Endoscopic Submucosal Dissection (ESD) in Colorectal Tumors

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Keywords

Endoscopic submucosal dissection ·
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Summary

Background: Endoscopic submucosal dissection (ESD) – initially developed for the treatment of early gastric cancer in Japan – is an attractive option for en bloc resection of larger sessile or flat colorectal neoplasia. **Methods:** A review of the current literature on colorectal ESD was carried out. **Results:** In contrast to conventional endoscopic mucosal resection (EMR), ESD for larger colorectal neoplasia yields high en bloc resection rates and very low recurrence rates. The frequency of delayed bleeding is similar for EMR and ESD. Higher perforation rates during ESD are mostly due to microperforations identified and treated during the intervention, and are therefore of minor clinical relevance. A major disadvantage of ESD is the necessity for high-level endoscopic skills and long procedure times. ESD also has the potential to replace laparoscopic surgery or transanal endoscopic microsurgery mainly due to its lower complication rates. **Conclusion:** ESD for the resection of larger flat or sessile colorectal lesions has potential advantages over conventional EMR or minimally invasive surgery. Due to the low incidence of early gastric cancer, experience with ESD will remain limited in Western countries. The spread of colorectal ESD will depend on adequate training opportunities and also on modifications yielding a reduction in procedure time.

Schlüsselwörter

Endoskopische Submukosadisektion ·
Kolonrektale Adenome · Kolorektale Frühkarzinome ·
En-bloc-Resektion · Perforation · Nachblutung

Zusammenfassung

Hintergrund: Die endoskopische Submukosadisektion (ESD) wurde zur Therapie des Magenfrühkarzinoms in Japan entwickelt. Sie ist auch eine attraktive Methode zur En-bloc-Resektion größerer sessiler oder flacher kolorektaler Adenome. **Methoden:** In dieser Übersicht wurde die Literatur zur kolorektalen ESD gesichtet und bewertet. **Ergebnisse:** Im Gegensatz zur konventionellen endoskopischen Mukosaresektion (EMR) ermöglicht die ESD eine deutlich höhere En-bloc-Resektionsrate und weist eine geringere Rezidivrate auf. Die Anzahl der Blutungskomplikationen unterscheidet sich nicht. Die höhere Perforationsrate ist von geringer klinischer Bedeutung, da es sich meist um Mikroperforationen handelt, die bei der ESD erkannt und therapiert werden. Der wesentliche Nachteil der ESD besteht in der deutlich längeren Interventionszeit. Gegenüber minimalinvasiven chirurgischen Therapieformen weist die ESD den Vorteil der geringeren Komplikationsrate auf. **Schlussfolgerungen:** Die kolorektale ESD hat Vorteile gegenüber der konventionellen EMR und auch gegenüber der minimalinvasiven Chirurgie. Aufgrund der geringen Inzidenz des Magenfrühkarzinoms wird die Erfahrung mit ESD in den westlichen Ländern begrenzt bleiben. Die Verbreitung der kolorektalen ESD wird hierzulande wesentlich von den Trainingsmöglichkeiten und auch von technischen Vereinfachungen abhängen, die eine Reduktion des Zeitbedarfs ermöglichen.

Introduction

Colorectal cancer incidence in Europe is high [1], and endoscopic screening for adenoma has been established with remarkable success [2]. Nevertheless, efficacy of screening endoscopy critically depends not only on a high adenoma detection rate but also on the completeness of endoscopic adenoma resection. Thus, occurrence of advanced adenoma is common after polypectomy [3], and it has been demonstrated that 27% of interval cancers developed at segments of previous polypectomy [4]. Moreover, incomplete polyp resection might account for up to 19% of interval cancers [5]. Even small-sized (10–20 mm) flat or serrated lesions are incompletely resected in up to one third of the cases [6]. In fact, endoscopic resection of sessile or flat lesions larger than 20 mm is usually not achieved en bloc, and recurrence rates of up to 31% have been reported after piecemeal (i.e. fragmented) endoscopic mucosal resection (EMR) [7]. Since histopathology cannot confirm completeness after piecemeal resection, short-term follow-up endoscopy within 2–6 months is the standard of care [8]. In contrast to EMR, endoscopic submucosal dissection (ESD) allows high en bloc resection and very low recurrence rates, even for larger flat or sessile colorectal lesions. Major disadvantages of ESD are high demands on technical skills, longer procedure times, and a higher perforation rate (the latter being probably of little clinical relevance since most perforations are treated during the ESD intervention). ESD has been developed and evaluated mainly in Asia, in particular in Japan; the experience with ESD is limited in the Western world.

Potential Indications for Colorectal ESD

En bloc resection by ESD is an attractive method for any large benign colorectal adenoma since histological confirmation of complete resection would eliminate the need for short-term endoscopic control after polypectomy. However, since ESD is technically demanding and needs long procedure times, more stringent criteria for colorectal ESD have been elaborated by the Japanese Colorectal ESD Standardization Implementation Working Group. These consensus recommendations include only larger-sized lesions (>20 mm) with suspected high-grade intraepithelial neoplasia or early cancer (laterally spreading tumor non-granular type, pseudodepressed or depressed lesions, irregular surface pattern suggestive of early submucosal invasion) or lesions with fibrosis including sporadic adenoma in chronic inflammation (e.g. ulcerative colitis) or residual carcinoma after previous endoscopic therapy [9, 10].

Practical Aspects of Colorectal ESD

ESD is performed with an endoscope equipped with an accessory water irrigation channel. Insufflation is done with carbon dioxide to reduce abdominal discomfort during long-lasting procedures [11]. Moreover, a transparent hood is attached to the tip of the scope to facilitate submucosal dissection. Also a careful characterization of the target lesion with high-definition or magnification endoscopy including chromoendoscopy is performed. Various classification systems are validated for the identification of malignancy and of deeper submucosal in-

Fig. 1. Example of an ESD procedure: **a** A large sessile lesion (Paris classification 0–Is/0–IIa) was detected in the ascending colon. **b** Target lesion is surrounded by marking dots to facilitate resection. **c** Submucosal injection of 4% gelatine solution with a small amount of indigo carmine; injection is carried out with a small bore needle outside the lesion to avoid submucosal bleeding. **d** Opening of the submucosal space with traction on the specimen by gravity. **e** Sub-total preparation, and **f** resection area with hemoclips to prevent delayed bleeding.

Fig. 2. Sample preparation and histopathological analysis. Special care is taken to correlate microscopic findings with endoscopy. Moreover, the margins of the specimen are meticulously inspected for residual adenoma/carcinoma. **a** ESD specimen pinned on corkboard to facilitate identification of margins. **b** Positioning of transverse sections. **c** Microscopic analysis allowing topographical correlation.

vasion (Paris classification [12], pit pattern classification [13], NICE classification [14]). In addition, endoscopic ultrasound is very useful for larger rectal lesions. After evaluation of the lesion, the borders are marked with coagulation current (figs. 1a, b). Next, submucosal injection is performed with a thin (25-G) injection needle (fig. 1c) using injection fluids that result in sustained elevation (e.g. glycerol, gelatin, or hyaluronic acid) and contain a small amount of dye (e.g. indigo carmine) for better visualization of the submucosal layer [10, 15–17]. A variety of knives are available for mucosal incision/submucosal dissection (e.g. dual, hook, insulation-tipped (IT), triangle-tipped (TT) [18–21]), some of them allowing also for submucosal injection (e.g. flush knife [22] or hybrid knife [23, 24]). Hemostasis during the dissection procedure is achieved either with the knife itself in coagulation mode or – in the case

of larger vessels – with dedicated hemostatic forceps or hemoclips. Submucosal dissection is then carried out paying attention to the patient's position to achieve traction on the specimen by gravity [25, 26] (figs. 1d, e). In difficult situations or locations, specific techniques or devices may be helpful to facilitate traction on the specimen [27, 28]. After the specimen is resected, hemostasis is secured by additional careful coagulation and/or hemoclips (fig. 1f). The specimen is then retrieved and stretched out (e.g. on a cork board) to facilitate further processing (fig. 2a). Cooperation with the pathologist is very important, and preparation of the ESD specimens should be performed to allow for correlation of the endoscopic/macrosopic appearance with histopathology. Particular care must be taken with the lateral and vertical margins in order to confirm complete resection of the lesion [29] (figs. 2b, c).

Clinical Studies on Colorectal ESD

Several large series on colorectal ESD have been published from Asian centers. However, most of the data are retrospective, and direct prospective comparative data on ESD versus EMR or surgery are not available. A recent systematic review reported resection rates of 90.5% (61–98.2%) for endoscopic en bloc resection and of 76.9% (58–95.6%) for histologically confirmed complete resection, with associated local recurrence rates of 1.9% (0–11%) [9]. In addition, there are several studies with >500 ESD procedures, including large single center series [25, 30], multicenter surveys [31, 32], and a prospective multicenter study [33]. These series confirm the high en bloc resection rates (up to 88.8% histologically confirmed complete resections) and the reported complication rates (perforation 4.8–5.4%, delayed perforation 0.4–0.7%, bleeding 1.5–1.7%). It was also demonstrated that ESD is feasible not only for the resection of adenoma or superficial cancers, but is also curative for submucosal invasive cancer. Thus, submucosal invasion limited to the upper 1,000 µm of the submucosal layer (sm1) is sufficiently treated with local resection if the tumor has a G1/G2 differentiation and no lymphatic or vascular invasion (L0, V0) [34–37].

When compared to EMR, data on ESD consistently show a higher en bloc resection rate/lower recurrence rate. Thus, in an analysis of 26 studies on EMR, en bloc resection for relatively smaller target lesions was possible in only 42.6% (19.2–91.8%) and recurrence rates were 17% (4.8–31.4%) for lesions resected in a piecemeal fashion [9]. In addition, several retrospective case series [38–41], a matched case control analysis [42], and a meta-analysis [43] were published on the comparative analysis of EMR versus ESD. All these reports show a higher efficacy of ESD for the resection of larger sessile or flat lesions, resulting in a lower recurrence rate. When analyzing risk factors for adenoma recurrence after EMR, associations were reported with size and morphology of the lesions

Table 1. Overview of European studies on colorectal ESD

Author, year [ref.]	Cases, n	Location (%)	Size, mm	Procedure time, min	En bloc rate, %	Perforation, %	Bleeding, %
Hurlstone et al., 2007 [57]	42	rectum (33.3)	31.0	n.a.	78.6	2.4	9.5
Farhat et al., 2011 [58], multicenter	85	rectum (84.7)	26.0	105	77.1	18.1	11.2
Probst et al., 2012 [59]	76	rectum (86.6)	45.5	176	81.6	1.3	7.9
Thorlacius et al., 2013 [61]	29	rectum (59.0)	26.0	142	72.0	6.9	3.3
Repici et al., 2013 [60]	40	rectum (100.0)	46.8	86.1	90.0	2.5	5.0
Sauer et al., 2013 [62]	83	rectum (18.0)	35.0	103	79.5	9.8	2.2

n.a. = Not applicable.

(higher risk of incomplete resection for serrated adenoma/flat adenoma), piecemeal resection, and number of fragments [6, 7, 44–46]. Data on complications after EMR/ESD show similar bleeding rates (EMR 0–11.1%; ESD 0.5–9.5%), but the perforation rate is higher for ESD (1.3–20%) than for EMR (0–5.8%). However, the vast majority of perforations occurring during ESD are small and easily treated during the procedure, and thus the actual need for emergency surgery does not differ for EMR versus ESD [31, 47–51]. ESD is technically demanding and does require long procedure times. Thus, a recent study comparing 1,029 cases of conventional EMR with 816 ESD procedures showed a significantly higher procedure time for ESD (96 min) than for EMR (18 min). Procedure times increased with the size of the lesion, although for very large lesions a comparison to laparoscopic surgery would be more appropriate [48, 49]. Comparative data are available for ESD versus surgery, but again without a formal head-to-head study. Two smaller retrospective studies found no significant difference for efficacy (including procedure time) and safety between ESD versus transanal endoscopic microsurgery (TEM) for the treatment of early rectal cancer [52, 53]. A recently published systematic review and meta-analysis of 11 ESD and 10 TEM studies showed higher en bloc resection rates and a reduced need for additional surgery for TEM, while recurrence rates were significantly lower after ESD and no difference in the overall complication rate was observed [54]. Finally, a comparative retrospective study from the National Cancer Center Tokyo found that ESD is equally effective as laparoscopic surgery for the treatment of early colorectal cancer, with significantly lower complication rates and shorter procedure times [55]. Indeed, the accompanying editorial called for an initiative to disseminate ESD for optimal treatment of early colorectal cancer [56]. While larger studies on colorectal ESD are almost exclusively from Asia, data on colorectal ESD from Western countries is mostly limited to the distal colon [57–62] (table 1).

Taken together, there are considerable advantages of ESD over EMR for the resection of larger sessile or flat lesions, in particular high en bloc resection rates and low recurrence rates. The major problem of ESD is the technical challenge and the relatively long procedure time. Compared with sur-

gery, ESD shows similar performance as TEM for rectal lesions, while a clear advantage – both for clinical outcome and procedure time – was observed in a single comparative study for ESD versus laparoscopic surgery for the treatment of T1 colorectal carcinoma. Nevertheless, there still is a need for prospective comparative trials to better define the role of ESD in comparison to EMR or surgery.

Training for ESD

Since ESD requires advanced endoscopic skills, thorough training is mandatory for its safe use in patients. Algorithms for colorectal ESD training are available mainly from Japan [25, 63–65]. Emphasis is put on theoretical knowledge, diagnostic skills, and attendance of ESD procedures performed by experts. Later, hands-on training is started under the supervision of experts, starting with gastric ESD at easily accessible sites (i.e. antrum), and then continuing on to more complex procedures including rectal ESD and finally ESD in the proximal colon. It has been demonstrated that complication rates during the learning curve for gastric ESD do not differ between supervised trainees and experts [66]. The situation for an endoscopist willing to learn ESD is very different in the Western countries where experience with ESD is limited, the incidence of early gastric cancer is low, and starting ESD hands-on training with small early gastric cancer lesions under expert supervision is not a generally available option [67–69]. Therefore, it has been suggested to start with observation of ESD procedures performed by Asian experts, followed by hands-on training on isolated stomachs and finally life animal procedures including management of complications, before actually attempting colorectal ESD under expert supervision in patients [70]. It has also been suggested that colorectal ESD should be started on smaller-sized lesions in the rectum, gradually increasing the level of difficulty of the procedures (larger lesions, more proximal location) [70]. Indeed, this concept – both animal experimentation and tutorials with Japanese experts – has been successfully implemented under the auspices of the European Society of Gastrointestinal Endoscopy [71].

Optimizing the ESD Procedure: Current Developments

Modifications of the ESD technique are aiming at simplifying resection, reducing procedure time, and minimizing the risk of complications. Thus, submucosal gel/elastic polymer injection has been evaluated in animal models. These substances allowed long-lasting elevation and more efficient dissection [72–74] and even had autodissective properties [75], thus greatly reducing procedure time. Moreover, the hybrid knife [23, 24] or flush knife [22] allow submucosal injection and dissection to be carried out with a single device. Finally, specific cutting devices are being evaluated, e.g. a mucosectome with a short cutting blade [76] or a submucosal dissector [77].

Conclusion

ESD is an attractive endoscopic treatment modality for larger sessile or flat adenomas/superficial or slightly submucosal invasive colorectal cancers. The advantages of high en bloc resection rates/low recurrence rates are currently bal-

anced by the high technical challenge of the method and the associated long procedure times. While colorectal ESD has recently become a standard procedure in major Asian endoscopy centers, propagation of ESD in Western countries will critically depend on opportunities for specialized training and probably also on technical developments to facilitate ESD and reduce procedure times.

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Disclosure Statement

The authors declare that there are no potential conflicts of interest relevant to the publication.

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