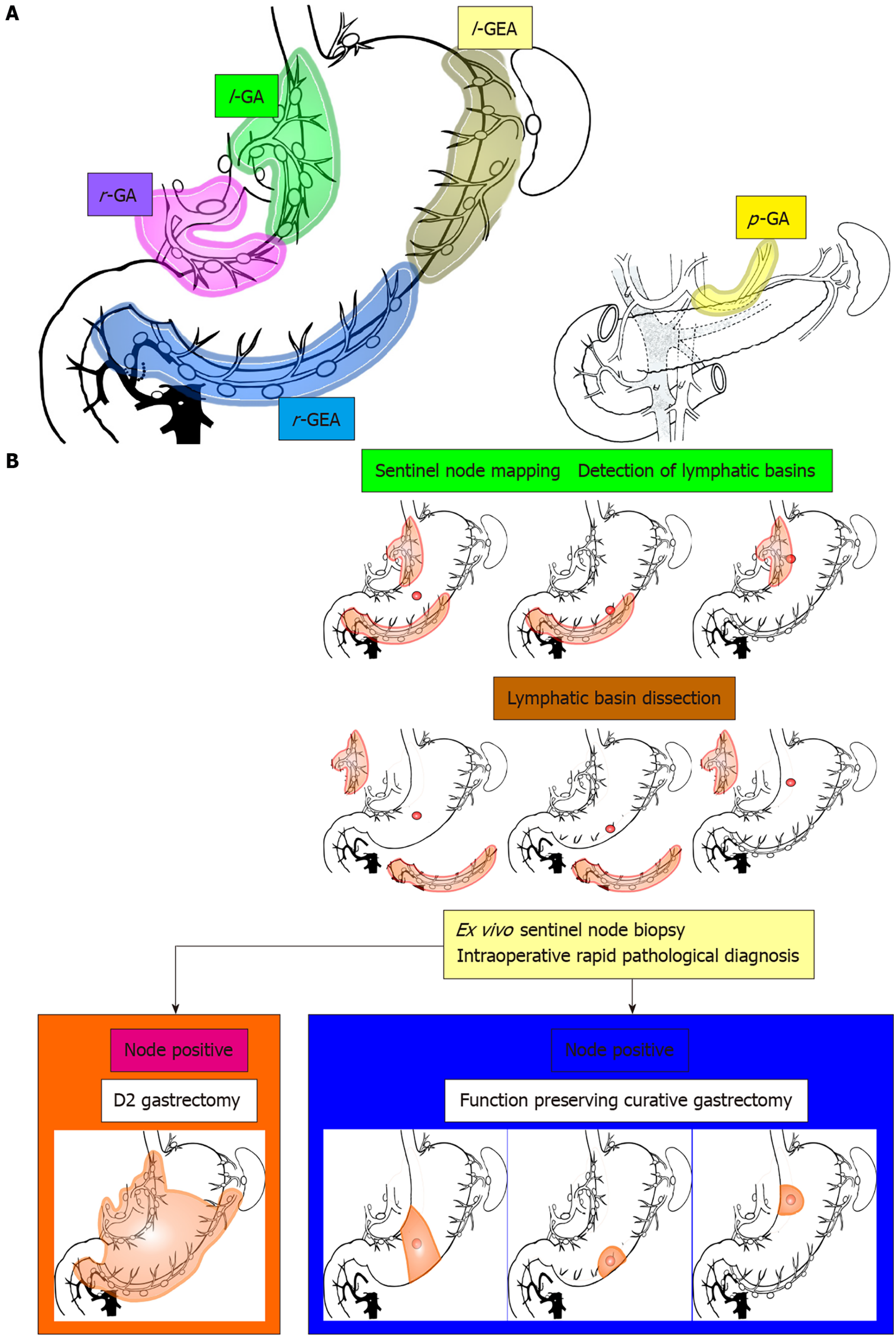

Figure 1 Lymphatic basins, lymphatic compartments, and the strategy of sentinel node navigation surgery. *l*-GA: Left gastric artery basin; *l*-GEA: Left gastroepiploic artery basin; *p*-GA: Posterior gastric artery basin; *r*-GA: Right gastric artery basin; *r*-GEA: Right gastroepiploic artery basin. Citation: Kinami

S, Nakamura N, Miyashita T, Kitakata H, Fushida S, Fujimura T, Iida Y, Inaki N, Ito T, Takamura H. Life prognosis of sentinel node navigation surgery for early-stage gastric cancer: Outcome of lymphatic basin dissection. *World J Gastroenterol* 2021; 27(46): 8010-8030. Copyright: The Authors 2021. Published by Baishideng Publishing Group Inc[38].

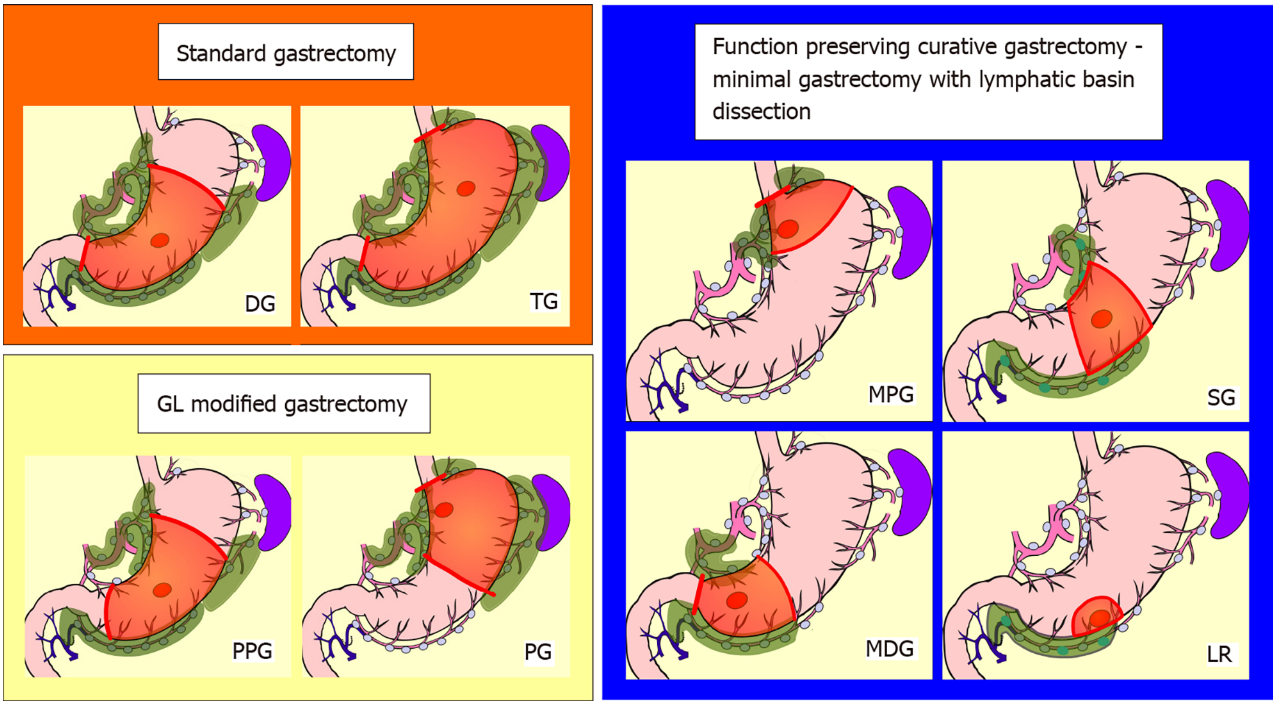

Figure 2 Schemas of standard gastrectomy, modified gastrectomy due to guidelines, and function-preserving curative gastrectomy with lymphatic basin dissection. Red circle: tumor; Green-colored area: extent of lymph node dissection; Orange area: extent of gastrectomy. The extent of nodal dissection in standard gastrectomy and modified gastrectomy according to the guidelines was D1+. In contrast, the extent of nodal dissection in lymphatic basin dissection was defined as D0. DG: Distal gastrectomy; GL: Japanese gastric cancer treatment guidelines; LR: Local resection; MDG: Minidistal gastrectomy; MPG: Mini-proximal gastrectomy; PG: Proximal gastrectomy; PPG: Pylorus-preserving gastrectomy; SG: Segmental gastrectomy; TG: Total gastrectomy. Citation: Kinami S, Nakamura N, Miyashita T, Kitakata H, Fushida S, Fujimura T, Iida Y, Inaki N, Ito T, Takamura H. Life prognosis of sentinel node navigation surgery for early-stage gastric cancer: Outcome of lymphatic basin dissection. *World J Gastroenterol* 2021; 27(46): 8010-8030. Copyright: The Authors 2021. Published by Baishideng Publishing Group Inc[38].

ICG FLUORESCENCE FOR LN DETECTION AND MAPPING IN GASTRIC CANCER

An increase of LN detection by ICG fluorescence *vs* white light has been confirmed in most of studies. Mean retrieval increases have varied from 7.9 LNs/patient[41] to 12.0 LNs/patient[42] and 13.7 LNs/patient[22]. The effects of ICG were also evaluated in a pooled analysis from two randomized controlled trials (FUGES-012 and FUGES-019 studies)[43]. Data from 514 patients showed a significantly increased mean number of LNs retrieved (an increase of 7.9 LNs/patient) in the ICG group compared to the non-ICG group. The sensitivity of fluorescence imaging for detecting all metastatic LN stations was 86.8%. The negative predictive value was 92.2% for non-fluorescent LN stations. Regardless of gastrectomy type, the diagnostic accuracy for detecting all metastatic LN stations in the D1 and D2 Lymphadenectomy for cT1-cT2 disease reached 100%. Kim *et al*[44] demonstrated that the activation of near-infrared fluorescence increased the detection of LN after a standard lymphadenectomy. A recent meta-analysis demonstrated that ICG was able to increase the mean number of harvested LNs by 6.93 LNs/patient (40.33 *vs* 33.40)[45].

Some studies observed an increased number of metastatic LNs detected by ICG[46], but a meta-analysis did not confirm this[45]. This may be due to metastatic LNs not staining or the presence of lymphatic vessels that are blocked. ICG does not have preferential uptake in metastatic LN, and frequently the overall percentage of fluorescent LNs and the percentage of metastatic fluorescent LNs are similar[44]. In addition, the number of LNs stained by ICG is small compared with the total number of LNs excised and often less than 60%[41,22,43].

The ability of ICG to visualize the anatomy of gastric lymphatic drainage was specifically evaluated in patients with advanced gastric cancer who underwent extended D2 Lymphadenectomy[11]. During surgery, ICG was injected in 11 patients along the greater and lesser curvatures of the anterior surface of the stomach. ICG stained only 37.8% LNs (260 of 687) removed by D2 Lymphadenectomy. ICG globally stained 30 of 75 (40.0%) metastatic LNs. In 4 out of 8 cases (50.0%), ICG signals were detected in all metastatic LN stations. Overall, ICG stained 21 of 28 metastatic LN stations (75.0%).

CONTROVERSIES FOR ICG USE IN GASTRIC CANCER

The usefulness of ICG fluorescent lymphography in gastric cancer remains controversial. A standardization of ICG concentration and method of injection is lacking. Several studies have proposed various dilutions of injected ICG. Dilutions vary from 5 mg/mL[16], 1.25 mg/mL[47], 0.5 mg/mL[40], and 0.05 mg/mL[11,48]. SM endoscopic preoperative injection and SS or SM intraoperative injection have been compared. Preoperative injection was observed to increase the number of detectable LNs for some authors[49], while others found that it did not increase the number of detectable LNs[50]. Taken together, these results suggest that preoperative ICG injection the day before surgery may facilitate comprehensive mapping of lymphatic drainage, and an increased concentration of ICG is likely needed for intraoperative injection[34,47,49]. Further research is warranted to definitively answer these questions.

The theory that the absence of metastasis in the SLN corresponds to an absence of metastasis in downstream LNs may not apply to gastric cancer due to the complexity of the lymphatic system of the stomach. It is difficult to accurately visualize the connections between the perigastric lymphatic network and the location of every single LN, which can lead to micrometastases or skip metastasis detection[10, 51-53]. The number of false negative SLNs has been shown to gradually increase from T1 to T3 gastric cancer[54] due to lymphatic obstruction by massive cancerous infiltration[43]. Kitagawa *et al*[14] suggested that SLN navigation surgery should only be performed on cT1 gastric cancer due to the higher risk of false negatives in cT2 gastric cancer.

SLN detection may avoid the need for an extended lymphadenectomy and limit the area of gastrectomy and preserving the pylorus or allowing a segmental gastrectomy. However, it has been reported that the patient's quality of life following laparoscopy-assisted pylorus-preserving gastrectomy is equivalent to that following laparoscopy-assisted distal gastrectomy[55]. Similarly, it was reported that patients who received a D3 Lymphadenectomy showed no significant difference in quality of life compared to patients who received a D1 Lymphadenectomy[56].

A multicenter study by Miyashiro *et al*[57] (Group multicenter trial JCOG0302) published in 2014 was prematurely suspended due to high false negative SLN detection. However, the authors concluded that false negative SLNs were a consequence of inadequate histological detection (only one slide and hematoxylin and eosin staining) and not due to ICG performance. A meta-analysis showed that the sensitivity of immunohistochemistry plus hematoxylin and eosin was superior to use of hematoxylin and eosin alone (0.99 *vs* 0.77)[35]. Unfortunately, the use of immunohistochemistry in clinical practice would likely be demanding.

There is little data regarding the effects of neoadjuvant therapy on ICG fluorescence. The histological fibrotic changes following chemotherapy may represent a possible limitation of ICG dissemination in the lymphatic system. Therefore, the intraoperative identification of peritumoral LNs may be impaired [41].

Finally, it is accepted that ICG fluorescence increases the number of LNs harvested, but the clinical utility is debatable because detection of metastatic LNs did not increase. In addition, an ICG-guided lymphadenectomy is not feasible due to the low percentage of LNs stained. Park *et al*[11] demonstrated in a series of patients with advanced gastric cancer that ICG detected only 37.8% of the total LNs and only 37.5% of metastatic LN stations were retrieved. This was likely due to obstruction of lymphatic vessels.

ICG FLUORESCENCE FOR GASTRIC CANCER: A WESTERN PERSPECTIVE

The incidence of gastric cancer in western countries is roughly 17%-25% of the incidence in East Asia [58]. Consequently, the experience of Western surgeons, with the exception of a few referral centers, may not be comparable to that in East Asia. In general, the experienced Asiatic surgeons believe that lymphatic mapping is unnecessary if accurate LN dissection and careful harvesting are performed. In advanced gastric cancer, however, mapping with ICG fluorescence could increase the quality of LN dissection in less experienced western centers and this must be considered.

The technique of ICG for SLN detection in gastric cancer is complex and requires training for at least 30 procedures[14]. Unfortunately, the opportunity to learn the SLN navigation surgery technique in Western countries is compromised by the fact that only a reported 20% of gastric cancers in the West are T1 at diagnosis compared to 50% in East Asia[59].

Historically, western surgeons have less experience with extensive lymphadenectomy for gastric cancer because DII lymphadenectomy became a standard of action only after the follow-up results from the Dutch D1 D2 trial were released[60]. As a consequence, western schools of surgery had less experience with LN mapping and SLN navigation surgery techniques prior to the recent widespread use of ICG. This explains why Eastern surgeons consider ICG to be a mere reintroduction of yet another tracer for gastric surgery, whereas for Westerners it represents an entirely new experience.

Another obstacle encountered when ICG was introduced in gastric cancer was the lack of clear guidance from the literature regarding the best dilution of ICG for the laparoscopic system. Also, since proprietary devices are obviously evolving, the latest version of the Olympus laparoscopic system, the Visera Elite III (Olympus Europa SE & Co.KG, Hamburg, Germany), which was acquired by our unit uses a different technique for NIFI from its predecessor, the Visera Elite II, and likely requires a higher dilution of ICG; we will explore this in the future. In the East, this issue was overcome by the considerable experience of surgeons who have structured customized techniques over the years; it could be the same for western surgeons as they continue increasing their practice. Although there are many useful indications online in the International Society for Fluorescence Guided Surgery (ISFGS) documents[61] our personal experience has led to cautious consideration for gastric cancer because the optimal dilution has not been well defined yet. We advocate that in the future, the ISFGS (https://isfgs.org/) in collaboration with laparoscopic equipment companies will define the best ICG dilution for each proprietary device.

ICG USE FOR GASTRIC CANCER IN CLINICAL PRACTICE

In our surgical unit, ICG fluorescence detection is still primarily performed by video-angiography with the Olympus Visera Elite II. This detection technology is based on the use of two optical filters located, respectively, in the light source and the proprietary ULTRA® infrared optics. These filters cut certain frequencies in the light spectrum that allow the system to detect light emission in the near infrared, a wavelength range from 800 nm to 2500 nm. The filter in the light source blocks the red component of visible light, allowing blue-green and infrared light to pass through, hitting the tissue and being reflected (the infrared is partly reflected and partly penetrates the tissue, reaching the ICG molecules that emit fluorescence). At this point, the filter in the laparoscopic optics blocks the infrared reflection while allowing the blue and green visible light components and fluorescence to pass through, and thereby enabling the two viewing modes (partial white light fluorescence and pure fluorescence) (Figure 3).

ICG is commercially available in 25 mg or 50 mg vials and is with saline-free water diluted in most studies. In our unit, endoscopic SM injection is performed the day before surgery. We inject four boluses, each containing 0.5 mg/0.5 mL of saline-free water, *via* a sandwich technique. An example of the visual effects of endoscopic injection are shown in Figure 4. Figure 5 illustrates the methods of dilution and injection.

ICG LYMPHOGRAPHY FOR GASTRIC CANCER: WHAT'S NEW

Theoretically, if all SLNs were histologically negative for cancer metastases, then endoscopic mucosal resection (EMR)/endoscopic submucosal dissection (ESD), instead of gastrectomy, may be appropriate for the curative resection of cT1 early gastric cancer that is outside the EMR/ESD criteria. Feasibility and performance of ICG staining after ESD was studied by Roh *et al*[62]. In their study, SLN-guided lymphadenectomy by ICG fluorescence was evaluated in 98 out of 290 patients who underwent gastrectomy after a non-curative ESD requiring standard lymphadenectomy according to the existing guidelines. ICG stained 8 out of 9 metastatic SLNs. The sensitivity was 88.9%, the negative predictive value was 99.9%, and the positive predictive value was 0.3%. The sensitivity and negative predictive value for detecting SLN metastasis by ICG was 100% if we considered the lymphatic stations because all metastatic stations were detected by at least one SLN stained with ICG. However, only 66% of LNs were stained by ICG, and only 9/4671 metastatic LNs were retrieved. The data are encouraging, but need further confirmation because there are concerns that some metastatic LNs may not be detected.

The SENORITA trial[63] is ongoing. This randomized controlled trial enrolled 580 patients and is confirming the usefulness of SLN navigation surgery for cT1 patients who do not meet the criteria for EMR/ESD. The trial is evaluating whether laparoscopic stomach-preserving surgery with SLN detected by ICG fluorescence achieves similar oncologic outcomes and improved morbidity compared to a standard gastrectomy with D1/D2 Lymphadenectomy. Preliminary data have demonstrated that the organ-preserving surgery was performed in 81.4% of patients, and postoperative complications occurred in 15% of those patients. The SENORITA 2 phase II trial[64] is comparing laparoscopic SLN navigation surgery to laparoscopic standard gastrectomy in patients with early gastric cancer after endoscopic resection.

The combination of laparoscopic SLN biopsy and EMR/ESD for cT1 early gastric cancer is a very attractive novel minimally invasive approach. Non-curative EMR/ESD curative and subsequent laparoscopic limited gastrectomy or full-thickness endoscopic resection combined with SLN navigation surgery has the potential to become the standard minimally invasive surgery for patients with early gastric cancer.

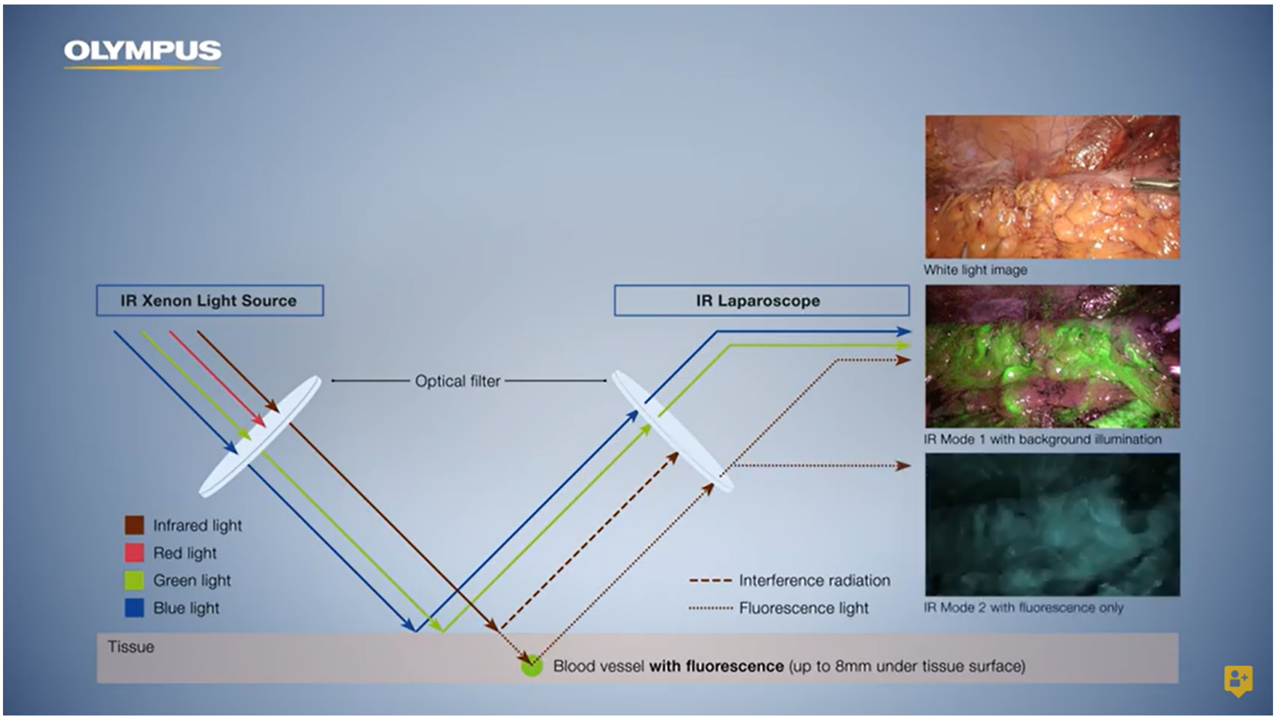

Figure 3 Olympus Visera Elite II near-infrared fluorescence imaging system. Copyright and courtesy of Olympus Europa SE & Co.KG, Hamburg, Germany.

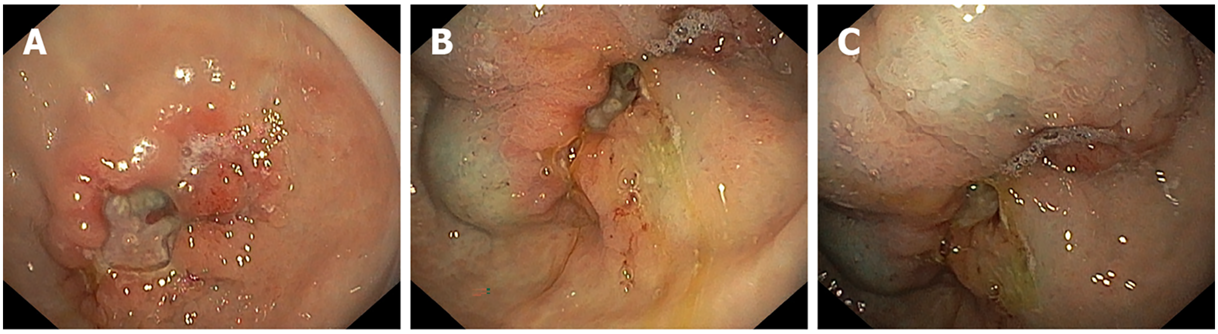

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Figure 4 Endoscopic submucosal indocyanine green injection in the stomach. A: Pre-pyloric neoplastic lesion; B: Appearance after two submucosal indocyanine green (ICG) injections; C: Appearance after four circumferential submucosal ICG injections.

CONCLUSION

ICG fluorescent lymphography is an attractive and feasible option in gastric cancer surgery. Endoscopic SM injection of ICG the day before surgery is a simple and effective approach. Alternatively, intraoperative SS staining is feasible. ICG staining increases LN visualization and increases the number of LNs retrieved during surgery. Currently, ICG staining is encouraged in cases of D1-D2 Lymphadenectomy because it has been shown to facilitate LN dissection and to increase the number of LNs harvested. However, ICG staining does not increase the number of metastatic LNs retrieved. ICG-guided SLN navigation surgery is a promising technique to reduce unnecessary extensive lymphadenectomy and gastric resection in patients with cT1. It may also be useful after a non-curative ESD.

However, further research worldwide and technique standardization are necessary to confirm the utility of ICG staining of SLNs. Current studies typically have small sample sizes, and there is a large number of studies from Asia, which has different experience from other areas due to the higher prevalence of gastric cancer in Asia. Another challenge is the low sensitivity of ICG staining of LNs that are not retrieved, which represents a potential risk of metastasis and prevents an exclusively ICG fluorescence-guided LN dissection. At this time D1/D2 Lymphadenectomy remains the standard of care for patients with gastric cancer with suspected cancer cell metastasis.

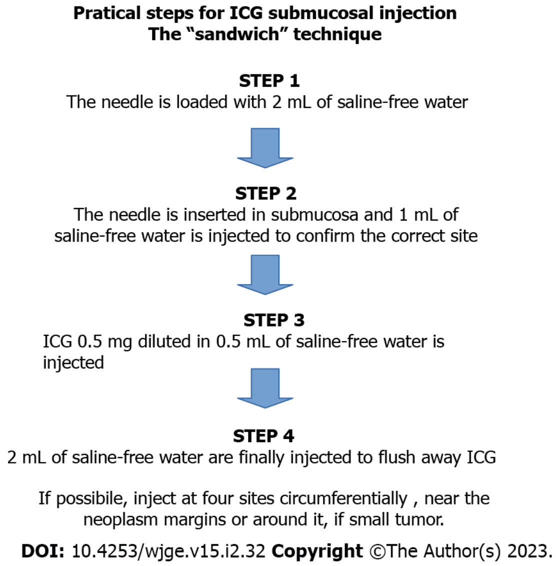

Figure 5 Practical steps for submucosal indocyanine green injection. ICG: Indocyanine green.

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FOOTNOTES

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MINIREVIEWS

Buried bumper syndrome: A critical analysis of endoscopic release techniques

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Abstract

Buried bumper syndrome (BBS) is the situation in which the internal bumper of the gastrostomy tube, due to prolonged compression of the tissues between the external and the internal bumper, migrates from the gastric lumen into the gastric wall or further, into the tract outside the gastric lumen, ending up anywhere between the stomach mucosa and the surface of the skin. This restricts liquid food from entering the stomach, since the internal opening is obstructed by gastric mucosal overgrowth. We performed a comprehensive search of the PubMed literature to retrieve all the case-reports and case-series referring to BBS and its management, after which we focused on the endoscopic techniques for releasing the internal bumper to re-establish the functionality of the tube. From the "push" and the "push and pull T" techniques to the most sophisticated-using high tech instruments, all 10 published techniques have been critically analysed and the pros and cons presented, in an effort to optimize the criteria of choice based on maximum efficacy and safety.

Key Words: Buried bumper syndrome; Percutaneous endoscopic gastrostomy; Endoscopic release techniques; Review

Core Tip: Buried bumper syndrome is the situation in which the internal bumper of the gastrostomy tube migrates from the gastric lumen into the gastric wall and thus its internal opening is obstructed by gastric mucosal overgrowth. We performed an analysis of the endoscopic techniques described in the literature for releasing the internal bumper to re-establish the functionality of the tube, in an effort to optimize the criteria of choice based on maximum efficacy and safety.

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INTRODUCTION

Buried bumper syndrome (BBS) is a rare but serious complication of percutaneous endoscopic gastrostomy (PEG) with one reported incidence of 0.3%-2.4% per PEG-patient per year[1-5], elsewhere raised from 2.0% to 6.7% of PEG placements[6,7]. This complication was first reported for 7 out of 125 PEG placements over a 2-year period in 1988[8], while two years later, in 1990, Klein *et al*[9] coined the term BBS and successfully treated their cases by pushing the gastrostomy tube into the stomach with a Savary dilator from outside.

The term BBS describes the situation in which the internal bumper of the gastrostomy tube migrates from the gastric lumen into the gastric wall or further, in the tract outside the gastric lumen, ending up anywhere between the stomach mucosa and the surface of the skin. Once the bumper has migrated, the gastrostomy track collapses, with subsequent epithelialization of its inner stoma with gastric mucosa of normal appearance, thus leading either to partial obstruction, leaving a thin fistula towards the stomach lumen, or to complete obstruction[3]. This results in mechanical difficulty or complete failure of feed delivery, rendering the tube useless[10].

BBS is thought to occur because of excessive and prolonged compression of the tissues-stomach plus abdominal wall-sandwiched between the external and internal fixators (bumpers), causing ischemia of the mucosa and subsequent ulceration at the bumper site[5,11], and finally leading to "burying" of the PEG bumper in the gastric wall[12]. A rigid or semi-rigid bumper, such as those made of polyurethane are considered more vulnerable to this pathogenesis[13]-the Sacks-Vine PEG system has been targeted on several occasions, and this is obviously the reason for the high rates of BBS in the bibliography[5,7].

An incompletely buried bumper can usually be easily removed, endoscopically, by using a pair of grasping forceps or a snare from the inside, while simultaneously pushing the tube from the outside. However, the management of a completely buried bumper is more challenging: Several methods have been proposed in case reports of one or two patients or, in some cases, a series of patients, but only some of them have been re-applied by other endoscopists, and none has yet been standardized, as it is likely that different treatment options are better for particular patients[14,15].

In the present analysis, we review all the published endoscopic techniques used over a 30-year period to release the buried internal bumper to re-establish the gastrostomy tube's functionality (Figure 1).

DESCRIPTION OF TECHNIQUES

The "push" technique

Klein *et al*[9] were the first to coin the term "buried bumper" syndrome, and the first to describe a simple technique to dislodge the buried bumper from the gastric mucosa. Fortunately for their cases, the continuity of the tube was still not totally obstructed, although the internal bumper was completely covered by the gastric epithelium; thus, passing a guidewire from the outside into the gastrostomy tube which has been cut short previously was the first step. A Savary dilator was then loaded over the guidewire and force was applied perpendicular to the abdominal wall, leading to the release of the internal bumper within the stomach lumen (Figure 2A).

The same technique was also described three years later by Gumaste *et al*[16], the only difference being that no guidewire was used. They simply shortened the tube externally and introduced a 36F Savary dilator into it, from the outside. The pressure was then applied to successfully dislodge the bumper from the mucosa and release it into the gastric lumen.

Similarly, Binnebösel *et al*[17], after cutting the external tube to a length of 5 cm, carefully inserted it into the gastric lumen, under endoscopic guidance, a 27-cm long, stainless steel probe with a diameter of 3 mm and a 3 cm tip with a narrowed diameter (2 mm). Slight pressure and gentle manipulation of the

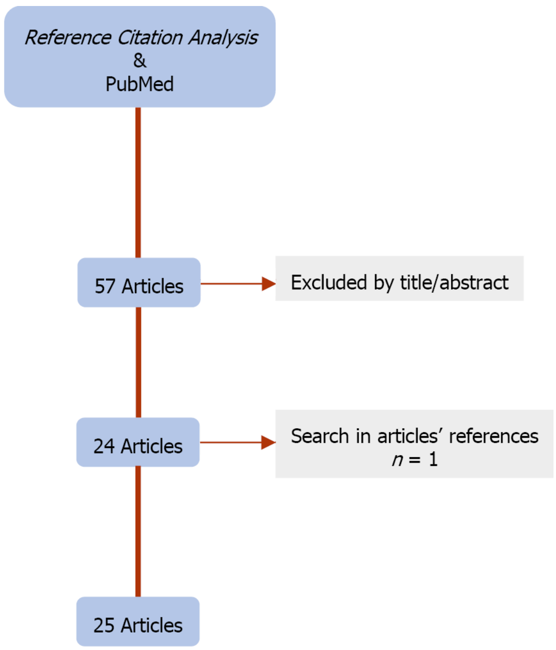

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Figure 1 Flow diagram of our Research Strategy.

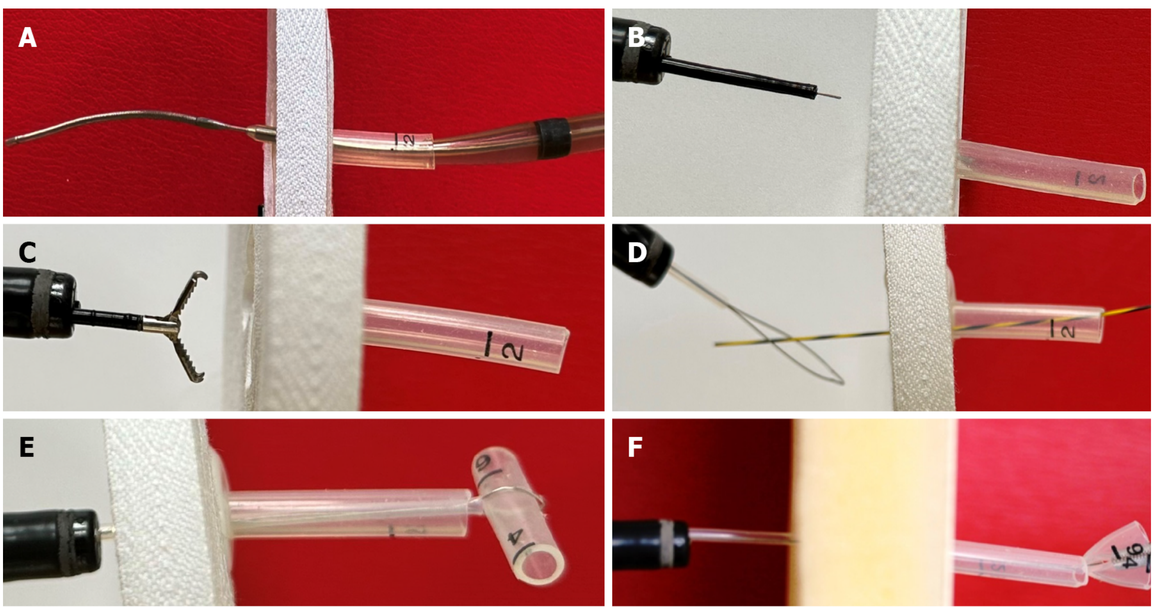

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Figure 2 Description of techniques. A: The "push" Technique: A Savary dilator loaded over the guidewire forced from the outside towards the gastric lumen to release the bumper into the stomach; B and C: The "needle-knife" technique: A pre-cut device was used first and then an alligator forceps pulls the bumper towards the stomach; D-F: The "push-pull T" technique: A T-piece attached to a snare is used to pull the bumper into the stomach.

PEG tube enabled the bumper to be easily luxated, through the mucosa, into the gastric lumen. A standard polypectomy snare was then passed through the gastroscope to grasp the PEG tube distally to the bumper. Following removal of the probe, the PEG tube was then able to be removed through the mouth along with the gastroscope.

The "needle-knife" technique

A few years after the first technique description, Ma *et al*[1] used a needle-knife papillotome to safely release the inner bumper. Unlike the previous technique, "violently" tearing away of the mucosa which had grown, was avoided. Using this pre-cut device, radical incisions into the gastric mucosa, from the center of the dome outwards, were made; the precise direction of the cuts was determined by external manipulation of the tube, to better expose the inner bumper under the mucosa. Final removal was then facilitated by grasping and pulling the bumper towards the gastric lumen with alligator forceps or a snare (Figure 2B and C).

Ma *et al*[1] applied their technique to a total of 9 BBS cases, in which the buried bumper was from a MIC-type gastrostomy tube.

Frascio *et al*[18], using the needle-knife technique proposed by Ma *et al*[1], failed to expose the internal bumper to remove a Sacks-Vine gastrostomy, performed 7 years previously. Then, subsequently, under local anesthesia, with a guidewire in place, two small cutaneous incisions were made, one on each side of the external part of the PEG tube, down to the bumper. The tube and bumper were then removed along the guidewire, without any opening of the peritoneum.

In the same manner, as Ma *et al*[1], El *et al*[2] initially inserted a flexible straight Teflon guidewire under endoscopic control from outside, and clamped the PEG tube over the wire, to allow adequate air insufflation of the stomach. Using the guidewire as the central point, cruciform incisions were made on the mucosal "dome" covering the internal bumper by using a needle-knife sphincterotome or an electrosurgical knife. During incisions, the PEG tube was gently pushed internally to allow stretching of the covering mucosa. When the bumper was completely revealed, rat-tooth forceps or a snare-through the gastroscope-was used to withdraw the PEG tube.

This technique was applied in 8 cases.

The "push-pull T" technique

Boyd *et al*[19] presented the "push-pull T" technique, citing the advantage of requiring only materials normally readily available in every endoscopic suite. The external part of the gastrostomy tube was first cut short, 3 cm above the skin. An endoscopy was performed, and a polypectomy snare was advanced toward the lumen of the buried bumper to exit *via* the tube. If the internal lumen opening was covered, a 0.035 soft-tipped guidewire was pushed from the outside and upon entry to the gastric lumen, it was grasped with the snare loaded to the gastroscope. The external end of the guidewire was then pulled manually, dragging out the snare through the gastrostomy tube. When outside, a 2-cm piece of the gastrostomy tube was inserted into the snare loop and securely grasped. The snare was pulled back from inside the gastroscope, to bring the short piece of the tube tight against the end of the external part of the gastrostomy, creating a "T" effect-hence the name of the method. A pair of Kelly clamps were used to secure the T-piece in place, tight against the residual PEG tube. The endoscope, snare, and attached T-piece were then slowly drawn back by the endoscopist, while an assistant pushed the Kelly forceps and the gastrostomy tube into the gastric lumen from outside. Once within the stomach, the Kelly forceps were released and the gastrostomy tube plus the T-piece was removed, along with the gastroscope (Figure 2D-F).

Horbach *et al*[20] completed this technique by proposing the following: first the use of a Hegar dilator inserted through the external part of the PEG tube to make it protrude into the gastric lumen. If it did not easily protrude, they incised the mucosa radially down to the central dome of the bumper either with a needle papillotome or the tip of a polypectomy snare. Once the gastric opening of the bumper became apparent, a snare was led through it and pushed to the external end of the tube, as previously. However, Horbach *et al*[20] proposed a 5-cm cut-off piece of the tube, instead of 2 cm, to be grasped by the snare; thus, by pulling the snare back into the stomach it formed an arrow shape, which more easily freed the bumper from the gastric mucosa towards the gastric lumen.

This technique was applied in 18 BBS patients-however, depending on the difficulty of each case, the buried bumper needed up to 5 sessions to be totally revealed.

The "new PEG against the old" technique

Venu *et al*[3] described by far the easiest technique for the removal of a gastrostomy with a buried internal bumper. The external part of the gastrostomy tube was cut 3 cm to 4 cm above the skin level. The long needle of a new PEG kit was inserted through the shortened tube stump under endoscopic control and advanced through the buried bumper to protrude into the gastric lumen, exactly as when a new gastrostomy is performed. Once in the lumen, the thread of the PEG kit was advanced through the needle and grasped with a snare introduced through the biopsy channel of the endoscope; the thread, along with the endoscope, was brought out/retrieved through the mouth. The thread was then looped onto the new PEG tube and pulled back through the mouth towards the stomach, by simply gentle traction from its external edge. The sense of slight resistance indicated engagement of the tapered tip of the new PEG tube in the lumen of the buried bumper. The stump of the old tube was then straightened sufficiently to facilitate traction and the stump tube with the buried bumper, followed by the new PEG tube, finally emerged through the abdominal wall. The old PEG was removed and the new one stabilized in the standard fashion (Figure 3A and B).

Similarly, Monib *et al*[21] used a guidewire passed from outside into the gastric lumen, instead of the needle and thread, to attach it to the distal end of a new PEG tube and continued the procedure as previously described. In order to facilitate the passage of the guidewire towards the gastric cavity they used a simple trick for the identification of the dimple corresponding to the center of the internal bumper: The water jet technique. This technique, initially proposed by Vu[22], involves flushing normal saline into the PEG tube from the outside and looking carefully from the inside-endoscopically. Despite some resistance, a small amount of fluid was finally observed trickling from the dimple.

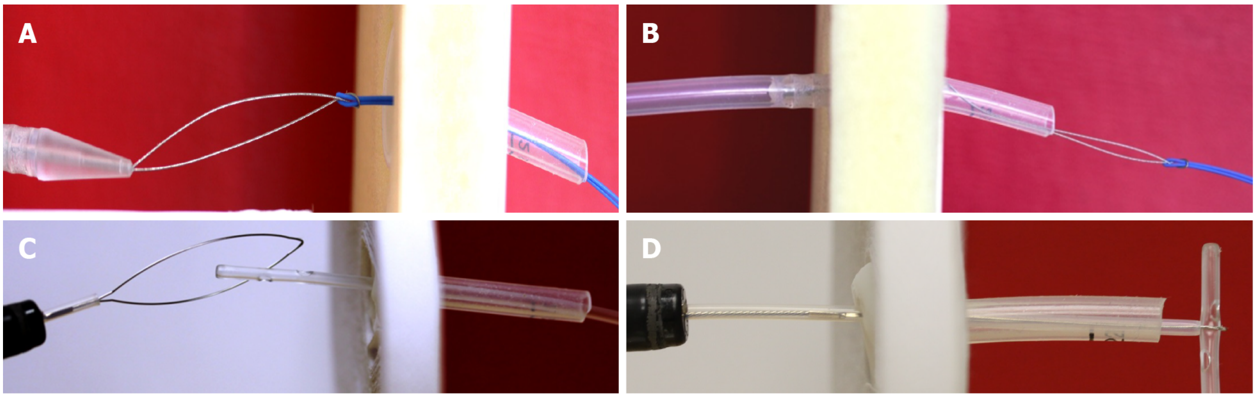

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Figure 3 Description of techniques. A and B: The "new PEG against the old" technique: A new, pull-type, gastrostomy pushed the buried bumper from inside the stomach; C and D: The "snare" technique: A polypectomy snare was used to grasp the catheter inserted from the outside. Traction applied to the snare, leads to dislodging the buried bumper.

The "snare" technique

Leung *et al*[11] proposed a new technique with two alternative options. Initially, the external part of the gastrostomy tube was shortened to about 5 cm to 7 cm and a ureteric catheter was passed through up to the gastric lumen, identified under endoscopic vision; after which the external part of the gastrostomy tube was securely tied over the ureteric catheter. A polypectomy snare, brought down through the endoscope, was used to grasp the intragastric part of the ureteric catheter. Traction was then applied to the snare, leading to the inversion of the tube and thus dislodging the buried bumper (Figure 3C and D).

Alternatively, the ureteric catheter was not tied to the gastrostomy tube. A polypectomy snare, advanced through the endoscope, was used to grasp the ureteric catheter; simple traction of the catheter from the outside guided the snare out through the shortened gastrostomy tube. The snare was then closed around the tip of the tube and traction applied to, as previously, to pull the gastrostomy tube into the stomach.

This technique was then a slightly modified by Turner *et al*[23], who replaced the urinary catheters, inserted from outside, with stent-grasping forceps in order to grasp the polypectomy snare advanced through the gastroscope-and bring it out through the short gastrostomy tube. A pair of scissors was used to cut the gastrostomy tube further as closely as possible to the skin surface; the snare then being pushed as far as possible down the tube to enfold the tube. By this method, after traction was applied to the snare, the PEG tube stump was not inverted, as previously, but became "concertinered" and popped through the mucosa.

The "papillotome" technique

In eight patients Müller-Gerbes *et al*[24] developed and evaluated another endoscopic technique for buried bumper release. A standard papillotome was inserted from the outside through the shortened PEG tube and over a guidewire into the stomach, under endoscopic control. Then the papillotome was bent and drawn back until its cutting wire was over the mucosa covering the internal bumper. Radical cutting was performed in at least 3 directions, by externally rotating the device over the bumper. After the sufficient release of the bumper, the papillotome was removed and a dilator was inserted in order to push the bumper from outside towards the gastric lumen; from which it was removed as a foreign body (Figure 4A).

Eight years later Müller-Gerbes *et al*[10], in a comparative study reported their experience in 82 cases, the largest series so far, 35 of which (42.7%) were successfully treated with a wire-guided papillotome.

Cyrany *et al*[4] modified the technique proposed by Müller-Gerbes *et al*[24] and applied it to 22 buried bumper cases. After a guidewire was inserted from outside, the overgrowing tissue covering the internal bumper was dissected by a needle-knife papillotome and argon plasma coagulator instead of a standard papillotome; after which, a dilator was passed over the guidewire into the gastrostomy tube to stiffen it and the tube was pushed into the stomach. Finally, the bumper was retrieved with a snare.

Alternatively, in some cases, a cannulotome was inserted into the stomach over the guidewire from outside, through the shortened PEG tube, under endoscopic supervision. The cannulotome was then bent and pulled slightly from the outside, the cutting wire dissecting the overgrowing tissue covering the bumper. Attention was given to the cutting direction: from the center of the buried bumper along the long axis of the tube, the length of the cuts not exceeding the radius of the bumper-three to five cuts usually being sufficient. Additionally, to avoid air leakage around the cannulotome inserted through the PEG tube, the use of a modified part of a dilator was proposed.

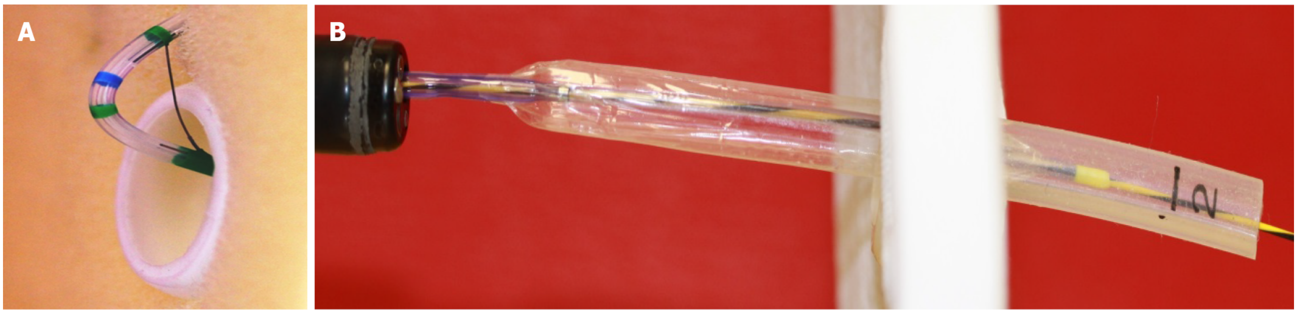

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Figure 4 Description of techniques. A: A standard papillotome was inserted from the outside under endoscopic control, bent, and drawn back, to perform at least 3 radical cuttings in the mucosa covering the bumper; B: The "balloon dilator" technique: A balloon dilator was endoscopically advanced to meet a guidewire inserted from outside; then was pushed over the guidewire into the tube and inflated to remain impacted. Traction of the balloon allowed the extraction of the bumper.

The same technique as that of Müller-Gerbes *et al*[24], slightly modified, was described again in 2014 by Born *et al*[25], who inserted a conventional Erlangen papillotome, instead of a standard one, over the guidewire into the stomach, and made incisions in all four directions. Then, a 10Fr bougie was advanced from the outside into the tube for stabilization, and all pushed into the stomach.

The "Flamingo" technique

Based on the Müller-Gerbes *et al*[24] technique, an endoscopic set, the Flamingo set (Medwork, Höchstadt, Germany), exclusively for radial incision of the granulomatous tissue over a buried bumper, was designed. This set contains the Flamingo device, a papillotomy-like catheter having a U-shape configuration at its end-the cutting wire being 30 cm in length for easy manipulation, a 35-gauge guidewire, and forceps for foreign body removal.

Hindryckx *et al*[26] were the first to use this commercially available Flamingo set, in 5 cases. The Flamingo device was introduced from the outside, through the shortened PEG tube, into the gastric lumen over a pre-inserted guidewire; it was then flexed by 180 degrees, into an inverted "U"-like the neck of a flamingo bird-to expose the bow-string, sphincterotome-like, cutting wire. Using an electrosurgical generator, at least 4 radial cuts were performed to expose the internal bumper, the PEG finally being released into the gastric lumen after external manipulation and retrieved endoscopically, using a snare or grasping forceps.

At the same time, Costa *et al*[27] presented a video case, while two years later Costa *et al*[28] reported a multicenter study comprising 53 cases.

The "endoscopic submucosal dissection devices" technique

Curcio *et al*[29] applied the endoscopic technique of endoscopic submucosal dissection (ESD) to un-roof the gastrostomy tube internal bumper. A guidewire was initially inserted through the PEG tube from the outside into the gastric lumen. An 8F feeding tube was then inserted over the guidewire to be used at the central point of the mucosal area to be dissected. Progressive radial endoscopic submucosal dissection was then performed using a water-jet Hybrid-knife T-Type (ERBE, Tübingen, Germany), until the whole bumper was exposed and the endoscopist was able to safely capture it first with rat-tooth forceps and then with a polypectomy snare, for removal through the mouth.

Wolpert *et al*[30] described a new endoscopic technique in which they mainly replaced the cutting of the overlying bumper mucosa using a Hook knife instead of a needle knife. This is a rotating L-shaped cutting wire designed for hooking tissue and pulling it away from the gastric wall, towards the lumen. They initially used a 15 mm through-the-scope dilation balloon passed externally *via* the PEG tubing and inflated to dilate the mucosal orifice. A Hook knife was deployed through the gastroscope to incise the gastric mucosa over the buried bumper by hooking the tissue, pulling it towards the lumen and then cutting it using diathermy under direct vision. The balloon dilator was then inflated again into the PEG tube to stiffen it; both the tube and the balloon catheter were clamped together and pushed toward the gastric lumen to force the bumper to exit into the stomach. The PEG was then removed as a foreign body.

Lazaridis *et al*[12] proposed the use of a 2.5-mm ball-tip, needle-type irrigation knife to dissect the overgrowing gastric mucosa, in order to insert biopsy forceps through the external opening of the PEG tube. This manipulation opened the track for insertion of the sphincterotome over a guidewire, as previously described. After the cuttings were performed, a 6-mm endoscopic balloon dilator was passed through the endoscope, and not from the outside, as proposed by Wolpert *et al*[30], fully inflated into the PEG tube, and traction was applied-as opposed to previously described pushing from outside into the stomach.

Nakamura *et al*[31] described buried bumper removal by means of a needle knife for mucosal incision and then an insulation-tipped diathermic knife for submucosal dissection of the bumper-covering mucosa. Upon free movement of the bumper, it was transabdominally removed through the fistula towards the gastric lumen and then through the mouth, along with the gastroscope.

The "balloon dilator" technique

Strock and Weber[32] used a method whereby a guidewire was inserted into the stomach through the lumen of the gastrostomy tube cut to 3 cm. An esophageal balloon dilator was then advanced through the endoscope into the stomach and manipulated into the gastrostomy lumen to meet the guidewire for insertion. Once insertion was achieved, the balloon was fully inflated so that it remained impacted in the tube. Traction of the balloon and the endoscope allowed the extraction of the bumper first and then, more easily, of the remaining gastrostomy catheter into the stomach. Afterward, the PEG catheter was removed from the stomach as a foreign body (Figure 4B).

The same technique was also successfully applied and then published as "a single step" maneuver by Christiaens *et al*[33], nine years later.

The "NOTES" technique

In the pick of "experimentation" with the innovative, most proposed endoscopic modality of surgery through natural orifices, Marks JM and the pioneer in percutaneous endoscopic gastrostomy, Marks *et al* [34] published a case of the successful rescue of a PEG tube in a neurological severely ill patient whose gastrostomy was inadvertently dislodged 3 d after PEG placement. A Folley catheter inserted immediately to maintain the tract failed to be inserted into the stomach. Thus, under conscious sedation only, with the patient in the intensive care unit, an intragastric abdominal exploration was performed: A standard gastroscope was inserted into the stomach and advanced through the previous gastric opening where the PEG tube had passed into the abdominal cavity. A guidewire was inserted into the peritoneal cavity through the external PEG site, grasped using a snare advanced through the endoscope, and brought back into the stomach and out through the mouth. A standard pull-technique PEG was then successfully inserted.

Six years later, Nennstiel *et al*[35], in an effort to treat a BBS in a 52-year-old tetraplegic patient, started by using a needle knife papillotome to reveal the PEG lumen; then, in an effort to push the tube from outside into the stomach with a bougie, the gastrostomy was, accidentally, totally dislodged from the gastric wall and fell into the peritoneal cavity. A pediatric gastroscope was then inserted into the stomach and advanced into the peritoneal cavity through the gastric opening in the anterior gastric wall. The PEG tube was grasped and brought back into the stomach and out through the mouth, while a new PEG was advanced through a guidewire inserted from outside into the peritoneal cavity, grasped with biopsy forceps and transferred, similarly, through the stomach out, through the mouth.

In recent years, the NOTES procedures are no longer used in daily practice. These techniques must therefore be kept only as an innovative idea from the past.

THE EFFECTIVENESS OF TECHNIQUES

The effectiveness of the techniques we have described practically cannot be evaluated, since they comprised improvisation by physicians in order to rescue the embedded internal bumper, in one or more cases, which were then published as a report of a case or a series. The procedure was never or rarely repeated exactly as described and never published again. Usually, with a particular technique as a basis, modifications/variations are applied, either because the endoscopist thinks these changes to be more effective, or because the specific instrument/s are not available, or, finally, because new, modern apparatus is available. The only exception was that of Furlano *et al*[36], who reported their difficulties in recovering a Freka-PEG-which has a hard, thin disk beneath which is an internal tubular crosspiece, also of hard plastic, not removable with traction from the outside- in a 2.5 year-old boy. They first, ineffectively, tried using forceps and then a snare; and then the method proposed by Leung *et al*[11]-which also failed. Finally, they tried the push-pull T technique proposed by Boyd *et al*[19], which succeeded. This publication was not used to suggest that the latter technique was better than the former. On the other hand, we pose the question as to whether the success of a method depends-apart from the depth of invasion of the internal bumper into the gastric wall-on the material of which it is made and its configuration.

Overall, it is not fair to compare the techniques with each other for effectiveness-each technique proved to be effective, as long as it had the desired end result for the patient, without apparent complication. The only exception is a comparative study by Müller-Gerbes *et al*[10]. In a cohort of 82 BBS cases, the largest series published, they compared 35 (42.7%) patients treated with a wire-guided papillotome with 22 (26.8%) treated with a needle-knife, in terms of bleeding. No bleeding was recorded after using the standard papillotome, but bleeding occurred in 7 patients (31.8%) after cutting with a needle-knife papillotome ($P < 0.05$). Furthermore, ten of the 22 patients (45.5%) treated with the needle knife experienced a serious adverse event and 1 patient finally died (4.5%).

Finally, we have to add a recent, retrospective study derived from 15 Gastroenterology Departments and comprising 53 BBS cases, for whom the commercially available Flamingo device, first tested by Hindryckx *et al*[26], was used for completely covered internal bumpers[28]. They reported a success rate of 96.4% (53 out of 55 procedures), but also a 12.7% rate (7 cases) of adverse events, all endoscopically managed. Adverse events were: Significant bleeding in 4 patients (7.3%), a small perforation in 2 patients (3.6%), a superficial laceration of the gastroesophageal junction during PEG extraction in 1 patient (1.8%), and sepsis within 48 h from the buried bumper removal, in 2 patients (3.4%).

DISADVANTAGES AND COMPLICATIONS

Mention should also be made of the disadvantages and complications from the application of these techniques, either as reported by the authors themselves, or as assumed in the comments of other authors, usually to support their own point of view and/or to promote their own modified technique as being more effective or safe (Table 1).

The cutting devices, such as the needle-knife papillotome, came into use as early as 1995 by Ma *et al* [1], are easier to use than cutting devices inserted from the outside, since they are applied through the endoscope, from the gastric lumen side[2,4], but carry the risk of an unpredictable bleed or perforation of the gastric wall. According to Hindrycks *et al*[26] the needle knife may fail to un-roof the buried bumper, because of a too-deep ingrowth of the bumper, as occurred in one of their cases. On the other hand, it is a common instrument in every endoscopic suite and can be easily handled by any endoscopist who is able to perform a sphincterotomy.

The standard papillotome, as the instrument proposed initially by Müller-Gerbes *et al*[24] to cut the mucosal tissue covering the internal bumper, is not designed for this procedure and hence, has less curving potential and less ability to rotate in order to make incisions in a stellate fashion. Moreover, a papillotome, like every other endoscopic apparatus, has a working length of about 200 mm, enough to pass and exit from an endoscope; it is thus too long to be easily manipulated out of the endoscope, as occurs when inserted from the skin side through the lumen of the gastrostomy tube into the stomach. Another disadvantage is the lack of rigidity throughout the 200 mm body, since it is designed to pass through, and therefore be supported by, the working channel of the gastroscope. It may, however, gain when inserted over a guidewire. Despite these difficulties, Müller-Gerbes *et al*[10] published their experience in 82 BBS cases, 35 of which (42.7%) were successfully treated with a wire-guided papillotome. The same applies to the conventional Erlangen papillotome used, over the guidewire, by Born *et al*[25] in an effort to modify the Müller-Gerbes technique.

The newest technological devices, such as the ERBE Hybrid-knife and the Olympus Dual-knife, Hook-knife, and insulation-tipped diathermic knife, designed for ESD procedures, are, of course, much safer and easier to handle[12,29,31]; however, these instruments are not among the standard equipment readily available in every endoscopy unit. Additionally, Hindryckx *et al*[26], reporting the use of the Hybrid-knife and Dual-knife in two BBS cases, revealed that the procedure took more than one hour to successfully complete. Perhaps the rotatable, L-shape Hook-knife may be safer, or simply give a sense of safety, since it is designed for hooking the tissue and pulling it away from the gastric wall towards the lumen and then cutting it using diathermy under direct vision, thus reducing the risk of inadvertent gastric perforation, as may occur when cutting towards the gastric wall[30].

DISCUSSION

The buried bumper syndrome is mainly attributed to excessive tissue compression-close around the site of tube passage-between the inner and outer bumpers of the gastrostomy. This prolonged pressure causes progressive tissue ischemia and subsequent gastric mucosal ulceration, leading to the lodging of the inner bumper in the gastric mucosa and further on into the gastric or even the abdominal wall tissues. In parallel, the mucosal healing process causes gastric mucosa to grow over the embedded inner bumper to cover the gap, leading to the progressive loss of its viability with regard to feeding delivery. Another mechanism proposed to be involved in the impaction of the internal bumper into the gastric mucosa is the traction of the tube toward the outside by the confused patient or accidentally by the caregiver, with a force insufficient to dislodge the gastrostomy tube totally from the abdominal wall, but to move it outwards sufficiently for it to be impacted somewhere between the mucosa and beneath the skin[13,23,37].

Although nothing can be proven without a double-blind observational study, the first argument is supported by the report of El *et al*[2], who found a very low incidence (0.9%) of BBS in a total of 879 patients subjected to PEG. They consider the main reason for this low complication rate in their patients to be the existence of a Nutrition Team supporting in- and out-patients, taking special care to “push, pull and rotate the PEG tube frequently in the early post-insertion period”, as the best way to prevent BBS. They additionally took great care to check against the placement of gauze pads underneath the external bumper[15], since this practice carries the risk of slightly pulling the gastrostomy outward, the

Table 1 Advantages and disadvantages of each endoscopic technique

No.	Technique	Cases[1]	Advantages	Disadvantages
1	The "push"[16,17]		Need of readily available endoscopic instruments	Applied to gastrostomy tubes removable only through the mouth
2	The "needle-knife"[1,2,18]	17	Easier to use through the endoscope, a common instrument	Applied to gastrostomy tubes removable only through the mouth; risk of bleeding/perforation
3	The "push-pull T"[19,20]	18	Need of readily available endoscopic instruments	Applied to gastrostomy tubes removable only through the mouth; need of multiple sessions, traumatic
4	The "new PEG against the old"[3,21,22]		Simple to be applied	Applied only in gastrostomy tubes able to be removed by traction
5	The "snare"[11,23]		Need of readily available endoscopic instruments	Applied to gastrostomy tubes removable only through the mouth
6	The "papillotome"[4,24,25]	112	The largest series published [24]	Applied to gastrostomy tubes removable only through the mouth; too long/not easily manipulated, lack of rigidity; difficult in handling endoscopic instruments out of the endoscope
7	The "Flamingo"[26]	58	Commercially available	Applied to gastrostomy tubes removable only through the mouth; bleeding/laceration/sepsis; Cost???
8	The "ESD devices"[12,29-31]		Easy to handle in experienced hands	Applied to gastrostomy tubes removable only through the mouth; not standard equipment; need of experience in ESD; Cost???
9	The "balloon dilator"[32,33]		Instruments readily available in an endoscopic suite	Applied to gastrostomy tubes removable only through the mouth
10	The "NOTES"[34,35]	2	Peritoneoscopy through a natural orifice (mouth)	Applied to gastrostomy tubes removable only through the mouth; no longer in clinical practice

[1]Number of cases referred to have been treated by the author.

PEG: Percutaneous endoscopic gastrostomy; ESD: Endoscopic submucosal dissection.

second scenario of the etiology of BBS is also verified.

In addition to the above, the incidence of BBS appears to be directly related to both the material of the bumper and its design. As early as 1995, both Ma *et al*[1] and Boyd *et al*[19] commented that among the published cases of buried bumper syndrome, most occurred among those having the Sacks-Vine feeding tube[8,38]; the propensity of this particular product to "migrate" into the gastric wall being attributed to both the composition and design of the inner bumper[9]. It was constructed from Tecoflex, a hard, medical grade, polyurethane and had a narrow, 2.4 cm long T-piece-design of internal bumper, beneath which lay an internal tubular crosspiece of hard plastic. Both this gastrostomy tube as well as the newest of similar design, were not removable by traction from the outside-all having a hard, thin, circular disk or triangle shaped internal bumper, which was totally inflexible. The design of such internal bumpers involves only a small surface area being in direct contact with the gastric mucosa, which may predispose it to increased local tissue pressure and necrosis, and thus the risk of impaction into the gastric mucosa[5,6,19].

In reinforcement of the above, the incidence of BBS seems to have decreased nowadays. Although the reported incidence of this complication is poorly assessed, coming only from series (larger or smaller) of patients from the same centre, there is a feeling that this frequency has decreased with the passing of the years. This can be attributed to the more sophisticated design of the tubes, and especially of the internal bumper, and of the more tissue-friendly materials, although there are still centres that traditionally stick to the use of gastrostomy catheters requiring endoscopy for their removal; and such catheters are generally harder and more rigid[39].

Whatever the mechanism by which the internal bumper gets buried, the material used, the internal bumper design and the degree of bumper impaction into the gastric wall, every endoscopist should be able to diagnose and treat this condition. The instrumental manipulation for recovering the bumper must be a safe procedure, for both the patient, being per se extremely fragile, as well as for the operator-endoscopist. And such a person cannot be someone who simply knows how to perform a gastrostomy, although, generally speaking, no one has a reasonable degree of experience in dealing with such cases because of their infrequency-0.25% of PEG patients per year-even in reference centres[20]. The use of the needle-knife might lead to complications, mainly gastric perforation, which is a much more serious event in comparison to leaving a gastrostomy buried and inactive[40]. On the other hand, the familiarity of some endoscopists with modern, complex invasive techniques, such as POEM, makes them extremely capable of removing a buried bumper-much more easily than a gastric tumor; so they no longer consider it necessary to publish it as yet another case report.

Coming now to the different techniques previously presented, it is true that in general, we cannot advise which method is the most appropriate, since its success depends on the very specific circumstances of each case, the first criterion being the type of PEG, with respect to the method of removal. When a gastrostomy can be removed by simple traction from outside, the only difficulty is the pushing of the guidewire from outside into the gastric lumen; where upon a new gastrostomy can be passed, either as a replacement tube from outside over the guidewire or as a new one pulled from the mouth. On the other hand, the necessity for endoscopy to remove any apparatus by mouth is what presents the greatest difficulty and which has led to the development of so many alternative techniques. Furthermore, it must be kept in mind that this type of tube is generally made from less flexible material, making the deep impaction of the bumper into the gastric tissue more likely.

The endoscopist should know in advance the exact type of the gastrostomy tube he has to deal with, since the internal bumper configuration will be of importance for the final decision as to the optimal removal strategy. This is why Braden *et al*[15] used endoscopic ultrasound to successfully localize the internal bumper in 11 patients. Unfortunately, the publications from which the techniques were retrieved are essentially reports of a single case or small case series. And most importantly, the majority of them do not mention the type of gastrostomy involved; only opportunely in some can we make deductions from the photos they provide. It is clearly one thing to try to uncover a dome-shape gastrostomy and quite another to have a Freka-type or formerly Sachs-Vine hard collar which cannot be pulled out.

Finally, the endoscopist should keep in mind that, when the removal of a gastrostomy needs endoscopy, the bumper must be almost completely exposed, and an invasive endoscopy takes time and is definitely burdensome for the patient, if we also take into account the general physical condition, age and underlying diseases; which is why there is always the option to “cut and leave alone”[40].

CONCLUSION

In conclusion, carefully performed and technically perfect gastrostomies, using high quality materials, in conjunction with post-operative care to avoid excessive pressure of tissues between bumpers will minimize the incidence of BBS. When the BBS case occurs, the ideal procedure has not yet been discovered; thus, the least invasive technique must be applied to solve the problem and subject the already severely ill patient to the least burden possible. In all cases, the success rate, procedure time, and, why not, the cost-effectiveness of the technique to be used should be assessed by the endoscopist in advance.

FOOTNOTES

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ORIGINAL ARTICLE

Case Control Study

Study of wrist-ankle acupuncture therapy for optimizing anaesthesia scheme of painless gastroscopy and improving painless gastroscopy related complications

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Abstract

BACKGROUND

Painless gastroscopy is a widely used diagnostic and therapeutic technology in clinical practice. Propofol combined with opioids is a common drug for painless endoscopic sedation and anaesthesia. In clinical work, adverse drug reactions of anaesthesia schemes are often one of the important areas of concern for doctors and patients. With the increase in propofol dosage, the risk of serious adverse drug reactions, such as respiratory depression and hypotension, increases significantly; the use of opioids often causes gastrointestinal reactions in patients after examination, such as nausea, vomiting, delayed recovery of gastrointestinal function and other complications, which seriously affect their quality of life.

AIM

To observe the effect of wrist-ankle acupuncture therapy on the anaesthesia regimen and anaesthesia-related complications during and after painless gastroscopy examination.

METHODS
Two hundred patients were selected and randomly divided into a treatment group (n = 100) and a control group (n = 100). Both groups were routinely anaesthetized with the nalbuphine and propofol regimen, gastroscopy began after the patient lost consciousness, and given supportive treatment and vital sign monitoring. If the patient interrupted the surgery due to intraoperative torsion, intravenous propofol was used to relieve his or her discomfort. The treatment group received wrist-ankle acupuncture on this basis.

RESULTS
The general data before treatment, American Society of Anesthesiologist (ASA) grade and operation time between the two groups was no significant difference. The Wakeup time, and the Self-ambulation time in the treatment group was significantly faster than that in the control group (P < 0.05). The total dose of propofol in the treatment group was 109 ± 8.17 mg, significantly lower than that in the control group (P < 0.05). The incidence of respiratory depression and hypotension was not significantly different, but the incidence of hiccups was significantly lower than that in the control group (P < 0.05). After the examination, the incidence of nausea, vomiting, abdominal distension, and abdominal pain was 11%, 8%, 6%, and 5%, respectively, which was significantly lower than that in the control group (P < 0.05). In addition, both the operators and the patients were more satisfied with this examination, with no significant difference between the groups (P > 0.05).

CONCLUSION
Wrist-ankle acupuncture treatment can optimize the painless gastroscopy and anaesthesia scheme, reduces propofol total dose; shortens patient Wakeup time and Self-ambulation time, improves patient compliance and tolerance, is beneficial to clinical application.

Key Words: Wrist-ankle acupuncture therapy; Acupuncture anaesthesia; Painless gastroscopy; Gastroscopy; Anaesthesia-related complications

Core Tip: The use of wrist ankle acupuncture can optimize the anesthetic regimen during painless gastroscopy, significantly reduce the total dose of propofol during the examination without affecting the examination operation and the satisfaction of the examiner and the patient, thus shortening the patient's awakening time and autonomous activity time, reducing the occurrence of hiccup during the examination and nausea, vomiting, abdominal distension, abdominal pain and other complications after the operation, It is beneficial to the development of painless gastroscopy in clinical practice, and improve the compliance and tolerance of patients.

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INTRODUCTION

Painless gastroscopy is a widely used diagnostic and therapeutic technology in clinical practice that can find common lesions of the oesophagus and stomach, such as gastritis, gastric cancer, reflux oesophagitis, oesophageal cancer, and gastroduodenal ulcer, in a timely and accurate manner[1,2]. The application of anaesthesia technology to the operation process can effectively reduce the fear and discomfort of patients, improve their compliance and tolerance during the examination process, and thus improve the detection rate of potential diseases and the timeliness of endoscopic treatment[3]. Propofol combined with opioids is one of the most commonly used anaesthetic prescriptions for painless gastrointestinal endoscopy in clinical practice and is a common drug for painless endoscopic sedation and anaesthesia[4]. The sedative and anaesthetic effect of propofol is characterized by quick onset, good drug effect and short recovery time. However, due to its lack of analgesic effect, it is often necessary to combine opioids to enhance the effect of anaesthesia and analgesia and reduce the dosage of propofol. In clinical work, adverse drug reactions of propofol anaesthesia schemes are often one of the important areas of concern for doctors and patients. On the one hand, with the increase in propofol dosage, the risk of serious adverse drug reactions, such as respiratory depression and hypotension, increases significantly; on the other hand, the use of opioids often causes gastrointestinal reactions in patients after examination, such as nausea, vomiting, delayed recovery of gastrointestinal function and other complications, which seriously affect their quality of life. Therefore, it is urgent to find a treatment plan that can reduce the dosage of propofol and the gastrointestinal reactions of patients after the examination.

Wrist-ankle acupuncture therapy is a shallow needling method[5,6] created by Doctor Zhang Xinshu according to the guidance and inspiration of the traditional Chinese medicine theory of meridians and collaterals by combining the "five needling", "twelve needling" and other acupuncture methods recorded in ancient books and records with long-term clinical practice. It has the characteristics of simple point selection, safety, simplicity, no need for electroacupuncture and other equipment, rapid and reliable effects, and no side effects[7]. Recently, the application of acupuncture anaesthesia in the field of digestive endoscopy has gradually achieved good results[8]. Therefore, this study observed the intervention treatment of patients with wrist-ankle acupuncture therapy and observed the influence of the anaesthesia scheme, drug dosage and occurrence of anaesthesia-related adverse reactions during and after painless gastroscopy. The aim was to provide a more optimized painless gastroscope gastroscope anaesthesia prescription scheme for clinical practice, help reduce the dose of anaesthetic drugs, shorten the time for patients to wake up and leave the hospital, reduce anaesthetic complications, facilitate the development of painless gastroscopy in clinical practice, and improve the compliance and tolerance of patients to treatment.

MATERIALS AND METHODS

Clinical data

This study was approved by the Medical Ethics Committee of Xiamen Hospital of Traditional Chinese Medicine and signed by all patients with informed consent.

Inclusion criteria were as follows: (1) Patients aged 18-65 years with BMI ≤ 28 kg/m^2; (2) ASA classified as I-II; and (3) No contraindication for gastroscopy.

Exclusion criteria: (1) Patients who have major diseases such as cardiovascular and cerebrovascular diseases and cannot cooperate with the examination; (2) Pregnant women; (3) Patients with propofol and opioid allergy or intolerance; and (4) Patients who take psychotropic drugs or drugs that affect the blood coagulation function before the operation.

General information: From January 2022 to July 2022, 200 patients without major diseases who were selected from the endoscopic treatment room of Xiamen Traditional Chinese Medicine Hospital for painless gastroscopy were randomly divided into the treatment group (n = 100) and the control group (n = 100) according to the sequence. There was no significant difference in general data between the two groups (P > 0.05), which was comparable, as shown in Table 1.

Treatment

All patients fasted for 8 h, completed health education before the examination, and confirmed contraindications of anaesthesia and gastroscopy. During the examination, the patients were placed in the left lateral position and given nasal catheter oxygen inhalation (6 L/min). The indwelling needle opened the venous channel and was connected to the multifunction detector to monitor ECG, SPO2, BP and other vital signs.

The control group was routinely anaesthetized with nalbuphine and propofol according to the Expert Consensus on Sedation and Anaesthesia in the Diagnosis and Treatment of Digestive Endoscopy in China[9]. Before administration, the patient performed several deep breathing exercises, including intravenous injection of nalbuphine (0.025 mg/kg), followed by intravenous injection of propofol (1.5 mg/kg), until the eyelash reflex disappeared, and after no response to shouting, gastroscopy was performed. If the patient showed movement, frowning or haemodynamic changes (heart rate increase of > 20 beats per minute, systolic blood pressure increase of > 20%the base value) during the operation, propofol (0.5 mg/kg) was added until the patient was sedated again.

The treatment group received wrist-ankle acupuncture treatment on the basis of the control group. A needle (32 gauge, 1 inch, 0.25 mm diameter × 25 mm) was used. For the acupuncture, point selection and acupuncture method of Huatuo brand in Suzhou, China, refer to Professor Zhang Xinshu's Wrist-Ankle acupuncture treatment point selection standard[6].

The following observation indicators were recorded from the patients in both groups: (1) Painless gastroscopy, including the Operation time (from the beginning to the end of the examination), the Wakeup time (from the end of the examination to the time at which the patient could correctly state his or her name and birthdate), the Self-ambulation time (from the end of the examination to the time at which the patient could walk steadily from his or her own bed), and the total dose of propofol during

Table 1 Comparison of the general data of the two groups of patients

Group	Gender		ASA grade		Median age (age)
	Male	Female	I	II	
Observation group (n = 100)	54	46	80	20	36 (19-56)
Control group (n = 100)	52	58	82	18	41 (21-62)
χ^2/t value	0.296		0.530		0.396
P value	> 0.05		> 0.05		> 0.05

ASA: American Society of Anesthesiologist.

the examination; (2) Incidence rate of complications (hypoxemia, hypotension, hiccup, *etc.*) during anaesthesia; (3) Occurrence of gastrointestinal reactions (nausea, vomiting, abdominal distension, abdominal pain, *etc.*) after the examination; and (4) Operator and patient satisfaction visual analog scale (VAS) scores for this examination.

Statistical method

SPSS 23.0 software was used for data analysis. The measurement data are expressed as (mean ± SD), and a t test was adopted. The counting data are expressed as [n (%)] using χ^2 analysis. The F test for analysis of variance was used for comparisons among multiple groups, and the difference was considered statistically significant if $P < 0.05$.

RESULTS

Comparison of gastroscopy in gastroscopy in gastroscopy in gastroscopy in the two groups

The duration of gastroscopy in the two groups was 4-6 min, with no significant difference ($P > 0.05$). However, the recovery time of patients in the treatment group was 3.26 ± 0.27 min, and the time of independent walking was 6.12 ± 0.87 min, which was significantly faster than that in the control group. The total dose of propofol in the treatment group was 109 ± 8.17 mg, which was lower than that in the control group, as shown in Table 2.

Comparison of complications between the two groups during anaesthesia

The incidences of common complications, such as hypoxemia, hypotension and hiccup, during painless gastroscopy in the two groups were 16%, 23% and 1%, respectively, which were significantly lower than those in the control group ($P < 0.05$). Shown in Table 3.

Comparison of gastrointestinal reactions between the two groups after examination

After the examination, the incidence of nausea, vomiting, abdominal distension and abdominal pain in the treatment group was significantly lower than that in the control group ($P < 0.05$), as shown in Table 4.

Comparison of the satisfaction scores of the operators and patients with painless gastroscopy

Both operators and patients were satisfied with this painless gastroscopy, and there was no significant difference in VAS scores between the two groups ($P > 0.05$), but the VAS scores of operators in the treatment group were still higher, at 9.89 ± 0.31, as shown in Table 5.

DISCUSSION

With the development of society and the improvement of economic levels, Chinese residents are paying increasing attention to their health. Gastroscopy has become one of the important items of routine physical examination and is widely used in the clinical diagnosis and treatment of gastric cancer, precancerous diseases, tissue mucosal lesions and other diseases[10,11]. However, in the process of gastroscopy, patients often suffer from tension, anxiety, nausea, vomiting and other discomforts, resulting in patients discontinuing or terminating gastroscopy due to fear or intolerance. With the intervention of anaesthesia technology, painless gastroscopy can effectively reduce the pain of patients and is gradually becoming a widely accepted examination method in clinical practice[12]. However, each anaesthetic and opioid has adverse reactions, such as respiratory depression[13]. When propofol is used for painless examination, the incidence of respiratory and haemodynamic complications reaches

Table 2 Comparison of gastroscopy in the two groups

Group	Operation time (min)	Wakeup time (min)	Self-ambulation time (min)	Total dose of propofol (mg)
Observation group (*n* = 100)	4.73 ± 2.41	3.26 ± 0.27	6.12 ± 0.26	109 ± 8.17
Control group (*n* = 100)	4.35 ± 2.33	6.71 ± 0.34	7.08 ± 0.61	149 ± 10.17
t value	0.487	4.250	3.129	6.213
P value	> 0.05	< 0.01	< 0.05	< 0.01

Table 3 Comparison of complications between the two groups during anaesthesia [*n* (%)]

Group	Hypoxemia	Hypotension	Hiccup	*F* value	*P* value
Observation group (*n* = 100)	16 (16.00)	23 (23.00)	1 (1.00)	14.89	< 0.05
Control group (*n* = 100)	21 (21.00)	30 (30.00)	13 (13.00)		

Table 4 Comparison of gastrointestinal reactions between the two groups after examination [*n* (%)]

Group	Nausea	Vomiting	Abdominal distension	Abdominal pain	*F* value	*P* value
Observation group (*n* = 100)	11 (11.00)	8 (8.00)	6 (1.00)	5 (5.00)	12.89	< 0.05
Control group (*n* = 100)	20 (20.00)	16 (16.00)	15 (0.00)	12 (12.00)		

Table 5 Comparison of visual analog scale scores for the satisfaction of operators and patients with painless gastroscopy

Group	VAS score of operator satisfaction	VAS score of patient satisfaction
Observation group (*n* = 100)	9.89 ± 0.31	8.45 ± 1.54
Control group (*n* = 100)	9.19 ± 1.02	8.28 ± 1.05
t value	0.596	2.471
P value	> 0.05	> 0.05

VAS: Visual analog scale.

20%-24.5%. The combined use of nalbuphine can reduce the dose of propofol to achieve a safer anaesthetic effect, so it has become a commonly used anaesthetic scheme in clinical practice[14,15].

At present, the combining of other methods to further reduce the dose and side effects of propofol has become the current research exploration field. Nondrug methods, such as a large number of studies on acupuncture analgesia, have shown that the combination of acupuncture and anaesthesia can effectively reduce the dose of anaesthetic drugs. Among these approaches, wrist-ankle acupuncture treatment is a simple, safe and reliable therapy[16]. Some literature shows that wrist-ankle acupuncture treatment can increase cerebral blood flow and accelerate the passage of the blood-brain barrier to propofol, shorten the onset time, and thus reduce the induced dose of propofol[17,18]. In this study, the gastroscopy operation time in the two groups of patients lasted approximately 5 min, and the examination process in the two groups of patients was successfully completed. However, the total dose of propofol in the treatment group was small, and the time to awakening and walking independently after the examination was significantly faster than that in the control group. This may be related to the reduction of propofol dose or increased β -endogpin secretion by wrist and ankle acupuncture treatment[19], which is worthy of further study. On the other hand, during the operation of painless gastroscopy, especially when the dosage of propofol is high, the risk of inducing respiratory tract depression and blood pressure fluctuation is high, which is the most common cardiopulmonary complication of painless gastroscopy[20]. In our study, the incidence of hypotension and hypoxemia in the wrist-ankle acupuncture treatment group was significantly lower than that in the control group, which should be related to the reduction in the propofol dose in the wrist-ankle acupuncture treatment group, thus reducing the incidence of respiratory depression and hypotension in patients. Moreover, the most common complication after painless gastroscopy is a gastrointestinal reaction. Patients often feel nausea, vomiting, abdominal distension, abdominal pain, *etc.*, within hours or even days after the examination [21,22]. Our study suggests that the incidence of hiccups, nausea, vomiting, abdominal distension and abdominal pain in the wrist-ankle acupuncture treatment group was significantly lower than that in the control group ($P < 0.05$). Further query of the literature revealed that acupuncture treatment with wrist-ankle acupuncture treatment can reduce sympathetic nerve activity and vagus nerve tension, thereby relieving gastrointestinal spasm to alleviate nausea and vomiting and reduce abdominal distension and abdominal pain[23,24]. The degree of pain of patients after gastroscopy was mild. Analysis of the satisfaction of operators and patients with painless gastroscopy showed that both groups had high satisfaction but that the VAS score for the satisfaction of operators in the treatment group was still higher, at 9.89 ± 0.31. This indicated that both patients and operators were more satisfied with the anaesthesia method of this examination; moreover, patients in the treatment group woke up and moved independently faster, so this method was more popular with doctors.

CONCLUSION

In summary, wrist-ankle acupuncture treatment can optimize the anaesthesia prescription during painless gastroscopy and significantly reduce the total dose of propofol during the examination without affecting the examination operation and the satisfaction of the examiner and the patient, thus shortening the patient's recovery time, and significantly reducing the probability of nausea, vomiting, abdominal distension and other complications after the completion of the procedure. This treatment is beneficial to the development of painless gastroscopy in clinical practice, and improves the compliance and tolerance of patients, that is worthy of clinical promotion.

ARTICLE HIGHLIGHTS

Research background

With the intervention of anaesthesia technology, painless gastroscopy can effectively reduce the pain of patients and is gradually becoming a widely accepted examination method in clinical practice. However, each anaesthetic and opioid has adverse reactions, such as respiratory depression. Recently, the application of acupuncture anaesthesia in the field of digestive endoscopy has gradually achieved good results.

Research motivation

This study observed the intervention treatment of patients with wrist-ankle acupuncture therapy and observed the influence of the anaesthesia scheme, drug dosage and occurrence of anaesthesia-related adverse reactions during and after painless gastroscopy. To find a treatment plan that can reduce the dosage of propofol and the gastrointestinal reactions of patients after the examination.

Research objectives

The aim was to provide a more optimized painless gastroscope anaesthesia prescription scheme for clinical practice, help reduce the dose of anaesthetic drugs, shorten the time for patients to wake up and leave the hospital, reduce anaesthetic complications, facilitate the development of painless gastroscopy in clinical practice, and improve the compliance and tolerance of patients to treatment.

Research methods

In this study, two hundred patients with painless gastroscopy from January 2022 to July 2022 were selected and randomly divided into a treatment group (n = 100) and a control group (n = 100). Both groups were routinely anaesthetized with the nalbuphine and propofol regimen, and gastroscopy began after the patient lost consciousness. If the patient interrupted the surgery due to intraoperative torsion, intravenous propofol was used to relieve his or her discomfort. The control group was given supportive treatment and vital sign monitoring, and the treatment group received wrist-ankle acupuncture on this basis.

Research results

The general data before treatment, American Society of Anesthesiologist (ASA) grade and operation time between the two groups was no significant difference. The Wakeup time, and the self-ambulation time was significantly faster than that in the control group. The total dose of propofol in the treatment group was 109 ± 8.17 mg, significantly lower than that in the control group ($P < 0.05$). The incidence of respiratory depression and hypotension was not significantly different, but the incidence of hiccups was significantly lower than that in the control group. After the examination, the incidence of nausea, vomiting, abdominal distension, and abdominal pain was significantly lower than that in the control group. In addition, both the operators and the patients were more satisfied with this examination, with no significant difference between the groups.

Research conclusions

Wrist-ankle acupuncture treatment can optimize the anaesthesia prescription during painless gastroscopy and significantly reduce the total dose of propofol during the examination without affecting the examination operation and the satisfaction of the examiner and the patient, thus shortening the patient's recovery time and significantly reducing the probability of nausea, vomiting, abdominal distension and other complications after the completion of the procedure.

Research perspectives

This treatment is beneficial to the development of painless gastroscopy in clinical practice, and improves the compliance and tolerance of patients. Therefore, drug anaesthesia combined with wrist-ankle acupuncture treatment is a safe, feasible, simple and effective method that is worthy of clinical application and promotion.

FOOTNOTES

Author contributions: Zheng LY, Wu LY, Lu H, and Mi SC performed the research; Mi SC and Lu H designed the research study; Xu ZJ and Lu H contributed to the collection and assembly of data; Lu H, Zheng LY, and Wu LY analysed the data; Zheng LY, Wu LY, and Mi SC wrote the paper.

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ORIGINAL ARTICLE

Retrospective Study

Stenting as a bridge to surgery in obstructing colon cancer: Long-term recurrence pattern and competing risk of mortality

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Abstract

BACKGROUND

Stenting as a bridge to curative surgery (SBTS) for obstructing colon cancer (OCC) has been associated with possibly worse oncological outcomes.

AIM

To evaluate the recurrence patterns, survival outcomes, and colorectal cancer (CRC)-specific death in patients undergoing SBTS for OCC.

METHODS

Data from 62 patients undergoing SBTS at a single tertiary centre over ten years between 2007 and 2016 were retrospectively examined. Primary outcomes were recurrence patterns, overall survival (OS), cancer-specific survival (CSS), and CRC-specific death. OS and CSS were estimated using the Kaplan-Meier curves. Competing risk analysis with cumulative incidence function (CIF) was used to estimate CRC-specific mortality with other cause-specific death as a competing event. Fine-Gray regressions were performed to determine prognostic factors of CRC-specific death. Univariate and multivariate subdistribution hazard ratios and their corresponding Wald test *P* values were calculated.

RESULTS

28 patients (45.2%) developed metastases after a median period of 16 mo. Among the 18 patients with single-site metastases: Four had lung-only metastases (14.3%), four had liver-only metastases (14.3%), and 10 had peritoneum-only metastases (35.7%), while 10 patients had two or more sites of metastatic disease (35.7%). The peritoneum was the most prevalent (60.7%) site of metastatic involvement (17/28). The median follow-up duration was 46 mo. 26 (41.9%) of the 62 patients died, of which 16 (61.5%) were CRC-specific deaths and 10 (38.5%) were deaths

owing to other causes. The 1-, 3-, and 5-year OS probabilities were 88%, 74%, and 59%; 1-, 3-, and 5-year CSS probabilities were 97%, 83%, and 67%. The highest CIF for CRC-specific death at 60 mo was liver-only recurrence (0.69). Liver-only recurrence, peritoneum-only recurrence, and two or more recurrence sites were predictive of CRC-specific death.

CONCLUSION

The peritoneum was the most common metastatic site among patients undergoing SBTS. Liver-only recurrence, peritoneum-only recurrence, and two or more recurrence sites were predictors of CRC-specific death.

Key Words: Obstructing colon cancer; Colorectal cancer; Endoscopic stenting; Competing risk analysis; Survival; Recurrence; Peritoneal metastasis

Core Tip: This is the first retrospective study with a 10-year period using the competing risk analysis of cumulative incidence function to evaluate survival and estimate colorectal cancer (CRC)-specific death based on the Fine-Gray model in patients undergoing stenting as a bridge to curative surgery (SBTS) for obstructing colon cancer (OCC). The duration of this study allows a thorough examination of the long-term oncological outcomes of SBTS, survival rates, recurrence patterns, and prognostic factors contributing to CRC-specific death. Our results showed that liver-only recurrence, peritoneum-only recurrence, and more than two recurrence sites are significantly associated with poor survival and prognostic factors for CRC-specific death in patients undergoing SBTS for OCC.

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INTRODUCTION

Colorectal cancer (CRC) ranks as the second most prevalent malignant neoplasm and the third leading cause of cancer-related death worldwide[1]. Malignant bowel obstruction at presentation can occur in approximately 8% to 25% of CRC patients[2-4]. Emergency surgery is the conventional treatment for acute malignant colonic obstruction but is often associated with substantial morbidity (40%-60%), mortality (15%-34%) rates, worse oncological outcomes, and higher rates of stoma formation[5-7]. Since the 1990s, self-expanding metal stents (SEMS) have been accepted and increasingly utilized for palliation of malignant colorectal obstruction, as well as stenting as a bridge to curative surgery (SBTS), as a feasible alternative to emergency surgery[8-14].

Despite the fact that SEMS had been reported to have relatively high technical success rates between 70.1% and 91.9%, and clinical success rates of 69.0% to 71.7%, SBTS with curative intent remains debatable primarily due to possibly worse oncological outcomes[15,16]. Stent-related tumour perforations and subclinical micro-perforations may result in tumour dissemination and seeding, hence likely increasing the risk of recurrence. The effects of tumour perforation, silent stent-related micro-perforation, and the potential risks of tumour seeding on recurrence and survival have been reported [17]. Moreover, among patients with CRC recurrence, comorbidities such as cardiovascular and pulmonary diseases typically compete with CRC as the cause of death. To date, however, no studies have investigated the long-term oncological effects of SBTS on CRC-specific death under the competing risk of other cause-specific death.

This study aimed to evaluate the recurrence patterns, survival outcomes, and CRC-specific death in patients undergoing SBTS for obstructing colon cancer (OCC). The traditional Kaplan-Meier survival function would filter non-CRC related mortality rather than recognizing that patients dying from other causes are no longer at risk of CRC-specific death and consequently skew the results without considering competing risks[18]. Similarly, covariate effects in the cause-specific Cox regression model refer exclusively to CRC-specific death without considering how covariates could influence competing risk events[19]. Therefore, competing risk analysis with cumulative incidence function (CIF) was used in this study to estimate the probability of CRC-specific death over time, treating other cause-specific death as a competing risk. The covariate effects of clinical characteristics and recurrence patterns on the CIF for CRC-specific death were analysed with the Fine-Gray model[20].

MATERIALS AND METHODS

Patient selection

Our institutional review board approved this study (IRB No. 2017/2481). 114 consecutive patients underwent SBTS for OCC over ten years from 2007 to 2016 at Singapore General Hospital. All patients underwent computed tomography (CT) scans of the abdomen and pelvis at presentation, and OCC was confirmed clinically and radiologically. Full-staging CT scans were performed at the time of diagnosis or within 30 days of presentation. Data from 62 patients with non-metastatic OCC who underwent SBTS were analysed after excluding patients with stage IV disease at diagnosis and those with endoscopic stenting deployment for anastomotic recurrence.

Data collection

Clinical, histopathological, biochemical, and oncological data were collected from our electronic health record system (Sunrise Clinical Manager version 5.8, Eclipsys Corp., Atlanta, GA, United States). Patient demographics, clinical and surgical characteristics, and recurrence patterns were analysed. Follow-up data included time to recurrence and date and cause of death. After CRC resection with curative intent, all patients were considered for adjuvant chemotherapy consisting of capecitabine and oxaliplatin. The protocol for clinical management and postoperative surveillance has been established in an earlier study [13].

Survival analysis and competing risk analysis

Overall survival (OS) and cancer-specific survival (CSS) were estimated using the Kaplan-Meier curves. OS is defined as the elapsed time from the date of diagnosis to the date of death or last follow-up, while CSS is defined as the elapsed time from the date of diagnosis to the date of death from CRC. Clinical variables correlated with CRC-specific death were categorized and included in the competing risk analysis. Cumulative incidence function (CIF) was applied to account for the competing event, with other cause-specific mortality treated as a competing risk for CRC-specific mortality. CIF of death by each level of prognostic covariates was estimated and tabulated. CIF curves of CRC-specific death and other cause-specific death were estimated and visualized. The Fine-Gray competing risk model, which is based on the subdistribution hazard ratio (SHR), was used to examine the probabilities of CRC-specific death and other cause-specific[20]. Univariate and multivariate SHR and their corresponding Wald test *P* values were calculated. The Fine-Gray regression is a multivariate time-to-event model considering that a person can only experience one of the two competing events. This model also considers censoring among patients who experienced no events throughout the follow-up duration.

Statistical analysis

All statistical analyses were performed in R statistical software (version 4.2.1). Results were presented as median (range) for continuous variables and count (percentage) for categorical variables. Statistical significance was set at P value < 0.05.

RESULTS

Patients, disease, and surgical outcomes

There were 62 patients with OCC undergoing SBTS with curative intent. None of them had distant metastases at presentation. 57 patients had successful stenting procedures. On the same day, one stent technical failure and one stent perforation required emergency surgery. Three patients had post-stenting minimal bowel decompression and were operated on within 48 h.

Patient demographics and clinicopathological information are summarized in Table 1. The median age was 70 (range: 37-90) years. 87.1% of the patients were ASA classification I-II. 75.8% of tumours were T3 staging, whereas 22.6% were T4 staging. 95.2% of tumours were moderately differentiated adenocarcinoma. Only three tumours (4.8%) had a mucinous component. 19.4% of patients had at least one extra-nodal tumour deposit. The median time to elective CRC resection was 10 (range: 5-23) d. Laparoscopic approach was performed in 46.8% of the cases, while three cases were converted to open surgery. During the elective surgery, one patient was discovered to have a sealed perforation at the stented tumour site. The postoperative complication rate was 21%, and 30-day and 90-day mortality rates were 1.6% and 3.2%, respectively. One patient sustained an anastomotic leak and died 12 d after surgery, while the second succumbed to pneumonia 46 days after surgery. Postoperative adjuvant chemotherapy was given to 50% of patients.

Recurrence pattern

Percentages of metastases status, recurrence patterns, and peritoneal involvement are shown in Figure 1. During the study period, 28 patients (45.2%) developed metastases (Figure 1A). The median time to detection of metastases was 16 (range: 3-69) mo. Among the 18 patients with single-site

Table 1 Demographics and clinicopathological characteristics of 62 patients undergoing stenting as a bridge to curative surgery for obstructing colon cancer

Variables	*n* = 62
Age (yr, median [range])	70.0 [37.0, 90.0]
Sex	
Female	25 (40.3)
Male	37 (59.7)
ASA classification	
I	11 (17.7)
II	43 (69.4)
III	8 (12.9)
IV	0 (0.0)
Diabetes mellitus	
No	50 (80.6)
Yes	12 (19.4)
Albumin (g/dL)	
Median [range]	3.65 [1.90, 4.60]
≥ 3.0	52 (83.9)
< 3.0	10 (16.1)
CEA (μg/L)	
Median [range]	5.75 [0.95, 84.4]
< 5.3	28 (45.2)
≥ 5.3	34 (54.8)
Tumour location	
Rectosigmoid	8 (12.9)
Sigmoid	26 (41.9)
Descending	17 (27.4)
Splenic flexure	11 (17.7)
Tumour staging	
T2	1 (1.6)
T3	47 (75.8)
T4	14 (22.6)
Nodal involvement	
N0	27 (43.5)
N1	23 (37.1)
N2	12 (19.4)
Tumour differentiation	
Well differentiated	2 (3.2)
Moderately differentiated	59 (95.2)
Poorly differentiated	1 (1.6)
Histology	
Adenocarcinoma	59 (95.2)
Mucinous adenocarcinoma	3 (4.8)

Tumour deposit(s)	
No	50 (80.6)
Yes	12 (19.4)
Microscopic margin involvement (R1 resection)	
No	58 (93.5)
Yes	4 (6.5)
Perineural infiltration	
No	40 (64.5)
Yes	22 (35.5)
Lymphovascular invasion	
No	43 (69.4)
Yes	19 (30.6)
Pericolic microabscess	
No	54 (87.1)
Yes	8 (12.9)
Stent failure	
No	57 (91.9)
Yes	5 (8.1)
Surgical approach	
Open	33 (53.2)
Laparoscopic	29 (46.8)
Stoma formation	
No	58 (93.5)
Yes	4 (6.5)
Adjuvant chemotherapy	
No	31 (50.0)
Yes	31 (50.0)
Perioperative major complication(s)	
No	58 (93.5)
Yes	4 (6.5)
Postoperative 30 d mortality	
No	61 (98.4)
Yes	1 (1.6)
Postoperative 90 d mortality	
No	60 (96.8)
Yes	2 (3.2)

Values are presented as median [range] or number (%). ASA: American Society of Anaesthesiologists; CEA: Carcinoembryonic antigen.

metastases: Four had lung-only metastases (14.3%), four had liver-only metastases (14.3%), and 10 had peritoneum-only metastases (35.7%); while another 10 patients had two or more sites of metastatic disease (35.7%; Figure 1B). The peritoneum was the most prevalent site of metastatic involvement, with 17 out of 28 patients (60.7%) having peritoneal involvement (Figure 1C).

Survival and CRC-specific mortality

The median follow-up duration was 46 (range: 0-154) mo. 26 (41.9%) of the 62 patients died, with 16

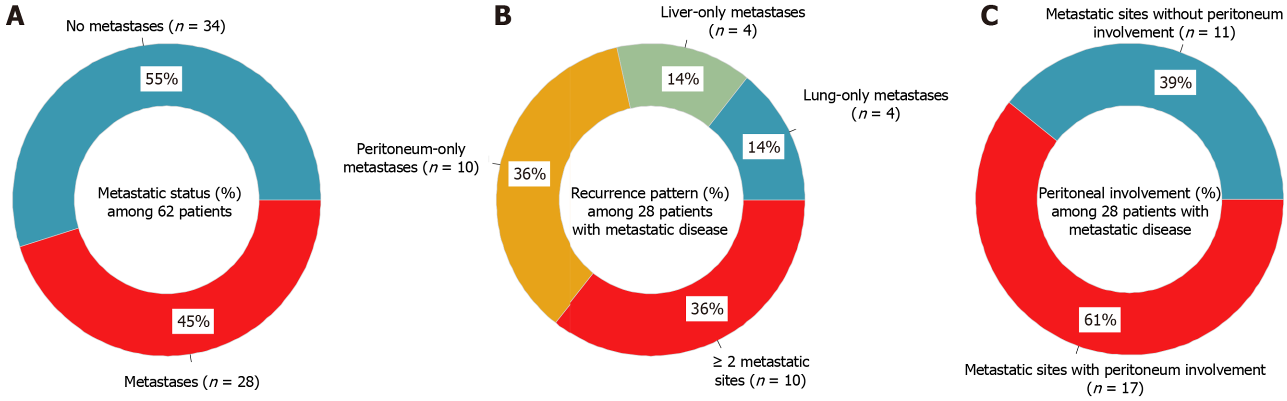

Figure 1 Metastases status and recurrence pattern. A: Percentages of metastases status; B: Recurrence pattern; C: Peritoneal involvement in 62 patients after endoscopic stenting followed by curative resection.

(61.5%) deaths attributable to CRC and 10 (38.5%) deaths owing to other causes. The 1-, 3-, and 5-year OS probabilities were 88%, 74%, and 59% (Figure 2A), while the 1-, 3-, and 5-year CSS probabilities were 97%, 83%, and 67% (Figure 2B). CIF curves for CRC-specific death under the competing risk of other cause-specific death are shown in Figure 3. The CIF curve for CRC-specific death climbed steadily and continuously, whereas the CIF curve for other-cause specific death climbed rapidly from 0 to 13 mo and subsequently steadied. This result suggests that most deaths unrelated to CRC occurred earlier after SBTS, between 0 and 13 mo. At 12-, 36-, and 60-month after endoscopic stenting followed by curative surgery, the CIF for CRC-specific death was 0.03, 0.16, and 0.29, whereas the CIF for other cause-specific death was 0.08, 0.10, and 0.12. CIF estimates for CRC-specific death by potential risk factors at 12, 36, and 60 mo are shown in Table 2. The highest CIF value at 60 mo was seen at liver-only recurrence (0.69), followed by peritoneum-only recurrence (0.65), lymphovascular invasion (0.64), ≥ 2 sites of recurrences (0.63), and T4 staging (0.62). The Fine-Gray regression of modelling SHR that corresponded to the CIF for CRC-specific death is displayed in Table 3. Poor differentiation and lymphovascular invasion (LVI) were strongly associated with CRC-specific death on univariate analysis, with SHR of 2.67 (95%CI: 1.50-4.76, $P < 0.001$) and 3.99 (95%CI: 1.55-10.3, $P = 0.004$) respectively. Liver-only recurrence, peritoneum-only recurrence, and ≥ 2 sites of recurrences were adverse prognostic factors on both univariate and multivariate analyses. Lung-only recurrence was not statistically significantly associated with CRC-specific death in our study ($P = 0.570$).

DISCUSSION

The use of SBTS in OCC offers advantages, including minimally invasive resection, reduced perioperative complications, and lower stoma formation rates. However, wider-scale adoption of this approach remains limited owing to worse oncological outcomes. To the best of our knowledge, this is the first study reporting the long-term recurrence pattern and competing risk analysis to evaluate CRC-specific death among this group of patients.

Successful bowel decompression after SEMS deployment permits not only the optimisation of comorbidities, hydration, and nutrition but also complete staging and assessment for synchronous cancers[21]. 46.8% of the patients underwent laparoscopic CRC resection, which has been associated with reduced postoperative discomfort, lower incidence of infectious complications, and attenuated immune response to surgery. The stoma formation rate of 6.5% in our study was close to the rate of 4.3% reported in another multi-centre retrospective study[22]. Moreover, our overall morbidity and mortality rates compare favourably against other similar cohorts[17,23]. Although the short-term outcomes of SEMS, including successful primary anastomosis and decreased morbidity and mortality rates, have been well established in several randomised controlled trials, controversy remains regarding their long-term oncological effects and impact on tumour recurrence[24-28].

A randomised study published in 2011 comparing 15 patients in the SBTS group *vs* 13 patients in the upfront emergency surgery group, reported a higher recurrence rate in the SBTS group (53.3% *vs* 15.4%, $P = 0.055$) after a mean follow-up of 37.6 mo, although the overall survival rates were similar between the two groups[24]. In our study, 45.2% of the patients (28/62) developed metastases after a median period of 16 mo. A clear predominance of 60.7% (17/28) in peritoneal metastatic involvement was observed among the 28 patients. Furthermore, 36% of these patients (10/28) had two or more sites of metastases, upon detection of recurrence during the follow-up period. The adverse oncological repercussions among patients with OCC treated with SBTS are clear. While stent-related tumour

Table 2 Cumulative incidence of colorectal cancer-specific death by potential risk factors after endoscopic stenting followed by curative resection

Variable	CRC-specific death (mo)		
	12	36	60
Age			
< 70 yr	0.00	0.22	0.37
≥ 70 yr	0.06	0.10	0.21
Sex			
Female	0.04	0.27	0.45
Male	0.03	0.09	0.20
Stent failure			
No	0.04	0.15	0.31
Yes	0.00	0.25	0.25
Surgical approach			
Open	0.06	0.16	0.22
Laparoscopic	0.00	0.15	0.40
T4 staging			
No	0.04	0.14	0.18
Yes	0.00	0.23	0.62
N2			
No	0.02	0.13	0.26
Yes	0.09	0.27	0.36
Tumour deposit(s)			
No	0.04	0.13	0.26
Yes	0.00	0.28	0.40
Microscopic margin involvement (R1 resection)			
No	0.04	0.15	0.29
Yes	0.00	0.25	0.25
Histology			
Adenocarcinoma	0.02	0.15	0.29
Mucinous adenocarcinoma	0.33	0.33	0.33
Poorly differentiated			
No	0.03	0.16	0.30
Yes	0.00	0.00	0.00
Perineural infiltration			
No	0.05	0.08	0.17
Yes	0.00	0.30	0.52
Lymphovascular invasion			
No	0.02	0.10	0.10
Yes	0.06	0.30	0.64
Pericolic microabscess			
No	0.04	0.14	0.29
Yes	0.00	0.29	0.29

Albumin (g/dL)			
≥ 3.0	0.02	0.15	0.26
< 3.0	0.10	0.21	0.56
CEA (μg/L)			
< 5.3	0.00	0.13	0.22
≥ 5.3	0.06	0.18	0.35
ASA classification			
I/II	0.02	0.12	0.28
III	0.13	0.38	0.38
Diabetes mellitus			
No	0.04	0.13	0.28
Yes	0.00	0.25	0.35
Perioperative major complication(s)			
No	0.04	0.15	0.29
Yes	0.00	-	-
Adjuvant chemotherapy			
No	0.03	0.07	0.21
Yes	0.03	0.24	0.37
Lung-only recurrence			
No	0.04	0.16	0.28
Yes	0.00	0.13	0.34
Liver-only recurrence			
No	0.04	0.12	0.24
Yes	0.00	0.38	0.69
Peritoneum-only recurrence			
No	0.00	0.07	0.12
Yes	0.12	0.38	0.65
≥ 2 sites of recurrences			
No	0.04	0.10	0.23
Yes	0.00	0.44	0.63

CRC: Colorectal cancer; ASA: American Society of Anaesthesiologists; CEA: Carcinoembryonic antigen.

perforation can result in intraperitoneal seeding of tumour cells, the radial expansion of the obstructing tumour caused by SEMS might promote tumour cell migration, elevating the risk of systemic metastasis [29,30]. Subclinical micro-perforations among these patients may contribute to tumour dissemination and seeding, thereby increasing the risk of peritoneal recurrence.

Recurrence, together with the presence and degree of lymph node metastasis, and LVI, are well-known prognostic factors influencing CRC survival. In our study, 41.9% of the patients died after SBTS, with 61.5% of deaths attributable to CRC. Our cohort's 5-year OS rate of 59% is comparable to similar patients undergoing SBTS reported by a previous study (5-year OS: 60%)[31]. The CRC-specific mortality was measured against the competing risk of other cause-specific mortality. The factors with the highest CIF (at 60 mo) of CRC-specific mortality were liver-only recurrence, followed by peritoneum-only recurrence, LVI, ≥ 2 sites of recurrences, and T4 staging. Liver-only recurrence, peritoneum-only recurrence, and ≥ 2 sites of recurrences were highly associated with CRC-specific mortality on both univariate and multivariate Fine-Gray regressions. Lung metastases were not associated with poor survival and CRC-specific death in our study.

Our findings are consistent with other studies, which have shown that CRC patients with liver metastases had considerably worse survival[32]. In addition, patients with peritoneal metastases had very limited survival, with only a median of 12 mo with systemic chemotherapy[33]. LVI has also been

Table 3 Fine-Gray regression analysis for colorectal cancer-specific death under the competing risk of other cause-specific death

Variable	CRC-specific death			
	Univariate		Multivariate	
	SHR (95%CI)	*P* value	SHR (95%CI)	*P* value
Age ≥ 70 yr	0.84 (0.33, 2.15)	0.710		
Sex (Male)	0.49 (0.19, 1.28)	0.150		
Laparoscopic surgery	1.28 (0.49, 3.33)	0.610		
Stent failure	0.58 (0.06, 5.51)	0.630		
T4 staging	1.23 (0.97, 1.57)	0.088		
N2	2.44 (0.88, 6.75)	0.086		
Tumour deposit(s)	2.02 (0.74, 5.56)	0.170		
Microscopic margin involvement (R1 resection)	1.68 (0.58, 4.84)	0.340		
Mucinous components	3.35 (0.72, 15.5)	0.120		
Poorly differentiated	2.67 (1.50, 4.76)	< 0.001	1.11 (0.32, 3.83)	0.870
Perineural infiltration	2.34 (0.89, 6.17)	0.086		
Lymphovascular invasion	3.99 (1.55, 10.3)	0.004	1.98 (0.61, 6.49)	0.260
Pericolic microabscess	1.12 (0.25, 5.04)	0.880		
Albumin < 3.0 g/dL	1.36 (0.38, 4.90)	0.640		
CEA ≥ 5.3 µg/L	2.45 (0.80, 7.53)	0.120		
ASA classification III	1.10 (0.68, 1.80)	0.700		
Diabetes mellitus	2.02 (0.75, 5.49)	0.170		
Perioperative major complication(s)	1.26 (0.16, 9.78)	0.820		
Adjuvant chemotherapy	1.37 (0.54, 3.46)	0.500		
Lung-only recurrence	0.69 (0.19, 2.51)	0.570		
Liver-only recurrence	4.25 (0.98, 18.4)	0.049	41.0 (5.01, 336)	< 0.001
Peritoneum-only recurrence	4.53 (1.79, 11.5)	0.001	23.2 (2.92, 185)	0.003
≥ 2 sites of recurrences	1.96 (1.19, 3.23)	0.008	5.28 (1.80, 15.4)	0.002

CRC: Colorectal cancer; SHR: Subdistribution hazard ratio; CI: Confidence interval; ASA: American Society of Anaesthesiologists; CEA: Carcinoembryonic antigen.

identified as an independent risk factor associated with decreased 5-year survival rates in CRC patients [34]. The prognosis for patients with LVI-positive tumours is poorer than those with LVI-negative tumours[35]. Furthermore, the prognostic heterogeneity in metastatic CRC is mainly attributable to primary tumour characteristics, the number of metastatic sites, and the pattern of metastasis, particularly peritoneal involvement, which portends a worse prognosis[36-38]. Survival probabilities are drastically reduced with multiple metastatic sites and the presence of peritoneal metastases. Our results highlight a substantial proportion of peritoneal metastatic disease developing among patients treated with SBTS, with the presence of peritoneum-only recurrence strongly associated with CRC-specific mortality.

The main limitations of this study are its retrospective nature and the relatively small cohort size. Nevertheless, the long-term recurrence and survival outcomes reported should offer a note of caution in the routine use of SBTS among patients with OCC. Future randomised comparative studies may be able to further evaluate the oncological impact of this treatment strategy.

CONCLUSION

The peritoneum was the most common metastatic site among patients undergoing SBTS for OCC. Liver-only recurrence, peritoneum-only recurrence, and two or more recurrence sites were predictors of CRC-

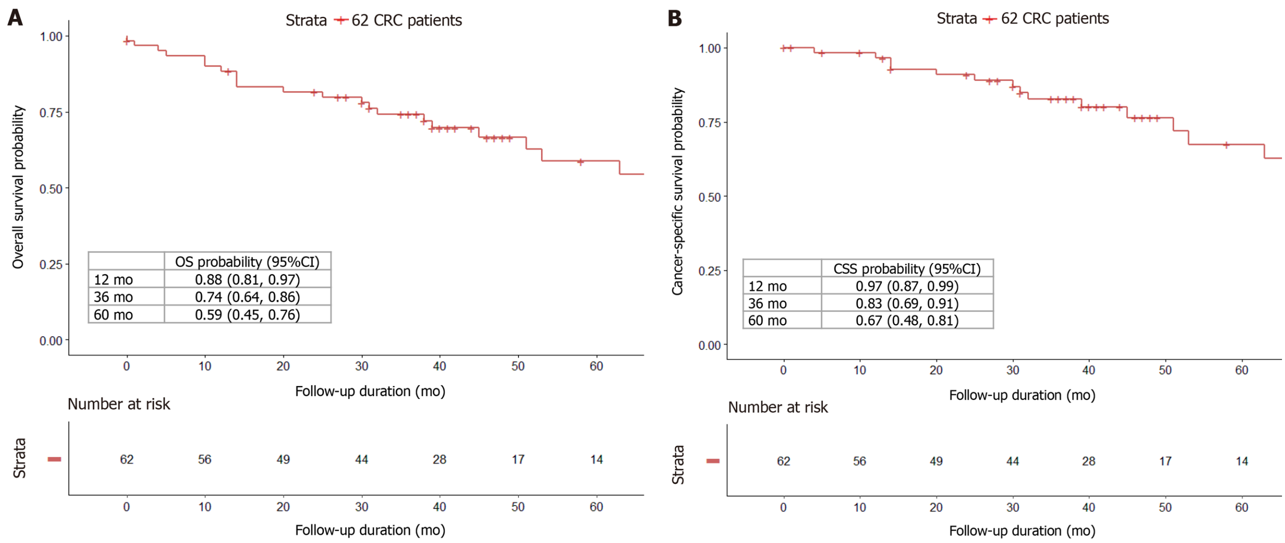

Figure 2 Kaplan-Meier survival curves. A: Overall survival; B: Cancer-specific survival in 62 patients after endoscopic stenting followed by curative resection. CRC: Colorectal cancer; OS: Overall survival; CSS: Cancer-specific survival; CI: Confidence interval.

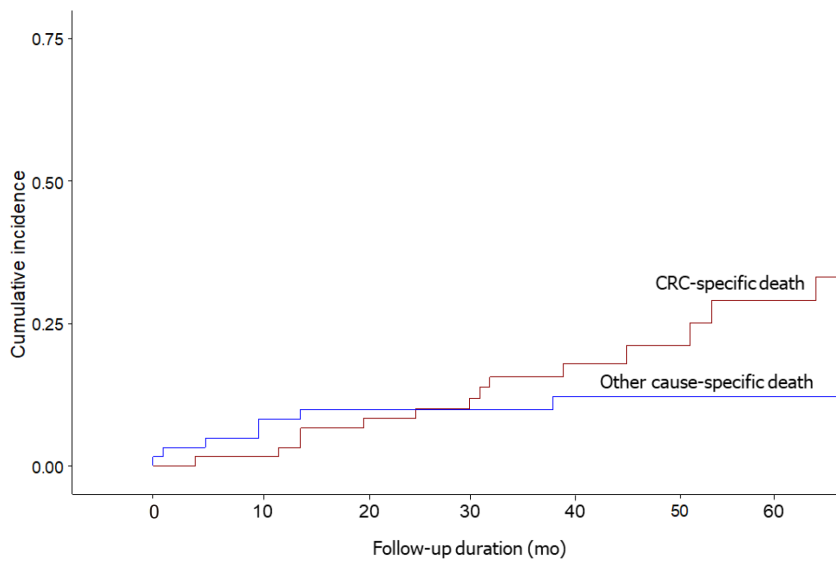

Figure 3 Cumulative incidence function curves. Cumulative incidence of time to death for colorectal cancer (CRC)-specific death and other cause-specific death in 62 patients after endoscopic stenting followed by curative resection. The red curve indicates CRC-specific death, and the blue curve shows other cause-specific death. CRC: Colorectal cancer.

specific death.

ARTICLE HIGHLIGHTS

Research background

Stenting as a bridge to curative surgery (SBTS) for obstructing colon cancer (OCC) has been associated with concerns regarding long-term oncological outcomes.

Research motivation

While SBTS may be associated with worse oncological outcomes, there are other competing risks that can affect colorectal cancer (CRC)-specific mortality among patients with OCC.

Research objectives

To evaluate the long-term oncological effects, recurrence patterns, survival outcomes, and CRC-specific mortality in patients who underwent SBTS for OCC.

Research methods

This study retrospectively examined long-term data from 62 patients who underwent SBTS at our institution over ten years from 2007 to 2016. CRC-specific mortality was evaluated by the competing risk analysis with cumulative incidence function. Fine-Gray analyses were performed to identify prognostic factors of CRC-specific mortality.

Research results

28 of 62 patients developed metastases after a median of 16 mo, with the peritoneum being the most prevalent (60.7%) metastatic site. In 46 mo of median follow-up, 26 (41.9%) patients died, of which 16 (61.5%) were CRC-specific deaths. Liver-only recurrence, peritoneum-only recurrence, and two or more recurrence sites were determined to be prognostic factors of CRC-specific mortality.

Research conclusions

The peritoneum was the most prevalent metastatic site among patients who underwent SBTS for OCC in this study. CRC-specific mortality most likely occurred in patients with liver-only recurrence, peritoneum-only recurrence, or two or more recurrence sites.

Research perspectives

The long-term recurrence pattern and factors contributing to CRC-specific mortality were reported.

FOOTNOTES

Author contributions: Chok AY and Tan EJKW designed the study and interpreted the data; Zhao Y performed the analysis and visualisation; Lim HJ and Ng YYR performed the literature review and clinical data collection; Chok AY, Zhao Y and Lim HJ drafted the manuscript; Chok AY, Zhao Y and Ng YYR edited the manuscript; Chok AY and Tan EJKW provided critical revision for final approval; all authors have read and approved the final version of the manuscript.

Institutional review board statement: This study was approved by Singapore Health Services (SingHealth) Institutional Review Board (IRB Ref. 2017/2481). All methods were carried out in accordance with relevant guidelines and regulations (Declaration of Helsinki).

Informed consent statement: Due to the study's retrospective design using de-identified data, written informed consent collection was waived by SingHealth Centralised Institutional Review Board.

Conflict-of-interest statement: All authors declare that they have no relevant or material financial interests that relate to the research described in this paper.

Data sharing statement: The data that support the findings of this study are available on request from the corresponding author at chokaikyong@gmail.com. The data are not publicly available due to privacy or ethical restrictions.

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CASE REPORT

Packed with pills - obstructing duodenal web in the setting of intestinal malrotation: A case report

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Abstract

BACKGROUND

The incidence of intestinal malrotation in adults has been reported to only be about 0.2%. Duodenal web as a cause of intestinal obstruction is rare, with an incidence of about 1:20000-1:40000. Furthermore, when described, these conditions are usually seen in early life and very infrequently in adulthood.

CASE SUMMARY

We report a case of a middle-aged woman with intestinal malrotation who presented with a three-month history of right-sided abdominal pain, early satiety, and a 22-pound weight loss. Patient underwent an esophagogastroduodenoscopy, which demonstrated numerous retained pills in a deformed first portion of the duodenum, concerning for a partial gastric outlet obstruction. An upper gastrointestinal series showed marked distention of the proximal duodenum with retained debris and the presence of a windsock sign, increasing the suspicion of a duodenal web. The patient subsequently underwent surgical intervention where a duodenal web with two lumens was noted and resected, opening the duodenum. There were over 150 pill capsules that were removed. The patient is doing well after this intervention.

CONCLUSION

Both intestinal malrotation and duodenal webs are infrequently encountered in the adult population. These pathologies can also present with nonspecific abdominal symptoms such as chronic abdominal pain and nausea. Hence, providers might not consider these pathologies in the differential for patients who present with vague symptoms which can lead to delay in management and increased mortality and morbidity.

Key Words: Intestinal obstruction; Intestinal malrotation; Duodenal web; Pill impaction; Duodenal distention; Case report

Core Tip: Intestinal malrotation and duodenal web are gut pathologies that rarely occur or become symptomatic in the adult population. It is even rarer to see an association between the two which leads to intestinal obstruction. Furthermore, adults may present with vague gastrointestinal symptoms which can delay management and increase mortality. We report a case of intestinal obstruction due to a duodenal web in the setting of malrotation in a middle-aged female.

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INTRODUCTION

The incidence of malrotation is around 1:500 and the symptomatic incidence is about 1:6000[1]. The incidence of duodenal web as a cause of intestinal obstruction is 1:10000-1:40000[2]. Intestinal malrotation is associated with various congenital obstructive anomalies, including duodenal atresia and stenosis. However, intestinal obstruction due to a duodenal web in the setting of malrotation has rarely been reported in the literature.

Both these pathological entities can present with vague symptoms such as abdominal pain and nausea. This can lead to delayed diagnosis and treatment, increasing mortality and morbidity. Furthermore, when described, this condition is usually seen in early life and very infrequently in adulthood.

Given the rarity of these diseases, there is limited data in the literature that can help guide better treatment options. Hence, we present a case of a middle-aged woman with intestinal malrotation who developed partial obstruction secondary to a duodenal web.

CASE PRESENTATION

Chief complaints

A 53-year-old woman presenting with three-month history of right-sided abdominal pain, early satiety, worsening nausea, and weight loss.

History of present illness

Symptoms started three months before presentation with worsening right-sided abdominal pain associated with early satiety, nausea and a 22-pound weight loss.

History of past illness

Patient has a past medical history of lupus nephritis status post renal transplant and known intestinal malrotation. Computed tomography (CT) of the abdomen showed large residual debris in the distal stomach and possible gastric outlet obstruction, without suspicious mass lesions or lymphadenopathy. The patient had been noted to have a mildly dilated duodenum and stomach on prior imaging and esophagogastroduodenoscopy (EGD), thought then to be due to her intestinal malrotation.

Personal and family history

The patient denied any family history of malignant tumors or abdominal pathologies.

Physical examination

On physical examination, the vital signs were as follows: body temperature, 36.9 °C; blood pressure, 118/77 mmHg; heart rate, 76 beats per min; respiratory rate, 18 breaths per min. Abdominal exam with no tenderness to palpation, non-distended, normal bowel sounds heard. No lymphadenopathy noted.

Laboratory examinations

Liver enzymes and bilirubin were normal (aspartate aminotransferase 22 U/L, alanine aminotransferase 14 U/L, total bilirubin 0.3 mg/dL, direct bilirubin 0.2 mg/dL, albumin 4.2 g/dL). No abnormalities were found on routine blood and urine analysis.

Imaging examinations

After presenting with the above concerning symptoms, she underwent another EGD. This demonstrated worsened gastric and intestinal distention with numerous retained pills in a deformed first portion of the duodenum (Figure 1). The endoscope could not be advanced past this region. Although no fixed obstruction was noted, it appeared that this persistent, partial gastric outlet obstruction was the etiology of her symptoms. Patient's colonoscopy was unremarkable. Both an upper gastrointestinal series (Figure 2) and CT showed marked distention of the proximal duodenum and multiple pills present, with the second portion of the duodenum appearing normal. Additionally, given the presence of a windsock sign on the upper gastrointestinal (GI) series, a duodenal web was on the differential diagnosis. The differential also included Ladd's bands, fibrous, compressive bands that are associated with intestinal malrotation.

MULTIDISCIPLINARY EXPERT CONSULTATION

The patient subsequently underwent surgical intervention. During the laparoscopic procedure, adhesions between the duodenum, retroperitoneum and liver were initially seen and lysed. However, they were not true Ladd's bands because they were not responsible for the obstruction. The exploratory laparotomy ultimately revealed a duodenal web with two lumens.

FINAL DIAGNOSIS

The final diagnosis was partial obstruction from duodenal web in the setting of intestinal malrotation.

TREATMENT

During the surgical intervention, the duodenal web was resected, opening the duodenum (Figure 3). There were over 150 pill capsules, likely those that the patient was taking for immunosuppression, that were removed (Figure 4).

OUTCOME AND FOLLOW-UP

The patient is doing well after this intervention, as she has regained her weight and is no longer suffering from abdominal pain.

DISCUSSION

Intestinal malrotation is a developmental anomaly of the midgut. In this condition, any deviation from a normal intestinal rotation around the superior mesenteric artery affects the process of fixation in the peritoneal cavity[3,4]. Rotational anomaly of the midgut is uncommon in adults. This disease is usually symptomatic during infancy, with nearly 90% of patients requiring medical intervention during the first year of life[5].

The incidence of intestinal malrotation in adults has been reported to only be about 0.2%[6]. However, certain cases are not symptomatic until much later in life. In adults who become symptomatic with an acute presentation, they may present with symptoms of nausea, vomiting, abdominal pain, and constipation. Peritoneal bands can also form and compress superior mesenteric vessels, leading to bowel infarction and obstruction. This can present with signs and symptoms of volvulus. Patients with chronic presentations usually present with vague abdominal pain and recurrent vomiting[5,7]. Though often difficult to diagnose, rapid recognition of these pathologies and prompt surgical treatment usually lead to successful outcomes.

The gold standard in diagnosing intestinal malrotation is an upper GI series. Any deviation of the ligament of Treitz from just left of the midline at the level of the gastroduodenal junction is diagnostic for malrotation[1]. A contrast barium enema (BE) can be used to help define the location of the cecum if

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Figure 1 Endoscopic findings of first portion of the duodenum containing multiple retained pills.

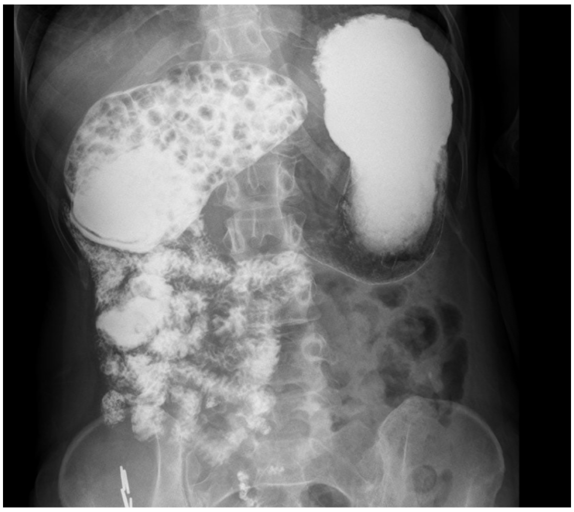

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Figure 2 Upper gastrointestinal series demonstrating proximal duodenal distention, multiple retained pills and a windsock sign.

an upper GI series is indeterminate. A contrast BE has been replaced as the gold standard for diagnosis given 20%-40% of confirmed malrotation cases have a normal cecal position[8]. A CT scan can also be used to identify abnormal intestinal locations.

The classical treatment for intestinal malrotation is the Ladd procedure. For patients with known intestinal malrotation presenting with symptoms of intestinal obstruction, peritoneal fibrous bands - also known as Ladd's bands - should be suspected. This procedure can be performed either laparoscopic or open, with similar outcomes[9]. During the procedure, the mesentery is untwisted, any Ladd's bands are dissected, and the small bowel is positioned on the right side of the abdominal cavity while the large bowel is positioned on the left[1]. An appendectomy is usually performed as appendicitis can lead to a misdiagnosis. The Ladd procedure is performed with a goal to reduce the risk of intestinal ischemia and volvulus by widening the mesenteric base and locating the small intestine.

Duodenal web as a cause of intestinal obstruction is rare, with an incidence of about 1:20000-1:40000 [2]. The concurrence of both intestinal malrotation and duodenal web leading to bowel obstruction is even rarer. The failure of recanalization of the duodenal lumen leaves behind a thin web consisting of the mucosa and submucosa without the muscular layer. Peristalsis causes the diaphragm to balloon distally, resulting in the classic appearance of a wind-sock[10,11]. This windsock sign can be visualized on sonography, upper GI series and endoscopy. Patients usually present early in life with evidence of proximal bowel obstruction; development of symptoms as an adult is very atypical.

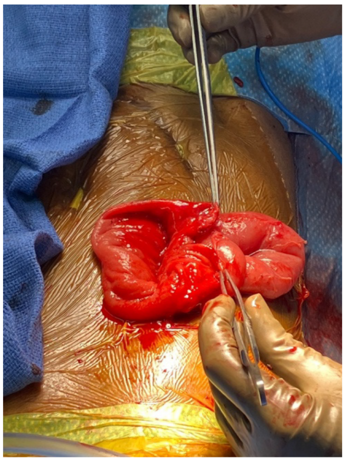

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Figure 3 Surgical image showing an opened duodenum after resection of the duodenal web.

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Figure 4 Post-surgical image of over 150 pill capsules removed.

Adults who develop a duodenal web usually present with upper abdominal distension, postprandial pain, and intermittent emesis secondary to partial or complete duodenal obstruction. However, nonspecific abdominal symptoms may also be observed. Moreover, this fenestrated membrane could be a site of impaction of food residues or foreign bodies[12]. In our case, the web caused a large buildup of pills at the duodenum. Diagnosis is made using contrast radiography or endoscopy, with the latter being much more sensitive as it can reveal the dilatation of the duodenum and the protrusion of the web in the lumen[13,14]. However, if one fails to visualize the second and third parts of the duodenum, a duodenal web may be missed[15].

Surgical treatment with complete excision of the web is the mainstay of management. If the excision is incomplete, the duodenal web may regrow and lead to recurrent obstruction. Before the mid-1980s, surgical repair was the only treatment available for duodenal webs, with endoscopy being relegated to a diagnostic role. However, with the advancement of therapeutic endoscopic techniques, treatment with procedures such as endoscopic membranotomy with laser, sphincterotome, high-frequency-wave snare/cutter, hot biopsy forceps, insulated-tip diathermic knife and needle knife have been reported[16-19]. It has been suggested that therapeutic endoscopy may be the preferred method of treatment of duodenal webs in adults given its efficacy, lack of invasiveness, is not associated with complications such as adhesion development, involves shorter hospital stay, and the procedures sometimes can be performed without general anesthesia[20].

CONCLUSION

The aim of this case report is to present a rare case of intestinal obstruction due to a duodenal web in the setting of malrotation in a middle-aged female. Both intestinal malrotation and duodenal webs are infrequently encountered in the adult population, and it is even rarer to see an association between the two. These conditions can present with vague symptoms such as chronic abdominal pain, which can lead to misdiagnosis, delay in management, and increased mortality and morbidity. Although the presence of both pathologies concomitantly is a very rare entity, duodenal web should be looked for and excluded in all cases of malrotation. Diagnosis can be made *via* endoscopy or contrast radiography. Although surgical treatment with excision of the duodenal web is the mainstay of management, given growing evidence in the literature, endoscopic management should also be considered. To date, reports of endoscopic treatment for duodenal webs have been free of significant complications. However, when considering treatment options, multiple factors should play a part in the decision, including patient's risk factors and technical abilities of the endoscopist. We present this case to increase awareness of this diagnosis, aiming to prevent delay of definitive diagnosis and management.

FOOTNOTES

Author contributions: Chew K and Kumar A contributed to manuscript writing and editing; Bellemare S and Kumar A supervised this study and captured the images used; all authors have read and approved the final manuscript.

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