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Endoscopic Resection of Superficial Colorectal Neoplasms

Expert Opinion Statement on behalf of the Swiss Society of Gastroenterology

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Abbreviations

AI	artificial intelligence
CSP	cold snare polypectomy
EFTR	endoscopic full thickness resection
EMR	endoscopic mucosal resection
EMRp	endoscopic mucosal resection in piecemeal technique
ESD	endoscopic submucosal dissection
ESR	endoscopic submucosal resection
HSP	hot snare polypectomy
IPB	intra procedural bleeding
LST	lateral spreading tumor
PES	post polypectomy electrocoagulation syndrome
PPB	post procedural bleeding
RCT	randomized controlled trial
SSL	sessile serrated lesion
TAE	transanal excision
TAMIS	transanal minimally invasive surgery
TAR	transanal resection
TEM	transanal endoscopic microsurgery

Abstract

Colonoscopy and endoscopic resection of colorectal neoplasms reduce the incidence and mortality from colorectal cancer. Endoscopic resection of smaller polyps is considered an essential skill for all endoscopists who perform colonoscopy whereas the resection of large and/or difficult polyps should be performed by experienced interventional endoscopists using advanced resection techniques if necessary.

This expert opinion statement on behalf of the Swiss Society of Gastroenterology summarizes recommendations of existing international guidelines and incorporates recent data, providing a concise manual for Swiss endoscopists performing colonoscopy and endoscopic resections of colorectal neoplasms in their daily practice.

Summary of main recommendations

1. Cold snare polypectomy (CSP) is recommended as the preferred technique for the resection of diminutive and small polyps (size ≤ 5mm and 6–9mm respectively) due to high rates of complete resection, adequate tissue sampling for histology and low complication rates.

2. Biopsy forceps resection should be avoided, due to the high rate of incomplete resection associated with this technique.

3. Hot snare polypectomy (HSP) is recommended to resect pedunculated polyps. Stalks > 10mm should be injected with adrenalin 1:10,000 to prevent bleeding.

4. Lesions sized > 10mm should be carefully assessed for the presence of submucosal invasion using advanced imaging techniques.

5. Hot snare polypectomy (HSP) with prior submucosal injection (also called EMR) is recommended for polyps sized 10–19mm.

6. Cold snare polypectomy (CSP) – also in piecemeal technique – can be considered in serrated lesions sized 10–19mm.

7. Complex lesions > 30mm and/or at difficult locations should be referred to an experienced center.

8. ESD is recommended for removal of colorectal lesions suspicious for superficial submucosal invasion and which otherwise cannot be removed *en bloc* by standard polypectomy techniques.

9. Endoscopic full thickness resection (EFTR) is a therapeutic option for the treatment of lesions, which are challenging to resect using standard endoscopic techniques (e.g. non lifting colorectal lesions, recurrences after previous endoscopic resection, lesions at difficult locations, early carcinomas and subepithelial lesions).

10. Virtual or dye-based chromoendoscopy in addition to high definition white-light endoscopy is recommended to detect residual polyp-tissue at the resection site after piecemeal polypectomy during the first follow-up endoscopy (after 3 to 6 months).

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1. Assessment and advanced endoscopic imaging of colorectal neoplasms

Advanced endoscopic imaging in colonoscopy is now well established as an important diagnostic tool[1]. It has evolved from a niche practice of expert endoscopists to common clinical practice and is especially relevant for evaluation of larger non-polypoid lesions to guide treatment decision, such as either endoscopic or surgical resection. Advanced endoscopic imaging in colonoscopy is built upon the core foundations of high-quality colonoscopy, such as good quality bowel preparation, the use of high definition colonoscopes, careful slow withdrawal and the use of spasmolytic medications when indicated[2].

1.1. Morphological assessment and description

The gross morphology of a polyp should be described according to the Paris endoscopic classification of superficial neoplastic lesions (Figure 1, appendix). It provides a common vocabulary for communication between endoscopists and is also useful for the estimation of the depth of invasion, which may influence the choice of resection technique. The use of such morphological description is also very important for the pathologists in their interpretation of resected malignant polyps[3].

Lateral spreading tumors

Lateral spreading tumors (LSTs) were first described by Kudo as tumors with predominant spread within the mucosa while still relatively flat. In the Paris consensus of 2002, LSTs were defined as nonpolypoid lesions larger than 10 mm in width that typically extend laterally and circumferentially along the colonic wall, rather than vertically and were classified as type 0-IIa. LST are distinguished based on their granular or non-granular, homogenous or non-homogenous appearance. They differ widely in their risk of submucosal invasion. Table 1 in the appendix shows the different subtypes with their risk of submucosal invasion.

1.2. Advanced endoscopic imaging Chromoendoscopy (image enhanced endoscopy)

Image enhanced endoscopy can be classified as dye-based or virtual chromoendoscopy. This technique can be used for both, lesion detection and lesion characterization. Combined with optical magnification image enhanced endoscopy helps for better lesion characterization as well as estimation of depth of invasion, which correlates with the risk of lymph node metastases.

Dye-based chromoendoscopy: Indigo-carmine, a contrast dye that accentuates mucosal surface irregularities, is commonly used for detection and delineation of the margins. It is also useful to accentuate the mucosal surface patterns. Cresyl violet is an absorptive dye that acts by staining cell nuclei. Combined with optical magnification, it is used to highlight the pit patterns of colonic polyps. The Kudo classification of colorectal polyps[4] (Table 2, appendix), which combines dye-based chromoendoscopy with optical magnification, has been validated for histopathological correlation.

Virtual chromoendoscopy: Virtual chromoendoscopy has greatly simplified advanced endoscopic imaging. Whereas dye-based chromoendoscopy only enhances the pit pattern of the colonic polyp, virtual chromoendoscopy such as NBI (Olympus®), BLI (Fujifilm®) and OE (Pentax®) use the narrow bandwidth blue and green wavelengths to improve the visualization of mucosal pit patterns and microvessels of the colonic polyps. These changes in surface and microvessels have been correlated with histology and depth of submucosal invasion in malignant polyps. The NBI International Colorectal Endoscopic (NICE) classification[5] (Table 3, appendix), which is based on three parameters – namely color, vessels and surface pattern of the polyp – is commonly used to predict polyp histology when optical magnification is not available. The Japan NBI Expert Team (JNET) classification system (Table 4, appendix) requires the use of optical magnification to examine the microvessel and microsurface patterns. Unlike the NICE classification, the JNET classification is able to differentiate to some extent adenoma with low grade dysplasia from adenoma with high grade dysplasia, intramucosal cancer or shallow submucosal invasion. This has relevant implications for the choice of endoscopic resection techniques, such as endoscopic mucosal resection (EMR) in the context of low grade dysplasia or attempting endoscopic submucosal dissection (ESD) to achieve en bloc resection if more advanced histology is expected. Nevertheless, there are also limitations with the JNET classification system and additional use of cresyl violet chromoendoscopy may still be required in borderline cases[6,7].

1.3. Stratifying lesion complexity

The so called "SMSA score" (Size, Morphology, Site, Access) is a simple tool to stratify lesion complexity (Table 5, appendix), developed and evaluated by UK experts[8]. This score stratifies lesions into 4 levels of difficulty (1 = easiest, 4 = most difficult). The validation of this score shows higher complication rates (8.6% vs 0%, p: 0.007) and lower clearing rates (87.5% vs 97.5%, p: 0.009) for level 4 polyps vs level 2 and 3.

2. Diminutive and small polyps (up to 10mm)

The vast majority of polyps detected during colonoscopy are diminutive (1–5mm) or small (6–9mm). Diminutive polyps represent approximately 60% of all detected polyps. The risk of advanced pathology or cancer in these polyps is very low. A real-time optical diagnosis by experienced endoscopists would allow to discard diminutive polyps after resection (also known as "resect and discard") and non-neoplastic polyps located in the sigmoid and rectum to be left in situ (also known as "diagnose and leave"). The two approaches mentioned above would help to reduce the number of polyps which are sent to the pathologists, resulting in saving costs for health care systems.

2.1. Optical diagnosis and artificial intelligence (AI)

Optical diagnosis raises several concerns: first when diminutive polyps are discarded, possible advanced histology is not diagnosed. However advanced pathology within diminutive polyps is very low, around 0.1% (range 0.1% to 12%, mostly estimated at the lower end of this range) and for cancer even lower, although not zero (range from 0% to 0.6%). Performance levels of endoscopists in correctly predicting the histology of diminutive polyps remain highly variable, underlining the necessity of training, auditing and performance monitoring once an optical diagnosis strategy is implemented. The usefulness of AI for optical diagnosis is unclear at this stage, however it is assumed that AI will play a major role in the future, assisting in detection as well as characterization of colonic lesions. Virtual chromoendoscopy and dye based chromoendoscopy can be used, under strict controlled conditions, for the real-time optical diagnosis of diminutive (≤ 5mm) colorectal polyps and may replace histopathological diagnosis. The optical diagnosis has to be reported using validated classifications, must be adequately photodocumented and should only be performed by experienced endoscopists who are adequately trained.

2.2. Resection

For the resection of diminutive and small polyps, cold snare polypectomy (CSP) is the preferred technique, due to its high rate of complete resections and its time effectiveness[9]. Additionally, CSP avoids electrocautery injury (in meta-analyses to date no perforation has been reported)[10] and nearly eliminates the risk of delayed bleeding. CSP is often even possible in anticoagulated patients, especially for polyps less than 10mm[11]. Lesions measuring 1–2mm may exceptionally be removed by forceps (e.g. if not accessible with the snare). The removal of larger lesions using a forceps has a high rate of incomplete resection, which is the reason why this technique should be avoided in daily practice.

Dedicated cold snares with thinner monofilament wires, smaller diameter and diamond-shaped are considered to be more effective in some studies, compared to traditional snares, although this is not definitive[12].

Direct suctioning immediately before resection may elevate the polyp and care should be taken to include a 1–2mm margin of normal tissue around the polyp, even if the defect becomes larger after resection. This margin lowers the risk of recurrence. The snare has to be positioned parallel to the mucosal surface, then firm downward pressure applied on the snare and resect after suctioning the gas. After removal, the application of clips is not necessary.

3. Pedunculated polyps

Pedunculated lesions are usually easily removed completely by hot snare polypectomy (HSP). However, the most common adverse events are intraprocedural bleeding (IPB) or post-polypectomy bleeding (PPB) – especially in large pedunculated polyps – due to the presence of a large blood vessel within the stalk (thick-stalked polyps contain more vessels in the submucosal layer than thin-stalked ones)[13] – whereas a perforation is rare after the resection of a pedunculated polyp.

3.1. Post-polypectomy bleeding (PPB) risk factors

Polyp-related risk factors

According to the available literature, polyp size > 10mm or stalk diameter > 5mm, polyp location in the right colon and the presence of a malignancy in the lesion comprise the most eminent polyp related risk factors[14]. With respect to size, the risk of PPB is most significant in pedunculated polyps with a head size > 20mm and/or a stalk diameter > 5mm.

Patient-related risk factors

Thienopyridine (Clopidogrel, Prasugrel) and anticoagulant drugs are the most relevant risk factor for PPB. Peri-procedural Clopidogrel use shows up to a threefold increased risk for PPB[15].

Endoscopist-related risk factors

Procedures executed by low volume endoscopists (< 250 annually) are associated with a higher complication rate[16].

3.2. Techniques preventing bleeding after resection of large, pedunculated polyps

Polypectomy of large pedunculated polyps is associated with an approximately 5-fold higher incidence of bleeding, particularly in polyps > 20mm, in which preventative measures can significantly reduce bleeding complications after polypectomy.

Adrenaline injection

RCTs showed that infiltration of the polyp stalk with adrenaline (1:10'000) significantly reduces IPB/PPB compared with no intervention[17]. Adrenaline (epinephrine) injection prior to colonoscopic polypectomy is effective and leads to an 8-fold reduction in bleeding episodes[18].

However, comparing adrenaline to saline injection before polypectomy of polyps > 10mm in size, the lower rates of bleeding found with adrenaline did not reach statistical significance[19]. Possibly, the volume-based tamponade effect explains this non-significant result.

Mechanical prophylaxis

Mechanical prophylaxis such as the use of endoloops or hemoclips may be superior to adrenaline injection in achieving hemostasis. Two RCTs involving polyps > 20mm in size, showed that application of such mechanical devices on the stalk, alone or in combination with adrenaline injection, significantly (up to 4-fold) decreased PPB compared with adrenaline injection alone[20].

In addition, complete closure after resection by clipping may be ideal to reduce the risk of delayed bleeding.

Positionning of the polypectomy-snare on the stalk

A morphometric study of the blood supply of pedunculated polyps has shown that the position of the snare on the stalk is not relevant for prevention of hemorrhage after resection[21].

Two other important aspects are limiting the perforation risk as well as incomplete resection. In order to guarantee these two additional aims, the optimal position to resect is in the midsection of the stalk[22].

There are however some additional considerations with respect to an oncological approach, as 40% of T1 carcinomas have a peduncular morphology. Lymph node metastases are less common in pedunculated compared to sessile malignant lesions. In addition, Haggitt level 4 (submucosal invasion beyond the stalk, Table 6, appendix) but not 3 (infiltration into the stalk) is considered a risk factor for lymph node metastases[23]. Therefore, in case of high suspicion of malignancy, positioning the snare more at the base of the stalk (concomitant with an increased perforation risk) is justified.

3.3. Approach to very large pedunculated polyps and/or at difficult locations

Polyp head too large (> 30mm) for polypectomy snare

The management of giant pedunculated colorectal polyps can be challenging; the injection of adrenaline into stalk and head of the polyp offers the additional advantage of reducing polyp size up to 80% (known as adrenaline volume reduction) and reducing the risk of bleeding; therefore facilitating assessment and removal of giant polyps while decreasing the need for piecemeal resection[24].

In case of insufficient effect of adrenaline volume reduction another possibility is (after previously prophylactic clipping or looping) to cut the stalk of the polyp using a knife (e.g. needle knife, insulated-tip knife)[25].

Difficult polyp location

To improve overview and accuracy of snare positioning as well as visibility in case of an IPB, the patient should be positioned in such a way that the stalk is hanging with gravity. As a result, at least the proximal part of the stalk is stretched and better accessible. Also, in case of an IPB, blood will flow away from the bleeding spot improving chances to stop the bleeding[26].

4. Large polyps sized 10–19mm

Hot snare polypectomy (HSP) is the preferred technique for the resection of polyps of this size. Prior submucosal injection reduces the risk of deep thermal injury and enhances the rate of en bloc resection. Therefore, submucosal injection following resection with an adequate snare is recommended in these situations.

Cold snare polypectomy (CSP) is rapidly evolving, showing lower rates of bleeding and deep mural injury in polyps up to 10mm. This technique has also shown to be very effective and safe in larger polyps (sized 10–19mm) resulting in 80% complete resection with no perforation, delayed bleeding or post polypectomy syndrome. A meta-analysis including 522 colorectal polyps (mean size 17.5mm; 10mm–60mm) which were resected by CSP showed excellent results with an overall adverse event rate of only 1.1% with no perforation. The complete resection rate was 99.3%. The rate of residual polyp tissue higher for adenomas (11.1%) compared to serrated lesions (1%)[28]. Therefore, especially for serrated lesions, piecemeal cold snare EMR can be recommended.

5. Large polyps sized > 20mm

Endoscopic mucosal resection (EMR) is the technique of choice for > 20mm. Using this technique a solution is injected into the submucosal layer, in order to separate the mucosa and the mucosal lesion from the proper muscle layer followed by snare resection of the lesion either en bloc (for lesions with signs of superficial submucosal invasion) or in "piecemeal technique" (for lesions with no signs of submucosal invasion). En bloc EMR is generally limited to lesions up to 20mm in size, larger lesions require advanced resections techniques for *en bloc* resection, e.g. ESD.

Large cohort studies show a success rate of > 90% for endoscopic treatment of large laterally spreading lesions and sessile colorectal lesions.

5.1. Submucosal injection

Solutions that are more viscous than saline, for which clinical safety has been proven (e.g. succinylated gelatine, hydroxyethal starch[29] glycerol, hyaluronic acid) provide superior technical outcomes and reduced procedural times in EMR. We recommend adding a biologically inert blue dye (such as indigo-carmine) to the injection solution since it provides better delineation of the margins of the lesion and easier detection of deep mural injuries. The "non-lifting sign" is a strong predictor of incomplete resection and is associated with deep submucosal invasion (submucosal infiltration level 3, sm3)[30] (Figure 7, appendix).

5.2. Resection

The goal of EMR is the complete resection of all visible polyp tissue either in "en bloc" or in "piecemeal technique". En bloc resection rates by EMR for lesions > 20mm are reported in 16–48% of the lesions[31]. Limited data exists, which compare different kinds of snares. The snare size should be selected depending on size, morphology and localisation of the polyp. Monofilament snares have a thin wire (< 0.4mm) providing a greater current density, making thermal injury to the colonic wall less likely. Polyfilament snares have a thicker wire that may better grip the lesion.

5.3. Adjunct therapy and clipping after resection

After resection of all visible polyp tissue, inspection of the resection margins is crucial to identify residual polyp tissue. Inspection using magnifying endoscopy has been shown to result in lower recurrence rates in a retrospective case control analysis. In a recent randomized trial from Australia, thermal ablation of resection margins reduced the recurrence rate from 21% to 5.2%[32]. This technique can be considered after piecemeal resection of large colorectal lesions.

Clipping after EMR

A recent large randomized trial showed a reduced bleeding risk after the application of hemoclips following EMR. The protective effect was limited to polyps > 20mm located in the proximal colon and the clipping had to be complete. Complete clipping reduced the bleeding risk from 9.6% to 3.3% for lesions at this location[33]. Complete clipping of the resection site is therefore recommended after resection of large colonic lesions in the right sided colon if technically feasible.

5.4. Complication rates of EMR

Post EMR bleeding occurs in 5–7%. Risk factors include proximal colon location and increasing lesion size. Perforation is an uncommon event with a rate of 1.4–1.5% in meta-analyses[34].

5.5. Follow-up after endoscopic resection: identification of recurrence after EMR

The recurrence rate after piecemeal EMRs (EMRp) is as high as 15–20%[35]. Therefore, an early endoscopic follow-up is recommended 3–6 months after EMRp. We recommend the use of virtual or dye-based chromoendoscopy in addition to high definition white light endoscopy for the detection of residual or recurrent neoplasia at a piecemeal polypectomy scar site. In order to identify recurrences after EMR, the use of virtual chromoendoscopy (e.g. NBI) in addition to high definition white light endoscopy improves the sensitivity from 67% to 93%. This effect was mainly due to the detection of flat recurrences[36]. Recurrences are usually diminutive in size and can be endoscopically removed leading to a definite complete resection rate of up to 93%[37].

Routine biopsies of post-polypectomy scars can be abandoned providing that a standardized imaging protocol with virtual chromoendoscopy is used by a sufficiently trained endoscopist.

5.6. Treatment of recurrences after EMR

Residual or recurrent polyp tissue detected at surveillance endoscopy can be treated effectively. Snare resection provides superior outcomes to other modalities [38]. Lesions or areas that are not amenable to snare resection can be treated by hot biopsy avulsion [39]. Alternative techniques for non-lifting areas in recurrent adenomas include cold avulsion in conjunction with thermal ablation. Alternatively endoscopic full thickness resection (EFTR) is an effective option for the treatment of mainly non-lifting recurrences after previous endoscopic treatment of colorectal lesions.

5.7. Lesions at difficult locations

Lesions at difficult locations (involvement of the ileo-cecal valve, behind folds, anorectal junction) should be referred to a tertiary centre. In a large cohort of lesions involving the ileo-cecal valve (mean size 35mm), complete adenoma clearance was achieved in 94% and surgery was avoided in 81% of these patients [40].

For polyps located in the appendiceal orifice, endoscopic full thickness resection (EFTR) or surgery should be considered if the distal margin of the lesion cannot be visualised and if more of 50% of the circumference of the appendiceal orifice is involved. The substantial risk of appendicitis has to be taken into account performing endoscopic full thickness resections in the region of the appendix.

6. Advanced endoscopic resection techniques

6.1. Endoscopic submucosal dissection (ESD)

Quality and training criteria

ESD is technically demanding and, particularly in the early phase of training, associated with higher rates of complications [41, 42]. Therefore, the ESGE most recently has defined 1) skills and competence requirements prior to start training ESD, 2) how training should look like and 3) what the knowledge and experience should be to maintain competence [43]. In brief, advanced endoscopy diagnostic practice is advised before initiating ESD training. Training in ESD should be considered only by fully-trained endoscopists with proficiency in EMR and adverse event management. Moreover, ESGE recommends performing at least 20 ESD procedures in animal models before human practice. In addition, supervision and observation of experts performing ESD in tertiary referral centers is recommended during the first 10 procedures in humans. The latter should be performed on carefully selected lesions, ideally small lesions (< 30mm), located in the gastric antrum or in the rectum. In fact, ESD can be performed and thus, learned relatively safe particularly in the rectum. Even with little prior ESD-training (< 5 procedures) rectal ESD can be performed safely [44] and location in the rectum rather than any other site indeed, was demonstrated to represent a predictive factor for success [45]. Endoscopists involved in ESD should have specific knowledge of the instrumentation, technique and electrosurgical equipment. Finally, correct estimation of the probability of performing a curative resection based on the characteristics of the lesion and knowledge on the benefit/risk relationship of ESD when compared with other therapeutic alternatives is mandatory. In order to maintain proficiency in ESD, ESGE recommends a minimum case load of 25 ESD procedures per year. Quality criteria to fulfill have been set at en bloc resection rate above 90%, perforation rate below 3%, with a lower than 1% need for surgery because of complications. Histopathology likewise is required to fulfill quality criteria [46] and correctly assess the presence of any unfavourable features decisive for basing a valid therapeutic decision on.

ESD-infrastructure and -setting

Lesions with suspected submucosal invasion and thus eligible for ESD require a discussion at multidisciplinary meetings prior to ESD. Additionally, the risks of ESD are significant and the procedure should be carried out in a facility with 24h emergency surgical, radiological and critical care support. Even in most advanced expert hands colonic ESD in comparison to rectal ESD is less safe in terms of clinically relevant complications [47]. Moreover, for lesions more suitable for ESD than EMR in the colon the current gold standard is laparoscopic surgical resection with no study showing better outcome with ESD than with laparoscopic surgery.

Decision making for or against ESD

If submucosal invasive cancer is likely to be present, the goal of removal needs to be *en bloc* and an R0 resection. If this is not achievable with standard techniques then ESD is primarily recommended. As for the choice between surgery or ESD the following arguments should be considered.

ESD is an excellent diagnostic measure providing optimal histological evaluation of all factors needed to declare resection being curative namely being en bloc R0, well-differentiated adenocarcinoma (G1/G2) and no more than Kikuchi level [48] sm1 (Table 7, appendix) (< 1000 µm submucosal invasion) with no lymphovascular invasion (L0 V0). Thus, ESD can help to avoid oncologically unnecessary surgery. Moreover, endoscopic resection of even high-risk T1 colorectal carcinoma prior to surgical resection has been reported not to associate with adverse effects on long-term outcomes [49].

In terms of surgical procedures as alternative it is important to distinguish different methods such as traditional surgical approach (transanal excision or resection/TAE or TAR), video-assisted transanal endoscopic (micro-)surgery (TEM) and its more recent derivative, transanal minimally invasive surgery (TAMIS). ESD may be advantageous as compared to TAR which inherits a higher risk of poor functional outcome and risk of abdomino-peritoneal amputation. Factors favouring surgery could be (extensively) pre-treated lesions being associated with fibrosis

known to increase technical demand and risk of perforation performing ESD[50]. Large lesion size and involvement of anal verge are indications for ESD as preferential treatment modality. Finally, local expertise should be taken into account in order to deliver the best decision on an individual case by case basis.

Special technical issues

The so-called hybrid-technique, namely endoscopic submucosal resection (ESR) with snaring after circumferential incision reducing procedure time for dissection (being the most difficult part of ESD) can be an option in certain circumstances particularly as a rescue therapy (e.g. emergency cases with unstable vital signs)[51]. In addition, its use in scheduled cases and as "optimized" hybrid ESD/ESR with submucosal dissection until the remaining submucosal tissue becomes approximately or less than 15mm has been advocated[52]. However, data are scarce and no firm valid recommendation can be made. Finally, two-step ESD has been used in extensive large rectal lesions[53] helping to avoid extensive procedure times.

6.2. Endoscopic full thickness resection (EFTR)

With the development of novel endoscopic closure techniques and tools, endoscopic full thickness resection (EFTR) is a therapeutic option for the treatment of lesions that are challenging to resect using standard endoscopic techniques.

EFTR enables the endoscopist for instance to treat epithelial lesions extending into the depth of the colonic wall or lesions which are associated with significant fibrosis, clinically appearing as non-lifting lesions as well as the resection of subepithelial tumors. Table 8 in the appendix shows common indications for endoscopic full thickness resection.

The most common used system for endoscopic full thickness resection in Switzerland is the full thickness resection device (FTRD, OVESCO®, Germany). The device consists of a cap with a preloaded snare wearing an adapted OTSC. Performing endoscopic full thickness resection with the FTRD the lesion is pulled into the cap by a grasper forming a duplication of the colonic wall. In the next step the preloaded clip is deployed and the lesion will be resected using the integrated snare (Figure 2, appendix).

After successful EFTR, the invagination of the colonic wall is visible with fatty tissue in the center part of the resection site, proving full thickness resection.

In a recently published meta-analysis[54] including also data from Switzerland[55], endoscopic full thickness resection showed a high rate of R0 resections of 84.9% with a very low rate of bleeding (2.2%), perforation (0.19%) and post polypectomy syndrome (2.3%). Due to the size of the device's cap, lesions up to a size of 20–25mm are suitable for endoscopic full thickness resection.

In early colorectal cancer, EFTR allows an exact histological risk stratification. As a result, it can avoid surgery for low-risk lesions in up to 50–70%[56].

7. Complications of endoscopic resections

7.1. Bleeding

Bleeding is the most common complication of colonoscopy and endoscopic procedures and may lead to serious hemorrhagic conditions. Immediate bleeding is defined as bleeding during the endoscopic procedure and delayed bleeding as a post procedural bleeding by appearance of melena or bloody stools at distance of the endoscopic procedure [57]. Delayed bleeding mainly occurs 2 and 7 days after the procedure but may be seen up to 14 days afterward [58, 59]. Immediate bleeding is secondary to a direct damage to vessels and can normally be treated endoscopically, during the procedure, allowing the resection to continue. Significant bleeding is defined as a decrease in hemoglobin level of ≥ 2 g/dL or the need for blood transfusion [60]. Several studies reported a bleeding rate up to 1% for standard colonoscopy with polypectomy and up to 11.9% for ESD procedures [61, 62]. A large meta-analysis showed a pooled immediate bleeding rate of 0.75% and 2.1% for delayed bleeding for ESD procedures [63].

The main recognized reported risk factors for a post polypectomy bleeding are poor bowel preparation, the size of the polyp, number of polyps removed, polyp histology, the localization in the cecum and an arterial bleeding during the procedure [64–67]. A size of resection ≥ 10mm, laterally spreading polyp, thick polyp stalk, juvenile or Peutz-Jeghers polyp are risk factors for a delayed bleeding [68]. The location in the right colon seems also to be an independent risk factor for delayed bleeding [69]. Patient's comorbidities, such as cardiovascular disease or chronic renal disease, an age ≥ 65 years and the use of anti-thrombotic and anticoagulation agents are also described risks for immediate and delayed bleeding [70, 71]. Single or concomitant use of aspirin, nonsteroidal anti-inflammatory drugs or clopidogrel represent an independent risk factor for bleeding [72].

Every resection site should be shortly examined with water lavage to reduce the risk of delayed bleeding. This control also permits to exclude the presence of a deep injury and muscle tissue, perforation as well as residual polyp tissue. The use of through-the scope (TTS) clips is the most common option for treatment of immediate bleeding and prevention of delayed bleeding [73, 74]. During endoscopic submucosal dissection (ESD), clips may interfere with the procedure and clipping should not be used or cautiously performed. As previously mentioned, other hemostatic methods as direct thermal therapy should be used, performed either by snare tip, bipolar cautery, dedicated thermal probes, hemostatic forceps (e.g. Coagrasper®) or directly by the tip of knife during the procedure time for ESD [75, 76]. In addition, most minor bleedings can be treated by conventional material in contrary to larger vessels, with significant bleeding, which should be managed by hemostatic forceps. In case of refractory oozing bleeding, argon plasma coagulation can be applied to the resection site. All thermal treatment should be cautiously used, to avoid deep thermal injury and potential perforation, especially in the right colon. Hemostatic forceps have the advantage to grasp precisely the incriminated vessels and deliver a proper coagulation. The electrosurgical settings depend on the preference of the manufacturer and the system which is used.

Adrenaline (epinephrine) solution injection may be used for either immediate or delayed bleeding. It should be used in combination with other treatment modalities, especially to reduce the rate of bleeding and to permit an optimal hemostasis [77, 78]. The use of over-the-scope clips (OTSC) can be also an effective salvage therapy in case of refractory hemorrhage [79]. Contact hemostatic powder spray (Hemospray®, Nexpowder®) is an option and showed successful results to treat bleeding and especially oozing bleeding [80]. However, it is recommended to use it as a bridge to a definitive hemostatic treatment given the risk of rebleeding in the first hours [81].

In case of delayed bleeding, it is recommended to determine the site of active bleeding by repeating colonoscopy or by angiography. The choice of diagnostic modality should be assessed individually depending on the hemodynamic instability, the volume of bleeding and the need for transfusion [82]. A meticulous examination should be done at the bleeding site after cleaning and mobilization of blood clots to ensure complete treatment of the responsible vessel. If endoscopic management fails (persistent hemorrhage and hemodynamic instability), an urgent interventional radiology or surgical evaluation is recommended.

Bleeding prophylaxis after EMR

Through-the scope (TTS) clipping decreases the risk of delayed bleeding after both EMR and ESD [83, 84]. Hemostatic forceps is the method of choice to reduce the risk of deep thermal lesion. A self-assembling peptide (PuraStat®) was recently licensed for use as a hemostatic therapy, especially after ESD. The latter is promising, by showing a good efficacy to prevent immediate and delayed bleeding in case of endoscopic resection [85].

The decision to use a certain hemostatic method depends on the protocol and experience of each center and the endoscopist's experience [86]. The methods must be adapted on the clinical presentation and the available equipment.

7.2. Perforation

Perforation can be classified as immediate or delayed.

Immediate Perforation is diagnosed during the procedure with visualization of a defect muscle layer, peritoneal fat, tissue or organ. Delayed perforation is diagnosed at distance of the procedure, depending on the clinical status and discovery on radiological examinations. Computed tomography of the abdomen and pelvis is the most specific diagnostic modality for colonic perforations [87].

Delayed perforation can ensue from an initially non-visible perforation during the procedure or by a true delayed perforation caused by deep thermal injury [88]. Several mechanisms are involved in colonic perforation as blunt injury, lateral pressure or retroflexion injury due to direct trauma with the tip or movement of the endoscope. Other mechanisms are passage of the endoscope through areas of pathology, barotrauma or iatrogenic due to unintentional resection or thermal injury during endoscopic procedure [89].

The perforation rate associated with diagnostic procedure is between 0.03% and 0.07%, for a pooled prevalence rate of mortality of 2.9 in 100'000 colonoscopies. Perforation rate is higher in case of therapeutic procedure around 0.1% to 0.15%. The rate of immediate and delayed perforation was 4.2% and 0.22% respectively in a recent meta-analysis in case of ESD [90, 91].

Risk factors for perforation

Risk factors can be divided into patient related factors (advanced age, multiple comorbidities, female sex), disease-related factors (inflammatory bowel disease, diverticular disease, bowel obstruction) and operator or procedure-related factors [92]. Lateral spreading or nonpolypoid morphology, submucosal fibrosis, polyps ≥ 10mm in size, multiple polyps and less experience of endoscopists are risk factors for perforation [93, 94]. The rectosigmoid colon is the most common site of perforation due to a more tortuous and challenging section. Owing to its thinner mural wall, the right colon and cecum are also at increased risk for perforation [95, 96].

Treatment of iatrogenic perforation

The indication of an endoscopic closure should take into account the quality of bowel preparation, comorbidities, clinical stability, time to diagnosis, the type and size of the perforation, the endoscopist's expertise and available devices [97, 98]. Endoscopic treatment is mostly indicated for intra-procedural iatrogenic perforations or perforations within four hours after the procedure [99]. Immediately after perforation recognition, intraluminal fluid should be suctioned as well as possible, tense pneumoperitoneum decompressed by needle puncture, and intravenous fluid and broad-spectrum antibiotics should also be administered [100]. Utilisation of carbon dioxide (CO_2) is widely recommended for all endoscopic procedures. Most small perforations (≤ 10mm) and minimal extraluminal contamination can be treated with the application of TTS clips in addition to antibiotics and fasting [101]. Larger or refractory perforations may be treated endoscopically using "endoloop and clips" technique or by over the scope clip (OTSC). OTSC permits to achieve a full-thickness and more durable closure in contrary to TTS clips which creates mucosal and submucosal apposition. OTSC success rate treatment for GI perforation is 85% and 92% for colonic perforations following polypectomy [102,103]. Different graspers, like bidirectional and anchor, exist and are useful to bring together the edges and allows also to close larger defects. The "endoloop and clips" technique may be attempted for perforations ≥ 20mm if OTSC is unavailable or in case of certain anatomical features [104]. Self-expandable metal stents have practically no indications in case of colonic perforations and should be reserved only for exceptional cases [105].

Although endoscopic and conservative management in selected colonoscopic perforations is associated with shorter hospital stay and lower mortality, emergent surgery should be performed in case of incompletely closed perforations, endoscopically intractable perforations, generalized peritonitis and uncontrolled sepsis. Mortality and morbidity are higher among those patients who undergo surgical treatment, especially in case of supplementary complications. One important paradigm is therefore to reduce the surgical delay time for reducing complications and morbidity [106]. Delayed perforation is linked with worse abdominal pain, longer hospitalization and morbidities, so it is crucial to identify these with early clinical reassessment, abdominal CT-scan and surgical evaluation [107].

7.3. Postpolypectomy electrocoagulation syndrome

Postpolypectomy electrocoagulation syndrome (PES) is the result of a transmural burn syndrome and localized peritonitis resulting from electrocoagulation injury to the bowel wall after endoscopic treatments, especially EMR and ESD[108]. Patients with PES typically present with fever, abdominal tenderness, localized peritonitis, inflammatory syndrome without evidence of perforation on abdominal radiography or abdominal CT-scan. The reported incidence rate ranges widely from 0.003% to 0.1% for EMR, and from 4.8% up to 14% for ESD[109, 110], with the cecum and the right colon most commonly involved. PES does not usually require surgical treatment: being conservatively managed with intravenous hydration, broad-spectrum antibiotics and bowel rest. The symptoms normally improve during the first 24 hours and patients with mild symptoms can be treated on an outpatient basis with oral antibiotics[111, 112] Prophylactic use of antibiotics is debated and may be effective for ESD and for high-risk patients including large polyp or tumor size, long procedure time, tumor location in the right colon and presence of submucosal fibrosis[113]. Other protective factors are described as the use of long lasting submucosal injection agent and the closure of the resection site with clips[114, 115].

7.4. Stenosis

Stenosis after endoscopic colorectal procedures is rare, with most occurring after ESD (overall incidence of 0.49%). Limited studies demonstrated that a circumferential resection of more than 90% is a significant risk factor for stenosis after ESD, as well as rectum or sigmoid location[116, 117]. Most patients with stenosis after EMR or ESD can usually be managed by (repeated) balloon dilation.

8. Follow-up colonoscopy after curative endoscopic resection

After piecemeal resection o large benign colorectal lesions a surveillance endoscopy should be performed after 3–6 months to detect and treat early recurrence if necessary. For details see also "Revidierte Konsensus-Empfehlungen zur Nachsorge nach endoskopischer Entfernung kolorektaler Polypen und Therapie des kolorektalen Karzinoms" (www.sggssg.ch/Empfehlungen).

9. Summary

The endoscopic approach to superficial colorectal neoplasms follows three steps: Detection, characterization and resection. Detection is influenced by colon preparation and withdrawal time. Special attention has to be taken on right sided, flat lesions which may be the cause of interval cancers. Characterization of the lesion using high definition endoscopy and advanced imaging techniques defines the correct resection strategy from simple cold snare polypectomy up to advanced resection techniques such as ESD and endscopic full thickness resection. Figure 3 in the appendix summarizes the process from diagnosis to management of superficial colorectal neoplasms.

10. Appendix

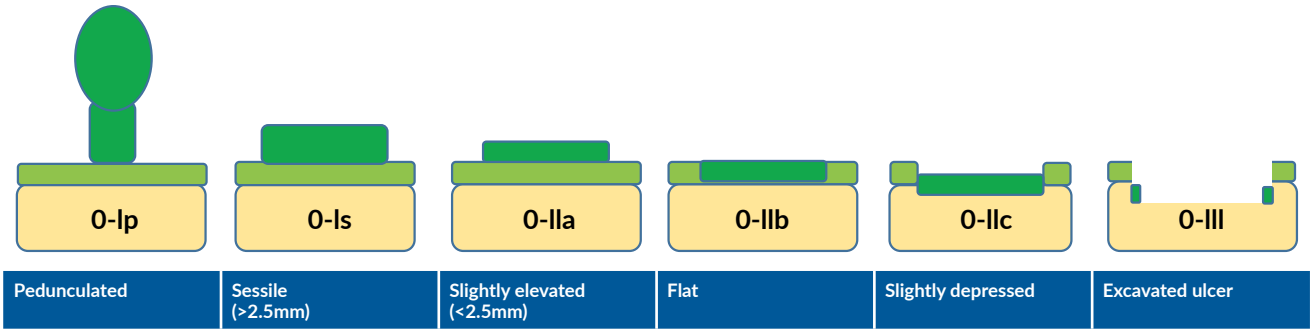


Figure 1. Paris classification: Gross morphology of polyps, adapted from [3].

LST subtype	Morphology	Paris Classification	Sm-invasion
Granular (LST-G)			
LST-G homogeneous type (LST-G-H)		0-IIa	0.8%
LST-G mixed type (LST-G-M)		0-IIa + Is	11%
Non-granular (LST-NG)			
LST-NG flat elevated (LST-NG-F)		0-IIa	14%
LST-NG pseudodepressed (LST-NG-PD)		0-IIc + IIa	36%

Table 1. Lateral spreading tumors and their risk of submucosal invasion, adapted from [3].

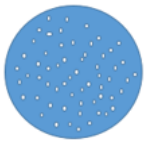
Kudo Type	Schematic	Characteristics	Interpretation
I		Round normal	Normal
II		Asteroid	Hyperplastic
IIIs		Tubular or round pit smaller than normal	Adenoma
IIIL		Tubular or round pit larger than normal	Adenoma
IV		Dendritic, gyrus, brain like	Adenoma
Vi		Irregular arrangement of pits	Superficial invasive
Vn		Loss or decreases of pits amorphous areas	Deep invasive

Table 2. Kudo classification of pit pattern, adapted from [4].

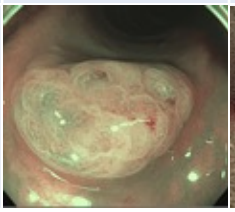
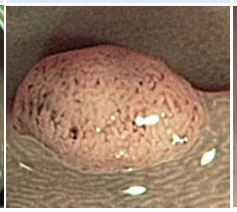
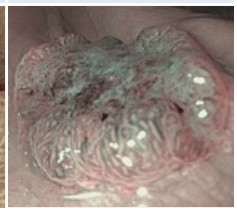
NICE Classification	NICE 1	NICE 2	NICE 3
Color	Same or lighter than background	Browner than background	Brown or darkbrown Pachy whiter areas
Vessels	None or isolated lazy vessels	Brown vessels surrounding white struktures	Disrupted or missing vessels
Surface pattern	Dark or white spots uniform in size or absence of pattern	Oval tubular or branched	Amorphous or absent
Most likely histology	Hyperplastic/serrated	Adenoma	Deep submucosal invasive cancer
Example			

Table 3. NICE classification, adapted from [5].

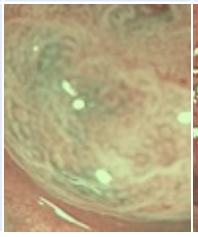
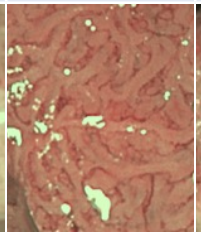
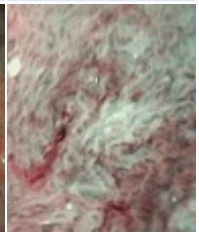
	Type 1	Type 2A	Type 2B	Type 3
Vessel pattern	Invisible	Regular caliber and distribution	Variable caliber irregular distribution	Loose vessel areas Interruption of thick vessels
Surface pattern	regular dark or white spots similar to surrounding	Regular (tubular, branched, papillary)	Irregular or obscure	Amorphous areas
Most likely histology	Hyperplastic Serrated lesion	Low grade dysplasia	High grade dysplasia superficial submucosal invasion	Deep submucosal invasive cancer
Example				

Table 4. JNET (Japan NBI Expert Team) classification adapted from [6].

Size	Points	Morphology	Points	Site	Points	Access	Points
< 10mm	1	Pedunculated	1	Left	1	Easy	1
10–19mm	3	Sessile	2	Right	2	Difficult	3
20–29mm	5	Flat	3				
30–39mm	7						
> 40mm	9						

Level 1: 4–5 points, **Level 2:** 6–8 points, **Level 3:** 9–12 points, **Level 4:** >12 points.

Table 5. SMSA score (size morphology, access site) and level of difficulty for resection, adapted from [8].

Level 1	Level 2	Level 3	Level 4
Submucosal invasion limited to the head	Submucosal invasion of the neck	Submucosal invasion of the stalk	Submucosal invasion beyond the stalk
			

Table 6. Haggitt levels (pedunculated polyps), adapted from [22].

sm1	sm2	sm3
Infiltration of upper third	Infiltration of middle third	Infiltration of lower third
		

Table 7. Kikuchi levels (sessile and flat colorectal lesions, depth of submucosal (sm) infiltration), adapted from [48].

Indications for EFTR
Non lifting colorectal lesions
Recurrences after previous EMR
Adenomas at difficult locations (diverticula / appendiceal orifice)
Early adenocarcinoma
Submucosal lesions
Diagnosis of neuromuscular intestinal disorders

Table 8. Indications for endoscopic full thickness resections (EFTR).

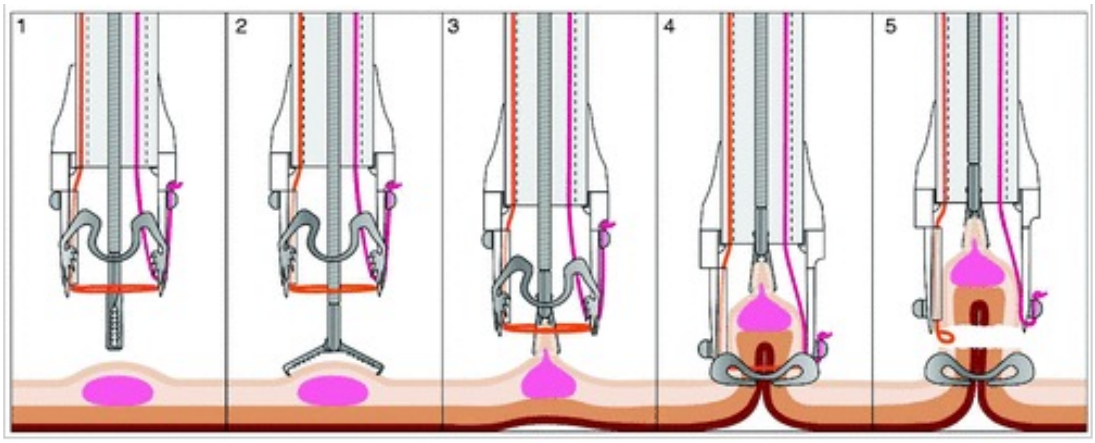


Figure 2. Technique of endoscopic full thickness resection (EFTR) using the full thickness resection device (FTRD) adapted from [54].

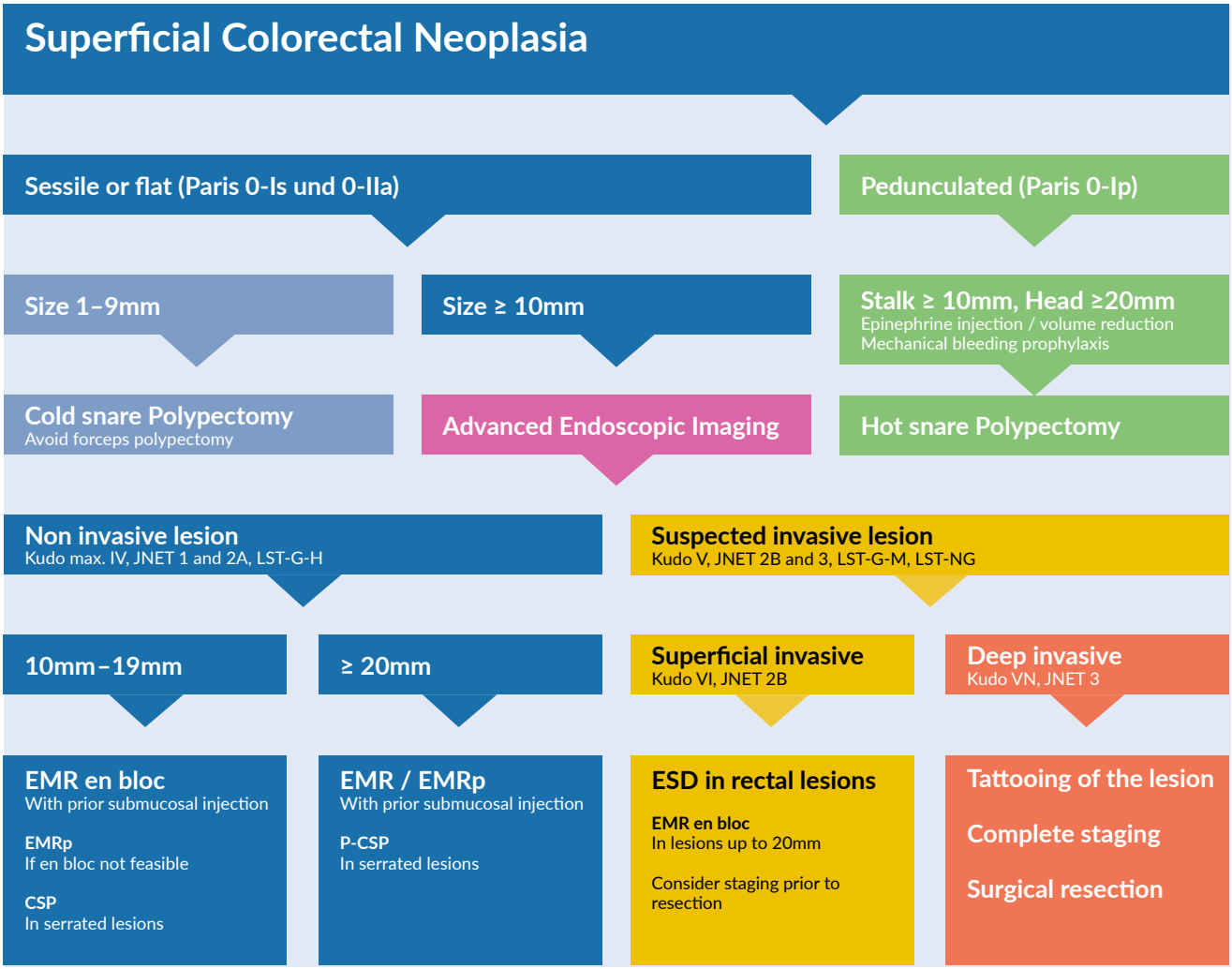


Figure 3. Summary of endoscopic management of superficial colorectal neoplasms.

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