Endoscopic Resection Techniques

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Keywords

Endoscopic resection techniques · Combined endoscopic and laparoscopic surgery, CELS · Indications in the gastrointestinal tract · Complication management

Summary

Cancers at an early stage of disease with a low risk of lymph node metastases or distant spread can be managed endoscopically. Different endoscopic techniques can be applied in the gastrointestinal tract. Furthermore, endoscopic and laparoscopic surgery can be combined in specific indications today. Most of all, resection-related complications can also be solved endoscopically.

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Introduction

Many of the gastrointestinal cancers are still diagnosed at an advanced stage, necessitating major surgery that is associated with significant morbidity and mortality. The outcome of such cases is often suboptimal for the patients. Cancers at an early stage of disease with a low risk of lymph node metastases or distant spread can be managed endoscopically.

Endoscopic mucosal resection (EMR) was pioneered in Japan for the management of early gastric cancer [1]. EMR is an endoscopic technique developed for the removal of neoplasms confined to the superficial layers (mucosa and submucosa) of the gastrointestinal tract and was introduced for rigid sigmoidoscopy in 1955 and then for flexible colonoscopy in 1973 [2, 3]. This has gained wider acceptance as a therapeutic option for various gastrointestinal lesions around the globe, and the indications have expanded to the whole gastrointestinal tract. EMR also has the advantage of providing an accurate local staging of the disease when compared with ablative therapies such as argon plasma co-

agulation (APC), photodynamic therapy, or radiofrequency ablation (RFA).

The commonly used techniques can be categorized as injection-, cap- and ligation-assisted EMR. Underwater EMR (UEMR) is a newer technique that is useful, particularly for salvage EMR.

Endoscopic submucosal dissection (ESD) was developed based on EMR techniques and was named after its approval as a new resection method in 2003. Regarding this procedure, an insulation-tipped knife (knife IT) is instrumental for performing ESD.

Compared to EMR, ESD can not only provide complete specimens for more reliable pathological examination but it can also be used to fully resect the tumor with a low rate of recurrence [4].

However, in some circumstances, a full-thickness resection may be necessary. Endoscopic full-thickness resection (EFTR) may be an adequate approach in challenging lesions such as adenomas or early cancers with severe submucosal fibrosis or small subepithelial lesions in the lower gastrointestinal tract (fig. 1). Furthermore, this novel technique has the potential to spare surgical therapy in a subset of cases [5].

A further approach for resection of gastrointestinal tumors is combined endoscopic and laparoscopic surgery (CELS). The technique was first described by Beck et al. [6] in 1993. It comes into consideration when the lesion is too large or in an anatomically difficult location for EMR or ESD. The advantages of CELS are direct optical control and exclusion of full-thickness defects as well as the possibility of surgical mobilization and, if necessary, immediate resection or conversion to standard surgical resection. Disadvantages are the staff and overall costs. CELS has to be performed in general anesthesia, and the patient must be prepared like for an operation. Furthermore, CELS cannot be performed when the patient has already had open surgery or if the lesion is located in a part of the abdomen which is not accessible by laparoscopy.

Before the start of any resection procedure, however, close visual inspection is indispensable to delineate the margins, particularly of flat lesions, because manipulation of the lesion may obscure landmarks. It may be helpful to mark the margins of the targeted lesion with superficial cautery marks with the tip of a snare or with APC.

Fig. 1. a–c Endoscopic full-thickness resection (EFTR) of a lesion with severe submucosal fibrosis.

Morphological Classification of Superficial Neoplasms

Neoplastic lesions in the gastrointestinal tract are regarded as superficial when their endoscopic appearance suggests that invasion is limited to the mucosa and submucosa. The subsequent Paris classification, which was developed at an international consensus meeting in 2002, reflected the structure of the Japanese Society of Gastrointestinal Endoscopists (JSGE) system, and type 0 was added to describe superficial lesions [5]. Type 0 is divided into three categories, i.e. protruding lesions (0-I), nonprotruding and nonexcavated lesions (0-II), and excavated lesions (0-III). Type 0-I is further subdivided into pedunculated (0-Ip) and sessile (0-Is) lesions. Type 0-II is divided into three subtypes: 0-IIa indicates slightly elevated lesions, 0-IIb refers to flat lesions, and 0-IIc characterizes depressed lesions. Type 0-III is an excavated lesion [7]. Various combinations of these classifications can be used to describe mixed elevated, flat or depressed lesions.

In type 0-I lesions, diameter is a reliable predictive criterion as the risk of submucosal invasion increases with the diameter. In type 0-II lesions, however, the morphologic subtype has a greater importance. Invasion of the submucosa is more frequent in depressed lesions (0-IIc). The incidence of submucosal invasion is high in type 0-III lesions.

Thus, the initial step is an endoscopic assessment of the lesions in order to see whether they are resectable based on the morphology. The JSGE has developed a guideline for the classification of advanced gastric cancers for the types 1–5 [8].

However, chromoscopy and electronic or optical image enhancement technologies are also very helpful to characterize lesions today [9, 10]. Furthermore, an accurate local staging is necessary prior to endoscopic resections. Endoscopic ultrasound is helpful in N staging, and the accuracy is improved significantly (90%) by the addition of fine needle aspiration (FNA) and the experience of the endoscopist [11]. Nevertheless, its value to predict the infiltration depth in early neoplasia is questionable.

The diagnostic accuracy is not satisfactory, especially in differentiating mucosal from submucosal disease [12]. For gastric carcinomas, for example, the accuracy of detecting sm1 invasion was only 65–79% [13, 14].

Histological Assessment

One of the most important predictors of lymph node metastasis is the depth of infiltration of the lesion. Mucosal lesions are subdivided into T1m1 where the disease is limited to the superficial epithelial layer, T1m2 where the disease involves the lamina propria, and T1m3 which extends and involves the muscularis mucosa. The submucosal involvement is similarly subdivided into T1sm1, T1sm2, and T1sm3 as evidenced by involvement of the superficial third, middle third, and deepest third of the submucosa.

The incidence of lymph node metastasis is negligible in mucosal involvement (T1m1–m3), and therefore these lesions are amenable to endoscopic curative management, whereas those with submucosal involvement raise the possibility of lymph node involvement, ranging from 0–8% in T1sm1 to 38–44% in T1sm2–3 lesions [15, 16]. Thus, deep submucosal invasion is considered as a definite indication for surgery and EMR is helpful regarding accurate local staging.

Techniques of Endoscopic Mucosal Resection

The procedure starts with injection of a solution into the submucosal space under the lesion, thus creating a safety cushion. The cushion lifts the lesion, facilitating capture and removal by using a snare while minimizing mechanical or electrocautery damage to the deeper layers of the gastrointestinal wall (fig. 2). EMR is particularly useful in managing large sessile and flat lesions of the colorectum. Polyps greater than 2 cm in size may be resected in a piecemeal fashion to avoid perforation. However, there are concerns regarding inadequate histological assessment and higher rates of recurrence following piecemeal resections.

The EMR techniques can be broadly divided into ‘suck-and-cut’ (suction) or ‘lift-and-cut’ (nonsuction) techniques. In certain cases, however, both techniques are used together.

In the ‘lift-and-cut’ technique, a submucosal injection is used to separate the muscularis propria from the lesion as this will reduce the chances of perforation.

In cases of invasive lesions, a nonlifting sign appears which clearly gives the operator an indication about the possibility of deeper invasion of the lesion and thus the unsuitability of performing EMR. Various solutions are used for submucosal injection. Normal saline is the most widely used agent, but it is absorbed

quickly. To overcome this, other agents such as hypertonic saline, 50% dextrose, sodium hyaluronate, 4% succinylated gelatin, and so forth are often used [17]. Injections are performed using an injection needle at one or multiple sites around the lesion.

Recently, a needleless injection using an automated pump has been made commercially available [18].

The suction technique using a multiband mucosectomy device (Cook Medical, Limerick, Ireland) is commonly used in Barrett's dysplasia, and this technique does not require submucosal injection [19]. A pseudopolyp is formed by band ligation, which is then resected with a snare (fig. 3). In cases of the EMR cap technique (Olympus, Tokyo, Japan), however, submucosal injection is used and the lesion is sucked into the cap and resected by employing a prelooped snare [20, 21].

Cap-Assisted EMR

Cap-assisted EMR also uses submucosal injection to lift the target mucosal lesion especially in the esophagus but also in special indications in the stomach and in the rectum. Dedicated mucosectomy devices have been developed that use a cap affixed to the tip of the endoscope. These single-use devices come equipped with a specially designed crescent-shaped electrocautery snare that must be opened and positioned on the internal circumferential ridge at the tip of the cap. The endoscope is then immediately positioned over the target lesion, and suction is used to retract the mucosa into the cap after which the snare is closed to capture the lesion. The caps are cylindrical and available with a fat circular-shaped (straight) or oval-shaped (oblique) tip, both with outer diameters ranging from 12.9 to 18 mm (fig. 4).

Ligation-Assisted EMR

In ligation-assisted EMR, a band ligation device (Duette Multi-Band Mucosectomy device; Cook Medical Inc., Winston-Salem, NC, USA) is attached to the endoscope, and the banding cap is positioned over the target lesion with or without previous submucosal injection. Suction is applied to retract the lesion into the banding cap, and a band is deployed to capture the lesion, thereby creating a pseudopolyp. An electrocautery snare is then used to resect the pseudopolyp above or below the band [7, 8].

The handle of the EMR band ligator allows insertion and advancement of a snare device through the endoscope working channel without requiring removal of the banding device. In addition, the band ligation device incorporates six bands, allowing potential resection at as many as six mucosal sites without the need to change the device.

Underwater EMR

In UEMR technique, luminal air is suctioned, and water is instilled to fill the gastrointestinal lumen and to immerse the target lesion. Water immersion allows lesion visualization without over-distension of the gastrointestinal tract wall.

It is postulated to 'float' the mucosa and submucosa away from the deeper muscularis propria layer which allows EMR without requiring submucosal injection [22]. This technique has the theoretic

Fig. 2. a–d Endoscopic mucosal resection of a polyp in the colon using first injection for lifting and then a snare to resect the lesions.

Fig. 3. a–d Ligation-assisted endoscopic mucosal resection: A band ligation device is attached to the endoscope and the banding cap is positioned over the target lesion with or without previous submucosal injection.

Fig. 4. a–d First, electrocautery is used to mark the lesion. The endoscope is then immediately positioned over the target lesion and suction is used to retract the mucosa into the cap after which the snare is closed to capture the lesion.

Fig. 5. a, b Endoscopic submucosal dissection can be used for circumferential tumors and provides complete specimens for more reliable pathological examination.

cal advantages of eliminating any risk of carrying neoplastic cells into deeper layers of the gastrointestinal tract wall by the injection needle, and first reports show an easier capture of flat lesions. This method has also been reported to be effective in managing recurrences after previous EMR as well as in patients with previous partial resections and biopsies of lesions [23], because these interventions may result in submucosal fibrosis, making lifting of the lesion with submucosal injection difficult. However, prospective studies are needed to evaluate this technique further.

Techniques of Endoscopic Submucosal Dissection

ESD is a novel technique that has been introduced as a means to extend the capabilities of the endoscopist to resect larger tumors and to obtain more reliable pathologic specimens [24]. It was developed based on EMR techniques and was named after its approval as a new resection method in 2003. In this procedure, an insulation-tipped knife is instrumental for performing ESD.

Nowadays, various types of endoscopic electrosurgical knives are used to incise and remove large neoplastic lesions en bloc with this technique.

Compared to EMR, ESD can not only provide complete specimens for more reliable pathological examination but it can also be used to fully resect the tumor with a lower rate of recurrence in comparison to EMR techniques in piecemeal fashion (fig. 5) [25].

A meta-analysis of 15 studies found that ESD, when compared with EMR, had higher en bloc and curative resection rates (odds ratio (OR) 13.9 and 3.5, respectively) as well as lower rates of local recurrence (OR 0.09) [26]. For tumors smaller than 20 mm, the complete resection rate is 82.6–97.7% while the recurrence rate is nearly 0% [27, 28]. If the tumor is larger than 20 mm, however, the complete resection rate drops slightly to 74–91.8%, but the recurrence rate remains 0–1% [29, 30].

During the ESD procedure, the operator should pay attention to the ‘lifting sign’ after submucosal injection, which can be used to determine the lesion depth. If the lesion is located in the mucous layer with a proper boundary to the muscularis propria and shows a positive ‘lifting sign’, it can be removed by ESD [29, 30]. However, the rate of perforation in ESD is higher than that for EMR as the submucosal layer is nearer to the muscularis and the incidence

of complications correlates with the operator’s technical proficiency [31]. Nonetheless, in some studies, the bleeding rate for ESD remains low (0.4–2.5%), although the risk of perforation is slightly higher (2.9–5.3%) [32, 33].

Adjunctive Techniques

In addition to EMR, further ablative techniques are used in an organ-specific manner for the ablation of residual tissue. In the esophagus, RFA or cryoablation is frequently used to ablate additional Barrett’s esophagus after EMR of the dysplastic lesions.

During resection of flat adenomas in the gastrointestinal tract, APC or hot biopsy forceps (also known as the hot avulsion technique) may be used to ablate residual adenomatous tissue at the base and edges of the resection site [34].

However, the application of APC to ablate residual adenomatous tissue was associated with a higher risk of adenoma recurrence [35]. Use of the snare tip with soft coagulation for residual tissue in the colon that cannot be removed by snare resection is currently being evaluated in a randomized controlled trial.

Submucosal Injection Solutions

Although submucosal injection is not essential for all EMR procedures, it is an integral part of injection-assisted EMR. The ideal agent should be inexpensive, readily available, nontoxic, easy to inject, and provide a long-lasting submucosal cushion. Normal saline solution is widely available and often used for injection-assisted EMR [36].

However, a cushion made with normal saline solution often dissipates within minutes. Multiple studies have demonstrated longer lasting cushions made of various agents including hyaluronic acid, hydroxypropyl methylcellulose, succinylated gelatin, glycerol, and a fibrinogen solution [17].

Staining dye (i.e. diluted indigo carmine or methylene blue) is frequently added to the injection solution to facilitate identification of the lateral and deep margins of the target lesion before and during the resection process. The staining dye may also improve the recognition of muscularis propria injury and intraprocedural perforation [37].

Technique of Combined Endoscopic and Laparoscopic Surgery

CELS offers the possibility to use either endoscopic resection under laparoscopic control or endoscopic resection with laparoscopic assistance and suture or an instant extension of the resection to a laparoscopic resection, if necessary. General anesthesia is inevitable, and the patient should be prepared like for open surgery. Position of the patient and placement of laparoscopic and endoscopic equipment are quite important. In case of lesions in the colon the patient is placed in the modified lithotomy position. The colonoscopist is positioned between the legs, while the laparoscopist is stationed opposite of the lesion. In case of lesions in the upper gastrointestinal tract the patient is placed in the French position or the beach chair position with spread legs. The endoscopist

is beside the patient while the laparoscopist stands between the patient's legs.

The camera port can be placed in the umbilicus. Importantly, endoscopy should be performed prior to the placement of further ports to evaluate optimal port position. Endoscopy should be performed with insufflation of CO₂ because room air can cause prolonged bulge of the intestine and therefore complicate laparoscopy. After the lesion is located and sufficiently mobilized to be accessible by endoscopy and laparoscopy, we prefer to attempt endoscopic resection first to avoid serosa perforation, if possible.

Endoscopic dissection technique does not differ from EMR or ESD techniques. Laparoscopic dissection should be performed with an ultrasound dissection device. Before laparoscopic full-thickness dissection, the dissection line can be marked endoscopically by coagulation needle or ink injection. The resected tumor can be collected in a laparoscopic salvage bag or retrieved endoscopically. Laparoscopic hand suture or autosuture stapling device is used for closure of the wall defect. A seal check with endoscopic gas insufflation after laparoscopic fluid application should be performed. If there are any signs of malignancy, the resection should be performed laparoscopically or in an open fashion according to oncological criteria.

Clinical Applications

EMR and ESD techniques as well as EFTR and CELS may be used for definitive therapy of premalignant and early-stage (T1aN0) malignant lesions of the digestive tract if there is limited submucosal invasion.

Nevertheless, EMR can also be used in a diagnostic manner to obtain larger histologic specimens (compared with the standard endoscopic tissue sampling techniques) and can provide an accurate histological T stage for these superficial malignancies [38–40]. In general, EMR should not be attempted if invasion into the deep submucosa or beyond is suspected.

Nonlifting of the lesion after submucosal injection is a predictor of deep invasion and indicates that the lesion is not amenable to endoscopic removal [41, 42]. However, EMR may be attempted if the nonlifting is thought to be a consequence of submucosal fibrosis related to previous manipulation (previous biopsy or attempted/incomplete EMR) of the lesion [43].

In addition, it has been shown that deep submucosal invasive cancer can be predicted with endoscopic imaging evaluation by using either the NBI international colorectal endoscopic classification (NICE classification) or the Kudo classification (using chromoendoscopy and magnification endoscopy).

Both NICE classification type 3 lesions and Kudo type V lesions predict deep submucosal invasive carcinoma, with endoscopic evaluation exhibiting areas of irregular disrupted or missing vessels along with an amorphous or absent surface/pit pattern [44, 45].

CELS can be used when EMR, ESD, or EFTR is not applicable or bear a great risk of perforation or injury of adherent organs. CELS can also be used when there is a high risk of deep submu-

cosal invasive cancer. In doubt of dignity, the surgeon can instantly convert the resection to a full segmentectomy. Although first reports of CELS resection in laparoscopically difficult regions like the duodenum exist, we think that these indications should be reserved to experts only [46]. CELS is predominantly and easier applicable in gastric and colonic lesions [47–49].

Esophagus

EMR and ESD are indicated for the treatment of superficial esophageal cancer and Barrett's esophagus-associated neoplasia (high-grade dysplasia (HGD) and intramucosal carcinoma) [50–52].

Barrett's Esophagus

EMR is commonly used for Barrett's esophagus-associated neoplasia. EMR is offered as a therapeutic option in patients presenting with focal high-grade dysplasia and mucosal cancer. Those patients with submucosal, vascular or lymphatic invasion should be referred for esophagectomy.

Techniques vary from focal EMR of nodular lesions with adjunct ablation techniques to complete EMR for eradication of the entire Barrett's segment. A randomized trial comparing cap-assisted with ligation-assisted EMR for the resection of Barrett's esophagus-associated neoplasia demonstrated that ligation-assisted EMR was significantly faster than cap-assisted EMR with median procedures times of 34 and 50 min, respectively ($p = 0.02$), with no differences in rates of adverse events or quality of the resection specimens [53].

A multicenter retrospective study from Europe evaluated patients who had Barrett's esophagus-associated neoplasia treated with complete EMR of Barrett's esophagus and demonstrated that 58% required additional thermal ablation to eradicate residual disease [50]. Neoplasia recurred in 6.2% of patients because a complete resection of lateral margins is histologically difficult to assess, especially in cases of piecemeal resection.

Another large series published by the Wiesbaden group showed a complete remission of Barrett's cancer in 95% of patients treated with EMR alone at 5-year follow-up. However, a significant proportion of patients (20%) developed metachronous lesions during follow-up, all of which were managed endoscopically [54].

Today, EMR of Barrett's-associated neoplasia is performed in conjunction with RFA or APC. Here, EMR is initially performed on any endoscopically visible abnormalities, followed by circumferential RFA or hybrid APC performed at least 6 weeks after EMR [55].

After initial complete eradication of Barrett's esophagus, sustained remission of neoplasia and intestinal metaplasia was achieved in 90% of patients at 5 years of follow-up.

Low-risk submucosal invasion (T1sm1) is also considered to be appropriate for endotherapy in certain centers [56]. This needs to be tailored according to the local guidelines and multidisciplinary opinion. EMR is considered to be therapeutic and curative when R0 resection is achieved. Follow-up endoscopies are performed to closely examine the edges of the previously resected area to exclude residual dysplasia.

Squamous Dysplasia and Cancer

Early lesions limited to the mucosa are amenable for endoscopic resection, and studies have shown a 5-year survival rate of up to 95% [57]. The incidence of lymph node metastases is negligible in m1 and m2 mucosal cancers, and EMR is usually recommended for squamous cell carcinoma of the esophagus confined to the lamina propria. However, esophageal squamous dysplasia and cancer are reported to show synchronous and metachronous lesions [58].

A meta-analysis that included 8 studies from Asia comparing results of ESD and EMR for endoscopic resection of superficial esophageal cancer (primarily squamous cell carcinoma) demonstrated that ESD compared with EMR had a significantly higher en bloc resection rate (97.1 vs. 49.3%; OR 52.76; 95% confidence interval (CI): 25.57–108.84) and a lower recurrence rate (0.3 vs. 11.5%; OR 0.08; 95% CI: 0.03–0.23); however, there was no difference in recurrence rate if the lesion size was less than 20 mm (OR 0.34; 95% CI: 0.06–2.08) [59]. In addition, the procedure duration was significantly longer for ESD compared with EMR. An earlier prospective study compared the outcome of patients with muscularis mucosal and superficial submucosal invasion treated by EMR. The overall 5-year survival rates were not different compared with surgery in 26 patients [60]. Another study from Europe included 39 patients with superficial squamous cancers, and the curative rates following EMR were around 90% [61]. A recent study from Japan compared ESD with EMR in 168 lesions and found that the curative rates were better with ESD compared with EMR. Nevertheless, the EMR cap technique was associated with 71% curative resections [62]. As a general rule, esophageal cancers with a diameter <2 cm, those involving less than one third of the circumference of the esophageal wall, and lesions limited to the mucosa of the esophagus could be managed by EMR with a curative intent.

Stomach

Both EMR and ESD are used for the treatment of early gastric cancer (EGC) in Japan as an alternative to surgery. The primary characteristics of EGC that are amenable to endoscopic treatment include elevated lesions less than 2 cm in size, depressed lesions less than 1 cm in size without ulceration, well or moderately differentiated adenocarcinoma of the intestinal type, and absence of lymph node metastasis on pretreatment staging studies. Asian data indicate that ESD is associated with lower local recurrence rates than EMR, although survival rates are similar [63]. A meta-analysis that included 9 retrospective studies evaluated the efficacy of ESD and EMR [63]. Although the mean duration for ESD was longer than EMR, the ESD group had a significantly lower local recurrence rate than the EMR group (0.7 vs. 6.4%; OR 0.10; 95% CI: 0.06–0.18). ESD is the preferred method for removal of EGC lesions in Asia because it allows histological assessment of lateral margins, which is not possible with piecemeal EMR, and is associated with lower local recurrence rates [64].

The risk of lymph node metastasis is about 0.4% for well differentiated cancers. Undifferentiated mucosal cancers should not be treated by EMR, as the risk of lymph node metastasis rises to 4% [65].

In one series of 308 patients, EMR successfully eradicated the cancer in 85% of cases. The complete endoscopic resection rate was lower in type 0-IIa lesions larger than 2 cm and in type 0-IIc lesions that were either larger than 1 cm or associated with undifferentiated adenocarcinoma. Commendably, the 5-year survival was 86%, a rate which is similar to results reported for aggressive surgical approaches [66]. In patients with small and differentiated mucosal gastric cancers, an excellent prognosis was noted with en bloc EMR. In 131 patients, the disease-specific 10-year survival and the overall survival rates were 99 and 64%, respectively [67].

Only few data exists about CELS and resection of EGC. Abe et al. [46] reported about a case of CELS resection of a 30-mm signet-ring cell carcinoma limited to the mucosal layer in a 62-year-old woman. Because of a risk of lymph node metastasis of more than 4%, they combined the resection with a local lymphadenectomy. For better detection of the lymph node basin they performed submucosal injection of indocyanine green around the lesion. In 2014, Hur et al. [68] reported of a series of CELS combined with selective lymphadenectomy in 9 patients with EGC. Although 2 patients showed infiltration of the submucosal layer, all margins were tumor-negative and none of the patients had lymph node metastasis. Short-term results revealed no tumor recurrence 6 months after the operation [68].

Duodenum

EMR could be used to remove periampullary or duodenal adenomas, neuroendocrine tumors, and subepithelial stromal tumors. Endoscopic snare papillectomy is increasingly performed with curative intent for benign ampullary lesions.

Nonampullary Duodenal Adenomas

Duodenal lesions not involving the major duodenal papilla can be removed with a variety of EMR techniques but carries an increased risk of bleeding and perforation because the duodenum has an increased vascularity and a thin wall. The majority of published reports on endoscopic removal of duodenal polyps originates from high-volume centers and is limited by low numbers of patients and a retrospective study design [69]. Reported success rates vary from 70 to 96% for nonampullary duodenal lesions [70].

In addition, the technique of UEMR has been reported for resecting nonampullary duodenal adenomas with high success rates for complete resection (83% at the index session); however, adverse events included delayed bleeding, water intoxication syndrome, and stricture formation [71]. A single-center study in 59 patients who underwent EMR of the nonampullary lesions showed that successful resection was accomplished in 93% of cases on the initial attempt. Recurrence was noted in 37% cases, though. Polyps >2 cm in size were associated with higher rates of adenoma and a higher incidence of recurrence [72].

A recent series including 5-year data on EMR of large nonampullary lesions showed a recurrence rate of 24%, but there were no significant complications [73].

Colorectum

Injection-assisted EMR is widely used for the resection of large or flat colonic lesions. Polyps greater than 2 cm in size may be resected in a piecemeal fashion to avoid perforation.

However, there are concerns regarding inadequate histological assessment and higher rates of recurrence following piecemeal resections.

A systematic review and meta-analysis demonstrated that local recurrence after EMR occurs in 3% of cases in which the lesion is removed en bloc and in 20% of cases in which the lesion is removed in piecemeal fashion [74].

For recurrences that were retreated with endoscopic therapy (APC and/or EMR), the subsequent recurrence rate was 21%, with successful eradication being achieved in 91.4% of recurrences after a mean of 1.2 additional sessions. Therefore, if a large adenoma (>15 mm) is removed in piecemeal fashion, the patient should have a repeat colonoscopy in 6–12 months to evaluate for local recurrence [75].

A meta-analysis comparing ESD with EMR for colorectal tumors that included 6 studies (1,642 total lesions) demonstrated that ESD had a higher en bloc resection rate and a lower initial local recurrence rate than EMR; however, ESD was more time-consuming and generally required hospitalization for observation after the procedure [76].

Typically, EMR in the colon is performed by using the injection-assisted EMR technique; however, UEMR without submucosal injection has also been reported [22].

When the UEMR technique was used, the complete removal rate for recurrences was significantly higher compared with injection-assisted EMR (88.9 vs. 31.8%, $p < 0.001$) in a nonrandomized clinical trial [77]. Furthermore, the recurrence rate was significantly lower in the UEMR group than in the EMR group (10 vs. 39.4%, $p < 0.02$).

Although several studies have reported no recurrence after endoscopic removal of malignant colonic polyps, the effectiveness of EMR for the treatment of these lesions has been questioned, and EMR should not be attempted for nonlifting lesions or lesions classified as Paris II-c/III [16, 76–82]. However, nonlifting lesions that have previously been manipulated (biopsy or attempted EMR) before referral for resection are usually amenable to EMR [78].

Nonlifting lesions due to submucosal fibrosis or those that have been previously sampled are difficult to resect even when performing an EMR or an ESD. The main advantage of the procedure performed with the full-thickness resection device (FTRD) (Ovesco Endoscopy, Tübingen, Germany) is the ability to easily and quickly resect the lesion and to close the colon wall defect in only two steps: first, grasping the lesion and releasing an over-the-scope clip (OTSC) and, second, resection with a snare above the clip. In contrast, the major limitation of the system is the maximum size of the lesion suitable for resection. In fact, the use of the FTRD is not recommended for the resection of lesions >30 mm [79].

The EFTR with the FTRD system is a ‘first clip and cut later’ technique. Wall duplication, with serosa-to-serosa apposition, is created when the OTSC is deployed after pulling the lesion into the

cap. Then, the tissue above the clip is resected with the snare. With this approach, the defect is safely closed before the resection itself has been performed.

Similar to EFTR, the CELS technique provides the possibility to perform a full-thickness resection. Compared to ESD and EMR, the full-thickness resection may enable the avoidance of piecemeal resections. Even lesions >30 mm diameter can be resected by CELS. Garrett and Lee [48] reported a low recurrence rate of 10% for patients with resection of benign polyps.

Complications

Bleeding and perforation are the major complications associated with EMR. In cases of esophageal EMR, no difference in complications was observed when the EMR cap technique is compared with the ‘ligation and cut’ technique. A circumferential mucosal defect involving over three quarters the circumference of the esophagus after EMR was significantly associated with the subsequent development of esophageal stricture [80]. Reported perforation rates during EMR for esophageal lesions are relatively low at less than 0.5% for physicians who are experienced in performing EMR [81].

However, a meta-analysis comparing adverse event rates for ESD and EMR for superficial esophageal cancers demonstrated that ESD comes with a significantly higher rate of perforation (OR 2.19; 95% CI: 1.08–4.47; $p = 0.03$) [82].

Bleeding is the most common complication occurring in up to 7–8% of patients undergoing standard EMR or ESD for EGC. Perforations are uncommon in gastric EMR compared with ESD (4%) [83]. High doses of proton pump inhibitors are usually given for 4–8 weeks to facilitate mucosal healing following upper gastrointestinal EMR. Injection of adequate amounts of submucosal fluid is of paramount importance to avoid perforations in the colon, especially in right-sided lesions. A recent series of colonic EMR in 182 lesions showed a perforation rate of 1% and bleeding in 12% of the cases [84]. Bleeding rates after EMR of large colonic polyps range from 2 to 11% [85].

The application of soft coagulation with the tip of a snare has been demonstrated to be both safe and effective for the treatment of intraprocedural bleeding during EMR of large colonic polyps [86]. Other methods including hot biopsy forceps, monopolar hemostatic forceps, bicap probes, APC, and endoscopic clips can be used for achieving hemostasis.

Prophylactic endoscopic coagulation of nonbleeding vessels by using coagulating forceps after EMR of colorectal lesions larger than 20 mm did not significantly decrease the incidence of delayed postprocedure bleeding compared with control subjects who received no additional therapy (5.2 vs 8.0%; $p < 0.3$). Risk factors for clinically significant postprocedural bleeding included a proximal colonic location, polyp size, and intraprocedural bleeding [86]. More frequent and minor complications include pain and postpolypectomy syndrome.

Perforation after EMR of colonic lesions is also rare (<1%) [16, 17, 87, 88]. A perforation can be identified by carefully examining

the resection defect. Small perforations recognized during the procedure can be successfully sealed by using endoscopic clips [88, 89]. Larger perforations may require urgent salvage surgery to prevent peritonitis.

If CELS is performed without full-thickness resection, complications are comparable to the ESD or EMR technique but have a risk of laparoscopic complications such as injuries to the abdominal wall or intra-abdominal organs in less than 0.4% of the cases [90, 91]. If a full-thickness resection is performed, complications could be injury to surrounding structures like the small bowel, ureter, or blood vessels. After closure of the wall defect, perforation or stenosis could occur. Still, major complications seem to be rather rare. Magrina [91] reported only two major leakages (1.6%) and an overall complication rate of 4.6% after 126 CELS resections for benign gastric tumors. Another possible complication in full-thickness resection of malign lesions could be seeding of tumor cells. However, Ikehara et al. [92] reported from 90 patients, who suffered gastric perforation during gastroscopic resection for adenocarcinoma, that none showed peritoneal dissemination even 50 months after the procedure. Nevertheless, the resected specimen should be handled with care and the tumor should not be opened or touched.

(When discussing all these data, surgeons and endoscopists should be aware that most data are gathered in Japan and other

Asian countries, where the regular body mass index (BMI) of patients is under 25 kg/m². Especially in laparoscopic surgery, a low BMI is pivotal for easier laparoscopy and good postoperative results.)

Conclusion

All of the above-mentioned techniques can be offered to all patients with an early cancer in the gastrointestinal tract if they meet the criteria for an endoscopic therapeutic option. Especially, because all other options, such as radiochemotherapy, can still be offered in order to achieve the best outcome of the patients after an initial endoscopic therapy.

Prior to starting an endoscopic therapy, however, all decisions should be discussed between all the important disciplines such as surgeons, radiologists, and chemotherapy experts.

Disclosure Statement

The authors declare no competing interests.

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