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Cold versus hot polypectomy/endoscopic mucosal resection–A review of current evidence

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Abstract

Background: Colonoscopy with polypectomy substantially reduces the risk of colorectal cancer (CRC) but interval cancers still account for 9% of all CRCs, some of which are due to incomplete resection.

Aim: The aim of this review is to compare the outcomes of cold and hot endoscopic resection and provide technical tips and tricks for optimizing cold snare polypectomy.

Results: Cold snare polypectomy (CSP) is the standard technique for small (≤10 mm) colorectal polyps. For large colonic polyps (>10 mm), hot resection techniques with use of electrocautery (polypectomy or endoscopic mucosal resection) were recommended until recently. However, the use of electrocoagulation brings serious adverse effects in up to 9% of the patients, such as delayed bleeding, post-polypectomy syndrome and perforation. In recent years, efforts have been made to improve the polypectomy with cold snare in order to avoid these adverse effects of electrocoagulation without compromising the efficacy of the resection. Several authors have recently shown that the complication rates of CSP of polyps >10 mm is close to zero and recurrence rates varies between 5-18%. Lower recurrence rates are found in serrated lesions (<8%).

KEYWORDS
cold snare polypectomy, colonic polyps, colorectal cancer, endoscopic mucosal resection, sessile serrated lesion

CLINICAL CASE

A 76-year-old male patient underwent screening colonoscopy and a 30 mm granular laterally spreading tumor (LST-G) was identified in the cecum (Figure 1). The lesion had no signs of submucosal invasion (SMI) by white-light endoscopy and narrow-band imaging (NBI). The patient has a mechanical mitral valve and was medicated with warfarin (currently under bridge therapy with enoxaparin). What is the best management strategy for this patient?

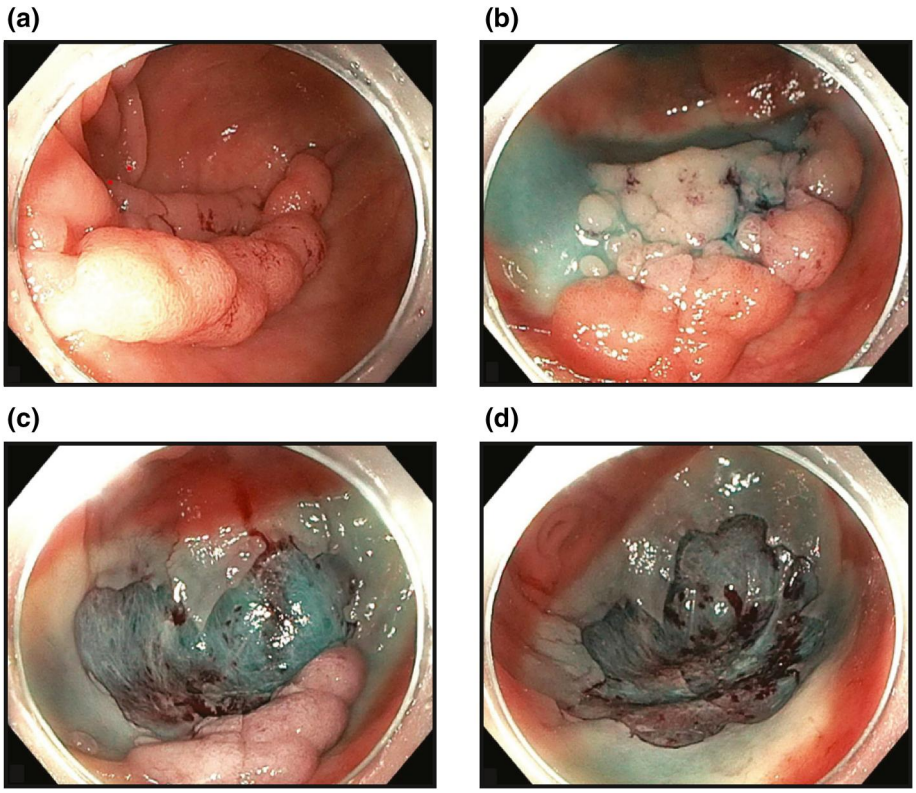

FIGURE 1 Granular laterally spreading tumor (LST-G) removed by cold-endoscopic mucosal resection (EMR) (courtesy of Dr. Dileep Mangira). (a), 30 mm LST-G in the cecum; (b), Initial lift of the polyp; (c), Cold-EMR ongoing; (d), Mucosectomy scar near the appendiceal orifice

NATURAL HISTORY OF COLORECTAL POLYPS

Colorectal cancer (CRC) ranks third in incidence but second in terms of cancer mortality overall.[1] Screening and surveillance colonoscopy with polypectomy substantially reduces CRC incidence and CRC mortality.[2]

The vast majority of polyps found at screening colonoscopy are diminutive (<5 mm) or small polyps (6-9 mm)[3] and the prevalence of advanced adenomas in polyps with <10 mm is around 12.5%.[3] Most CRC arises from premalignant lesions that can be detected and removed by colonoscopy, but post-colonoscopy cancers (interval cancers) still account for 9% of all CRCs.[4] Incomplete colonoscopy, missed lesions, rapidly growing lesions, iatrogenic tumor seeding, and incomplete resection of lesions may explain interval CRCs, highlighting the importance of accurate inspection and complete removal of all polyps.[5]

Formerly, conventional adenomas were considered the precursor lesions of sporadic colon cancer. The serrated pathway allowed the classification of sessile serrated lesions (SSLs) in hyperplastic polyps (HPs, non-neoplastic), sessile serrated adenoma/polyps (SSA/Ps), and traditional serrated adenoma (TSA) (both neoplastic), being SSA/Ps the precursors of about 30% of sporadic CRCs.[6]

Unlike conventional adenomas, SSA/Ps miss dysplasia, although dysplasia can develop with lesion progression.[7] The 10-year risk for developing CRC is around 2.5% for patients with a SSA/Ps without dysplasia, 4.4% for those with a SSA/P with dysplasia, and 4.5% for TSAs, contrasting with a rate of 2.3% for those with a conventional adenoma.[8]

Sessile serrated adenoma/polyps account for 5%–7% of interval CRCs.[9] These lesions are more difficult to detect and commonly missed, and frequently inadequately resected due to ill-defined margins.

HOW TO DIAGNOSE AND CHARACTERIZE COLONIC NEOPLASTIC LESIONS

Improved optics in colonoscopy allow a more accurate characterization, which can help in the prediction of SMI risk that is important to select lesions in which en bloc resection should be pursued. The risk of SMI increases with size, being 4.6% in LSTs 10–19 mm and reaching 16.5% in LSTs ≥30 mm. Location in the distal colon (Odds Ratio 2.50 vs. proximal colon), fold convergence, irregular surface, and demarcated depressed area were also associated with SMI.[10,11] Another important feature is the morphology of LSTs. Non-granular LSTs more often contain SMI than granular LSTs: 11.7% versus 5.9%.[10] In addition, depressed or sessile morphology in non-granular LSTs and discrete nodules in granular LSTs were also associated with a higher risk of SMI.[12]

Virtual chromoendoscopy has further improved lesion characterization (of histological type and invasion depth). The NBI International Colorectal Endoscopic (NICE) classification allows the distinction of HPs, adenomas, and deep submucosally invasive cancers

and can be used to accurately select lesions for endoscopic or surgical treatment. Indeed, Hayashi et al. performed a validation of the NICE3 features (brown or black relative to background; areas of disrupted or missing vessels; amorphous pattern or its absence) and reported that presence of any one of the three features had 94% accuracy and 96% negative predictive value for SMI.[13] The non-lifting sign in lesions without prior endoscopic manipulation or attempted resection is also associated with deep SMI.[14]

However, in lesions with indication for endoscopic therapy, the Japan NBI Expert Team classification may also be useful since it differentiates between hyperplastic/serrated polyps, low grade intramucosal neoplasia, high-grade intramucosal neoplasia/shallow submucosal invasive cancer, and deep submucosal invasive cancer.

Given that the majority of LSTs are benign and non-invasive, piecemeal removal by endoscopic mucosal resection (EMR) is an attractive option to resect those without suspicion of SMI, given its advantages when compared with more difficult and time consuming en bloc resection techniques such as endoscopic submucosal dissection (ESD). However, the benefit of using hot resection is currently under heated debate, especially for serrated and adenomatous lesions where a deeper resection (provided by conventional EMR) may not be needed.

CURRENT MANAGEMENT FOR COLORECTAL LESIONS

Small and diminutive polyps–Always prefer cold snare resection

For a few years, polypectomy with cold biopsy forceps was used for diminutive polyps. However, cold snare polypectomy (CSP) has been found to be superior for completeness of resection (even for diminutive polyps) and decreased polypectomy time.[15] Thus, currently polypectomy with biopsy forceps is reserved for polyps 1–3 mm in size in which polypectomy with cold snare is technically difficult or not possible.[16]

European guidelines also recommend CSP for sessile polyps 6–9 mm, as this technique have lower rates of delayed bleeding, lower frequency of post-polypectomy syndrome (PPS), and shorter procedure duration when compared to hot-snare polypectomy (HSP)[16] (Figure 2). In a systematic review and meta-analysis, the complete resection and polyp retrieval rate were similar between HSP (95% and 97%) and CSP (94% and 97%), while HSP was associated with longer colonoscopy and polypectomy time (mean difference: 7.1 min and 30.9 s, respectively). Hot-snare polypectomy was also associated with higher delayed bleeding rates, although not statistically significant (relative risk 7.35, $p = 0.06$) possibly due to the low number of patients with this event in both groups.[17] However, in anticoagulated patients an randomized controlled trial (RCT) demonstrated a significantly lower rate of post-procedural bleeding (PPB) after CSP (0% vs. 14%, $p = 0.27$). The presence of injured submucosal arteries was more frequent in HSP group and is the possible reason for this difference.[18]

Larger polyps (>10 mm)–To heat or not to heat?

Outcomes of hot resection

The standard approach for flat/sessile polyps >10 mm was HSP/hot EMR until recently, being en bloc resection preferred for lesions <25 mm, and piecemeal resection reserved for situations where en bloc resection is unfeasible or unsafe due to perforation risk.[16] The European Society of Gastrointestinal Endoscopy (ESGE) recommends the use of submucosal injection (EMR) for polyps ≥20 mm, although it can also be considered for polyps 10–19 mm.

The cited benefits of using electrosurgical current include easier transection through thick tissue, prevention of bleeding by instantaneous vascular coagulation, and ablation of marginal tissue. However, electrocautery can also produce vascular structures and wall injury resulting in PPB, perforation and PPS.

Several studies assessed the outcomes of EMR, being meta-analysis on this topic summarized in Table 1.

EMR achieves complete endoscopic resection in 99.5% of the cases (95% CI 98.6%–100.0%),[21] although histological complete resection is lower (ranging from 35% to 58%) given that most of the times larger lesions are resected in a piecemeal fashion (Table 2). However in non-malignant lesions, the most important outcome is the absence of recurrence and not a histological complete resection, and recurrence rates after piecemeal EMR are around 15%–20% in most studies, being most of the times (>90%) amenable to further endoscopic resection.[19,21] Use of argon plasma coagulation, intra-procedural bleeding and size >40 mm were associated an increased recurrence risk,[19,37] while the use coagulation of the post-EMR defect margin can reduce this rate to 5.2%.[38]

Intra-procedural bleeding rates after EMR of polyps >10 mm is reported to be as high as 7.7% (Table 1).[21] In a multicenter study clinically significant post-EMR bleeding after resection of polyps ≥20 mm was 6%, of which 55% were managed conservatively.[39] Perforation is an uncommon but serious event after EMR, occurring in 1%–2%.[21,40] The incidence of PPS, a condition which frequently implies patient admission and medical therapy, varies between 0.2% and 7.6% and is higher with polyps larger than 20 mm, located in the right colon and non-polypoid lesions.[41,42]

It is clear that adverse events are most of the times related with the use of electrocautery, and thus an interesting question emerged – can these lesions be treated by cold snare/EMR, maintaining the efficacy of snare resection while avoiding the harms of electrosurgical current?

The lost son–Cold snare/cold EMR

The fact that electrocoagulation brings adverse effects has raised awareness for the implementation of cold snare also in larger polyps,

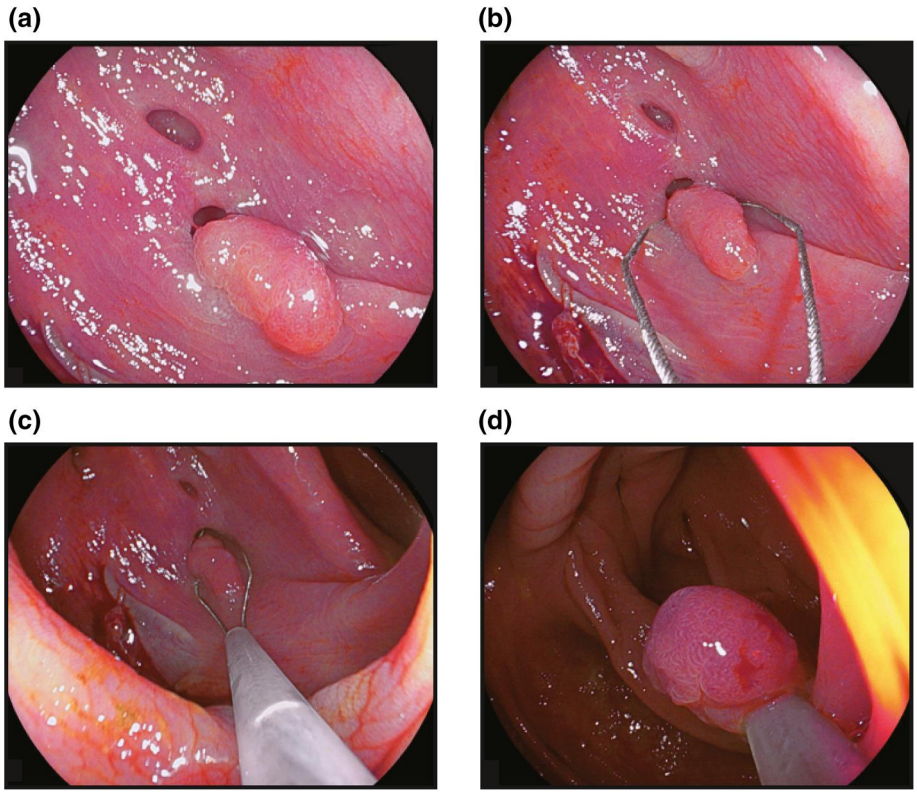

FIGURE 2 Cold snare polypectomy of a small adenoma. (a), Small adenoma, reaching into a sigmoid diverticula; (b), Positioning of the snare tip; (c), Applying pressure towards the colonic wall resulting in bending the snare to get more contact to the mucosa. This causes friction that ensures tissue collection into the snare while closing the snare; (d), Before transection of the mucosa you can make sure the snare position is optimal if normal mucosa can be seen inside the adenoma. Further retraction close to, or even into the beginning of the working channel while cutting ensures immediate specimen collection into a polyp trap

TABLE 1 Summary of systematic reviews evaluating conventional (hot) endoscopic mucosal resection

	Studies	No. of LST	Size, mm	Complete endoscopic resection, *n* (%)	En bloc resection, *n* (%)	R0 resection, *n* (%)	Recurrence rate, *n* (%)	Perforation, *n* (%)	IPB, *n* (%)	PPB, *n* (%)
							493/3405 (14.5%)			
Belderbos T, 2014[19]	33	NA	>10	NA	NA	NA	**En bloc resection:** 40/1039 (3.8%)	NA	NA	NA
							Piecemeal resection: 453/2312 (19.6%)			
Arezzo A, 2015[20]	11	3161	>20	NA	822/2358 (34.9%)	166/458 (36.2%)	384/3034 (12.7%)	47/3161 (1.5%)	89/3078 (2.9%)	
Russo P, 2019[21]	49	3021	>10	NA (99.5%)	NA (37.7%)	NA (36.2%)	NA (12.6%)	NA (1.2%)	NA (9.6%)	
									NA (7.7%)	NA
Chandam S, 2020[22]	11	1049	NA	NA	694/1188 (58.4%)	226/297 (76.1%)	64/254 (25.2%)	NA	72/790 (9.1%)	NA
Zhao HJ, 2020[23]	12	1906	>10	NA	815/1906 (42.8%)	92/128 (71.9%)	233/1469 (15.9%)	28/1568 (1.8%)	68/1633 (4.2%)	

Abbreviations: IPB, intra-procedural bleeding; NA, Not available; PPB, post-procedural bleeding.

TABLE 2 Summary of studies evaluating cold snare polypectomy of polyps ≥10 mm

Author, year	Patients	No. of polyps/ SSL	>20 mm *n* (%)	Injection (+/−)	Median follow-up (IQR), months	Recurrence rate *n* (%)	Adverse events per lesion			
							IPB *n* (%)	PPB *n* (%)	PPS *n* (%)	Perforation *n* (%)
Adenoma + SSL										
Choksi N, 2015[24]	15	15/0	11 (73.3%)	+	NA	NA	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/15 (0%)
Muniraj T, 2015[25]	30	30/15	15 (50.0%)	+	NA	5/27 (18.5%)	0/30 (0%)	0/30	0/30	0/30
Piraka C, 2017[26]	73	94/14	37 (39.4%)	+	5.4 (1.1-16.2)	7/72 (9.7%)	1/94 (0%)	0/94 (0%)	0/94 (0%)	0/94 (0%)
Murakami T, 2019[27]	NA	74/7	NA	-	NA	4/74 (5.4%)	NA	0/74 (0%)	NA	0/74 (0%)
Mangira D, 2020[28]	186	204/135	204 (100%)	+	5.0	9/164 (5.5%)	4/186 (2.2%)[a]	7/186 (3.8%)[a]	0/186 (0%)[a]	0/186 (0%)[a]
SSL										
Tutticci NJ, 2018[29]	99	163	74 (45.4%)	+	5.1	1/134 (0.7%)	1/163 (0.6%)	0/163 (0%)	NA	0 (0%)
Rameshshankar R, 2018[30]	10	29	9 (31.0%)	+	NA	1/29 (3.4%)	0/29 (0%)	0/29 (0%)	0/29 (0%)	0/29 (0%)
McWhinney CD, 2020[31]	312	566	NA	+	12.4	18/225 (8.0%)[b]	NA	4/223 (1.8%)[a]	0/223 (0%)[a]	0/223 (0%)[a]
Kimoto Y, 2020[32]	300	474	97 (20.5%)	-	7.0	0/384 (0%)	8/300 (3%)[a]	0/300 (0%)[a]	0/300 (0%)[a]	0/300 (0%)[a]
Yoshida N, 2020[33]	100	160	0 (0%)	-	18.0 (12.0-24.0)	5/101 (5.0%)	2/160 (1.3%)	0/160 (0%)	0/160 (0%)	0/160 (0%)
Comparative studies										
Tate DJ, 2018[34]										
Piecemeal CSP	34	41/41	NA	-	6.0 (5.0-7.0)	0/15 (0.0%)	0/41 (0%)	0/41 (0%)	0/41 (0%)	0/41 (0%)
EMR	20	20/20	NA	-	NA	1/9 (11.1%)	NA	NA	NA	NA
Ket SN, 2019[35]										
CSP	241	346/206	0 (0%)	243+	NA	NA	3/346 (0.9%)	0/346 (0%)	0/346 (0%)	0/346 (0%)
HSP	207	258/77	0 (0%)	128+	NA	NA	15/258 (5.8%)	4/258 (1.6%)	2/258 (7.8%)	0/258 (0%)
Hatem VA, 2020[36]										
Piecemeal CSP	121	156/156	156 (100%)	Both	6.0 (4.0-8.0)	4/92 (4.3%)	0/121 (0%)[a]	0/121 (0%)[a]	NA	0/121 (0%)[a]
Piecemeal EMR	353	406/406	406 (100%)		6.0 (5.0-9.0)	14/307 (4.6%)	18/353 (5.1%)[a]	5/353 (1.4%)[a]	NA	2/353 (0.6%)[a]

Abbreviations: CSP, cold snare polypectomy; EMR, endoscopic mucosal resection; HSP, Hot snare polypectomy; IPB, intra-procedural bleeding; NA, Not available; PPB, post-procedural bleeding; PPS, Post-polypectomy syndrome; SSL, sessile serrated lesions.

[a]Per patient.

[b]Thirteen visible lesion and five positive scar biopsies.

being the main concern the potential of incomplete resection and increased recurrence.

Current ESGE guidelines recommend hot snare/hot EMR as the standard treatment for lesions >10 mm, although referring that in certain situations there may be a role for CSP to reduce the risk of deep mural injury.[16]

In recent years, several authors have assessed the safety and efficacy of CSP for polyps >10 mm, and a 2019 meta-analysis

including eight studies (522 polyps, median size 17.5 mm) reported a complete resection rate by CSP of 99.3%, with a recurrence rate at follow-up colonoscopy of 4.1%. Recurrence rates after cold resection were higher in polyps ≥20 mm (15.4%) and adenomas (11.1% vs. 1.0% for SSLs), but are comparable to reported recurrence rates of hot EMR.[43] A more recent study also analyzed recurrence of cold piecemeal EMR of 204 large polyps and found recurrence rates of 5.5% at first endoscopic surveillance and 3.5% at second surveillance (18 months after CSP), being cecal location and involvement of endoscopy fellow associated with recurrence.[28]

Studies have also shown a remarkably low adverse event rate. Even in larger polyps, most single-arm studies report adverse event rates close to zero (Table 2). The CSP perforation rate was zero in all studies due to the lack of thermal wall injury. A systematic review and meta-analysis also found that that cold EMR was associated with significantly lower rates of PPB (0% vs. 2.3%, $p = 0.03$).[44]

In particular, SSLs may be the ideal lesions for cold EMR – they have a comparatively thin mucosal layer which is only slightly thickened beyond the normal surrounding mucosa and submucosa, they generally have little or no submucosal fibrosis, and they have a lower risk of dysplasia and recurrence when compared with adenomas.[29,45] In this context, several authors assessed CSP specifically for serrated lesions.[31–33] A systematic review analyzed 1137 SSP ≥ 10 mm compared the outcomes of cold and hot EMR and found a lower residual polyp rate in the cold EMR group in univariate analysis (0.9% vs. 5.0%), although there were no differences in multivariate regression analysis.[44] Since this systematic review, recent studies confirmed low recurrence rates after CSP of SSL (0%–8%; Table 2). Significant factors associated with residual SSPs include larger polyp size, sessile component, presence of dysplasia, use of adjunct modality, submucosal fibrosis, and lifting difficulty.[45]

However, comparative trials between the two approaches are still scarce, but there is a recent comparative trial showing similar technical success and recurrence rates between cold and hot EMR, while adverse events were significantly more frequent in the hot EMR group (5.1% vs. 0%).[36]

Similar to recurrences after conventional EMR, recurrences after cold EMR are generally amenable for re-endoscopic resection, and although, there is not yet comparative data one may speculate that recurrences after cold EMR are easier to treat since it is possible that the more superficial resection leads to less fibrosis.

Technical issues and tips and tricks to effective resection

Cold snare polypectomy

Cold snare polypectomy of colonic polyps should be part of early endoscopic education in colonoscopy. In basic, cold EMR is not varying from conventional EMR technique, but some things need to be addressed.

First, we strongly recommend using a dedicated snare for CSP. There are so called hybrid snares, which also enable HF-resection with the same device and that may be cost effective if small and large polyps need to be removed in the same patient. A comparative study demonstrated that the use of dedicated cold snare is superior to traditional snares in terms of technical success rate, complete resection, and reducing procedure duration for CSP, especially of small polyps, in a porcine model.[46] According to a systematic review and meta-analysis, the complete histological eradication of diminutive polyps achieved by dedicated CSP was superior to traditional CSP.[47] However, in a later human prospective trial no differences were found between traditional and dedicated snares regarding complete polyp resection and post-polypectomy adverse events.[48] Nevertheless, cold snares have the advantage that they keep the inner part of the snare open for a longer time compared to traditional oval shaped snares which makes it easier to resect especially small polyps.[49]

The lesion should be approached in a way that the working channel is pointing towards the lesion. In smaller lesions, perpendicular orientation is also possible as most cold resection snares have small and soft wires that can be bended easily. Then, open the snare completely and place the region of the snare that meets the sheath of the snare close to the border of the lesion. While closing the snare, slowly suck away the gas from the lumen, allowing extra tissue to stay inside the snare and to avoid slipping of the tissue outside the snare while closing. In this moment, it is helpful to gently apply pressure to the snare towards the mucosa either by pushing the sheath gently forward or by using the wheels of the endoscope. If the lesion is captured by the snare, you can either choose to recapture or to directly resect by giving the assistant the hint to fully close the snare. This will lead to cutting of the mucosa. To avoid snipping of the specimen in an uncontrolled way, we recommend performing the resection as close to the working channel as possible or even to pull the tissue slightly into the working channel while applying suction through the endoscope. Doing so, most specimens will directly be led into the endoscope and can be sucked into a polyp trap.

In case of small lesions or lesions that may not be captured inside the snare because they are too flat, the suction polyp and resect method can be used. In this technique, the lesion is sucked into the working channel for a short moment leaving a suction polyp that than can easily be resected. If this is not working or the lesion is large and flat, a submucosal injection might facilitate capturing the tissue inside the snare.

After resection, frequently small bleeding activities can generally be noticed. In general, bleeding is not more compared to biopsy sampling.

In case, blood is disturbing or compression of sustained bleeding is needed, before injection using a needle or clipping, we advise to use the endowasher or other irrigation through the scope for direct installation of a submucosal cushion which helps to stop bleeding in most cases. An additional benefit is the stretching of resection surface that allows to carefully inspect the resection site regarding remnant adenomatous tissue. Cold snare polypectomy results in a cold snare defect protrusion (CSDP) in about 11%–35% of patients,

appearing as a white cord in the center of the snaring defect.[50,51] Histopathological examination of CSDP rarely contains residual polyp; it consists of muscularis mucosa and submucosa and therefore do not require additional resection.[52]

Cold snare piecemeal resections

Before thinking about cold snare piecemeal resection, it is important to understand the differences between EMR, ESD, and cold snare resection. While EMR and ESD always cut and resect in a submucosal plane, cold snare resection cannot always resect the complete mucosal layer and is therefore reserved for completely superficial lesions.[50]

A study investigating the nature of the resection site of cold snare resections took biopsies from the resection site of 257 polyps <10 mm and could identify muscularis mucosa as the basis of resection site in a significant proportion of specimens.[52] Histologic matched pair analysis of polyps resected with EMR versus cold snare showed a significant higher proportion of positive or unclear resection margins in CSP and a significant lower depth of resection (76 vs. 335 µm).[53] However, these results must be interpreted with caution, as histology of resected specimen is not always predictive for the recurrence of adenoma in a control endoscopy.

Mangira et al. published a series of 204 polyps >20 mm that were resected in piecemeal CSR. Recurrent polyps were found in 5.5% after 150 days and 3.5% after 18 months, with only minor complications. Also, in an observational trial of 163 polyps >10 mm (average 17.5 mm) resected by piecemeal CSR, only in two cases biopsy samples of the resection margin were positive and only one recurrent adenoma was found after a follow up pf 5 months.[29]

A study investigating on the need for submucosal injection could demonstrate that submucosal injection is not mandatory. In this study 474 SSL were resected without submucosal injection and only one recurrent adenoma was found after 7 months follow up.[32]

Piecemeal CSP therefore is a suitable technique that shows promising data but still data from RCTs are lacking. The reports of low recurrent disease rates paired with the low resection depth may advocate to use piecemeal CSP also outside the colon. Only few data are available for the use in duodenal piecemeal resections.[24] Feasibility and a low rate of perforations have been reported. Late perforations after EMR can be devastating and lethal.

In general, piecemeal CSP of adenomas in the colon without the risk of SMI or even invasion into the deeper mucosal layers is safe and suitable and may be used more frequently. Piecemeal EMR is the alternative method of choice in these cases. Another alternative in cases of polyps reaching the size of the applied snare but need to be en bloc resected, is underwater EMR which can lead to a higher proportion of R0 en bloc resections in these cases, which has been shown in several meta-analysis.[22,54]

CONCLUSIONS

Given its potential safety advantages, CSP may provide a paradigm change in the practice of polypectomy. This technique appears to be feasible and as effective as conventional EMR for lesions without suspicion of SMI, having the advantage of increased safety, with very rare adverse events (<1%).

Comparative trials of the different techniques are thus needed to provide more conclusive evidence, although data from single-arm studies encourage consideration for dismissing electrocautery for most resections, especially for SSL and lesions in the proximal colon.

What is the best management strategy for this patient?

A 30 mm LST in the right colon, without features of SMI, in an elderly patient with increased risk of PPB due to anticoagulant use, is probably best managed with cold EMR in order to avoid adverse events, while preserving effectiveness.

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CONFLICT OF INTEREST

Jochen Weigt received payments and honoraria for lectures and presentations as a speaker and received medical equipment for scientific purpose from Fujifilm. All other authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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