

Thermal ablation of mucosal defect margins to prevent local recurrence of large colorectal polyps: a systematic review and meta-analysis




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submitted 4.1.2022

accepted after revision 31.5.2022

Bibliography

Endosc Int Open 2022; 10: E1127–E1135

DOI 10.1055/a-1869-2446

ISSN 2364-3722


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 Supplementary material is available under <https://doi.org/10.1055/a-1869-2446>

ABSTRACT

Background and study aims Endoscopic mucosal resection of large non-pedunculated colorectal polyps is characterized by a high risk of recurrence. Thermal ablation of the mucosal defect margins may reduce recurrence in these lesions, but a systematic overview of the current evidence is lacking.

Methods We searched PubMed, Embase and Cochrane until July 2021, for studies on thermal ablation of mucosal defect margins of large non-pedunculated colorectal polyps. Main goal of this meta-analysis was to identify pooled risk difference of recurrence between thermal ablation vs. no adjuvant treatment. Secondary goal was to identify pooled recurrence rate after snare tip soft coagulation (STSC) and argon plasma coagulation (APC).

Results Ten studies on thermal ablation of mucosal defect margins were included, with three studies on argon plasma coagulation, six studies on snare tip soft coagulation and one study comparing both treatment modalities, representing a total of 316 APC cases and 1598 STSC cases. Overall pooled risk difference of recurrence was -0.17 (95% confidence interval [CI] -0.22 to -0.12) as compared to no adjuvant treatment. Pooled risk difference was -0.16 (95% CI -0.19 to -0.14) for STSC and -0.26 (95% CI -0.80 to 0.28) for APC. Pooled recurrence rate was 4% (95% CI 2% to 8%) for STSC and 9% (95% CI 4% to 19%) for APC.

Conclusions Thermal ablation of mucosal defect margins significantly reduces recurrence rate in large non-pedunculated colorectal lesions compared to no adjuvant treatment. While no evidence for superiority exists, STSC may be preferred over APC, because this method is the most evidence-based, and cost-effective modality.

Introduction

Large (≥ 20 mm) non-pedunculated colorectal polyps are prevalent in current endoscopy practice, and when considered benign, the primary approach for these lesions is endoscopic mucosal resection [1]. Endoscopic mucosal resection (EMR) is associated with fewer complications than more invasive resection techniques such as endoscopic submucosal dissection (ESD) or surgery [2, 3]. However, the pitfall in EMR of large colorectal polyps remains the higher risk of recurrence, mostly reported between 15% to 20% at 6 months [1,4]. Risk factors for recurrence after endoscopic resection are widely studied and the most important factors include piecemeal resection, lesion size ≥ 4 cm and intraprocedural bleeding [5].

In the search for effective measures to lower the recurrence rates after (piecemeal) EMR of large colorectal lesions, experience is gained with regard to adjuvant treatment measures. Adjuvant treatment refers to additional treatment of the mucosal defect after all visible neoplastic tissue has been removed. Argon plasma coagulation (APC) and snare tip soft coagulation (STSC) are techniques that are often used in this setting. Ablation of mucosal defect margins with APC or STSC is increasingly performed in order to prevent local recurrence [6, 7].

With thermal ablation of mucosal defect margins only recently emerging, not all current guidelines incorporated firm statements regarding this adjuvant measure. The European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline for colorectal polypectomy and endoscopic mucosal resection (2017) stated that the role of adjuvant thermal ablation of the EMR resection margins to prevent recurrence requires further study [8]. However, the American Society for Gastrointestinal Endoscopy (ASGE) recently published a renewed guideline about endoscopic removal of colorectal lesions, in which the use of adjuvant thermal ablation of the post-EMR margin is incorporated as a conditional recommendation with moderate-quality evidence [7].

To investigate and summarize current evidence on thermal ablation of mucosal defect margins, we set out to perform a systematic review and a meta-analysis assessing the effect of adjuvant thermal ablation, compared to no adjuvant treatment, of mucosal defect margins on recurrence of large colorectal polyps removed by EMR.

Materials and methods

This systematic review was conducted according to a predefined protocol that has been registered in the international prospective registry for systematic reviews (PROSPERO): CRD42020189860. Our study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [9].

Search strategy and inclusion criteria

The electronic databases of PubMed, EMBASE and Cochrane were searched for articles published between January 1990 and July 19, 2021. The search terms comprised synonyms for “colon” or “rectum”, “colonoscopy”, “colorectal polyps” as do-

main and “adjuvant or additional treatment” or “argon plasma coagulation” or “snare tip soft coagulation” as intervention. The search was performed after consultation of a search expert. The full search can be found in **Supplementary Material 1**. Studies for inclusion were selected after removing duplicates. Studies were eligible for inclusion if they were written in English, published in peer-reviewed journals and reported original data from randomized clinical trials or observational studies. Studies were included if thermal ablation was used as an adjuvant treatment, meaning that all neoplastic tissue was removed during the EMR and no residual tissue was detected during careful inspection of the EMR-defect. Studies were excluded if thermal ablation was used as an adjunctive treatment on residual neoplastic tissue after EMR.

Study selection

Two authors (LWTM and RMMB) independently screened titles and abstracts identified by our search. Subsequently, independent assessment of full-text articles for final inclusion was performed. We cross-checked reference lists of included studies and screened references that cited the included articles. Consensus was reached by discussion and in case of disagreement or uncertainty about eligibility by consultation with senior authors (AAMM and LMGM).

Data collection

A predesigned data extraction form was used to extract relevant data of included studies. Two authors (LWTM and RMMB) independently extracted the data. Disagreement was resolved by discussion between the two authors. If no agreement could be reached, this was discussed with senior authors (AAMM and LMGM). Data were extracted based on the 6-month follow-up interval. When a study did not report outcomes at 6 months, data were extracted based on the 12-month follow-up interval. This follow-up interval of 6 months is in line with current surveillance guidelines stating that first surveillance colonoscopy should be performed at 6 months.

We extracted the following data: author, year of publication, country, study design, randomization, blinding, number of participating centers, number of patients, number of included lesions, size in mm, % proximal location, type of ablative therapy, follow-up interval, and outcome.

Local recurrence and risk difference

The main goal was to identify local recurrence (at 6–12 months) after endoscopic resection. Local recurrence was assessed for all adjuvant treatment modalities, as well as separately for STSC and APC.

As a secondary goal, pooled recurrence rates for STSC and APC were calculated for comparison.

Sensitivity analysis was performed to evaluate the recurrence and risk difference in studies only including lesions from a size of ≥ 20 mm, thus leaving out two studies that included lesions from a size of ≥ 10 mm or ≥ 15 mm. Furthermore, a second sensitivity analysis was performed to account for potential case overlap in STSC studies from one research group (Australia). For

this analysis, pooled estimates were calculated with only one study of this specific research group included.

Assessment of methodological quality

Two authors (LWTM and RMMB) independently evaluated the methodologic quality and potential risk of bias in included studies. We used the Quality in Prognostic Studies (QUIPS) tool for randomized studies, as recommended by the Cochrane Prognosis Methods Group [10]. In addition, the Newcastle-Ottawa Scale (NOS) was used for quality assessment of both non-randomized and randomized studies. We defined the components of the NOS according to our research question. For “representativeness of the exposed cohort” we evaluated whether there was no selection based on location, size or complexity of the lesions. For “selection of the non-exposed cohort” we evaluated whether the controls were derived from the same population as the exposed group, and whether there were reasons to believe that the non-exposed group did not receive adjuvant treatment for a specific reason (e. g. other resection technique used, inexperienced endoscopist). “Representativeness of the exposed cohort” and “selection of the non-exposed cohort” together composed the evaluation of possible selection bias. For “ascertainment of cohort” we evaluated whether it was clear that adjuvant treatment methods were applied fully and correctly. For “demonstration that outcome of interest was not present at the start of the study” we evaluated whether the study described no visible residue present at the first resection. For “comparability” we evaluated the study controlling for exposure vs. non-exposure, baseline characteristics and both cohorts being samples of the same general population. Hence, potential confounding bias was evaluated. For “assessment of outcome” definition of recurrence had to be described and documented in the studies. For “follow-up long enough for outcome to occur” we used a minimal follow-up period of 6 months. Finally, “adequacy of follow-up” was defined by description of loss-to-follow-up by the different studies, where <15% loss-to-follow-up, evenly distributed over groups, was acceptable [11].

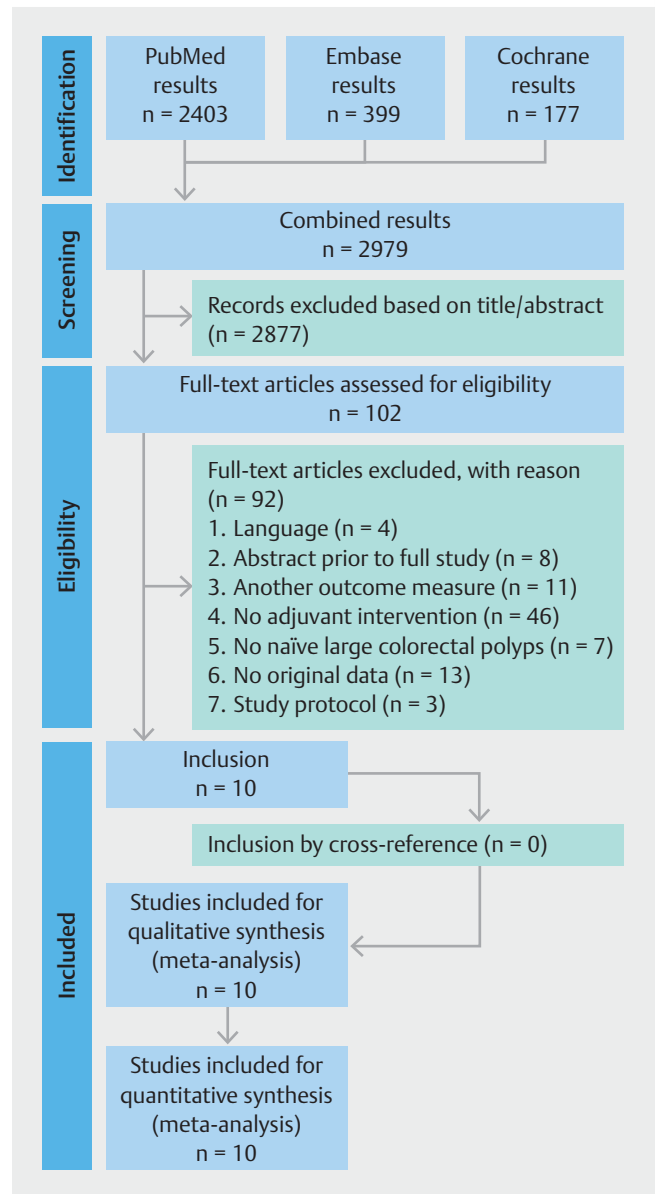
Disagreement was resolved through discussion and consensus was reached by coordination with senior authors (AAMM and LMGM).

Statistical analysis

Pooled risk differences (RDs) along with 95% confidence intervals (CIs) were calculated using random-effect models with Mantel-Haenszel method. R statistical program version 4.0.5 was used to process all collected data [12]. The Metafor package version 3.0.2 was used for calculations and plotting [13].

Secondary, pooled recurrence rates after STSC and APC treatment were calculated by applying generalized linear mixed models with a logit link to the raw data (recurrence yes/no), where a random intercept on study level was included to account for the study effect.

Heterogeneity was assessed with the Q test for significance and with the inconsistency index (I^2), where a value of >50% was considered as substantial heterogeneity between studies. Funnel plots with Egger’s test for asymmetry were constructed to test the possible effect of publication bias [14]. Crude esti-



► Fig. 1 Study flowchart.

mates were used for statistical analysis. A two-sided $P \leq 0.05$ was considered statistically significant.

Results

Included studies

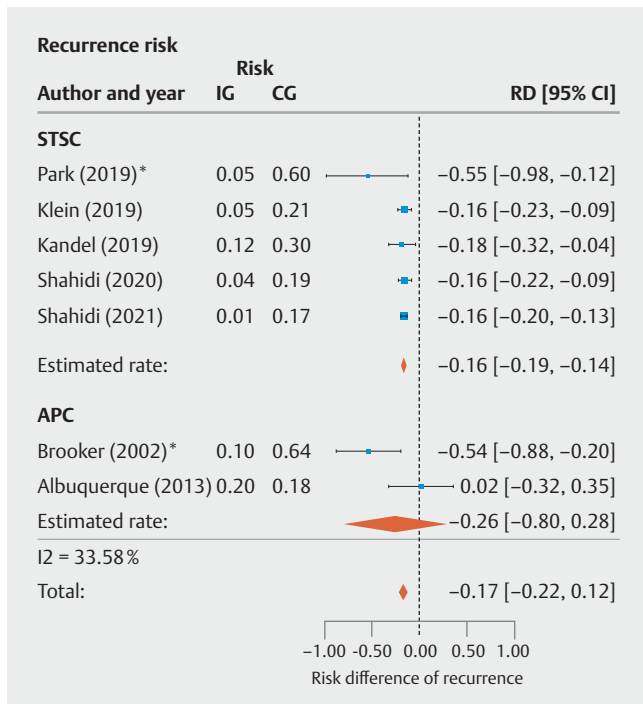
Our search identified 2979 papers, of which ten met our inclusion and exclusion criteria (► Fig. 1). Study characteristics are shown in ► Table 1. APC was evaluated as adjuvant treatment modality in three studies, while STSC was evaluated in six studies. One additional study retrospectively compared both treatment modalities, with 50 patients receiving APC and 51 patients receiving STSC. The ten included studies represented a total of 316 APC cases and 1598 STSC cases.

▶ **Table 1** Baseline study characteristics.

Author, year	Country	Study design	Randomization	Blinding	No. of participating centers	No. of patients	No. of lesions	Size in mm (mean±SD or median + IQR)	Proximal location (%)	Type of ablative therapy (settings)	Follow-up interval	Outcome – local recurrence		P value
												Intervention group	Control group	
Albuquerque, 2013 [19]	Brazil	RCT	Yes	No	1	20	21	34 (± 13)	43%	APC 60W Gasflow 2.0L/min	3 and 12 months	2/10 (20%)	2/11 (18.2%)	NR
Brooker, 2002 [18]	UK	RCT	Yes	No	1	21	21	26 (± 10)	62%	APC 45–55W right, 65W left colon Gasflow 2.0L/min	3 and 12 months	1/10 (10%)	7/11 (63.6%)	0.02
Kandel, 2019 [16]	USA	Prospective cohort	No	No	1	120	120	28 (± 11)	82%	STSC 20–80W Soft coag mode	6 months	7/60 (12%)	18/60 (30%)	0.01
Katsinelos, 2019 ¹ [24]	Greece	Retrospective cohort	No	No	1	101	101	41 (± 13)	16%	STSC 20W Soft coag mode APC 50W right, 70W left Gasflow 1.5L/min	3, 6 and 12 months	7/51 (13.7%)	8/50 (16%)	0.34
Klein, 2019 [6]	Australia	RCT	Yes	No	4	416	416	30 (IQR 25–45)	52%	STSC 80W Soft coag mode Erbe effect 4	6 and 18 months	10/192 (5.2%)	37/176 (21.0%)	<0.001
Park, 2019 [21]	South Korea	Retrospective cohort	No	No	1	156	176	22 (± 10) ²	NR	STSC 80W Soft coag mode Erbe effect 4	3–12 months	8/171 (4.8%)	3/5 (60%)	0.002
Raju, 2020 [25]	USA	Retrospective cohort, no control group	No	No	1	246	246	35 (IQR 30–45)	80%	APC 30–35W Gasflow 0.8L/min	6 and 18 months	11/246 (4.5%)	NA	NA
Shahidi, 2020 [22]	Australia	Prospective cohort	No	No	2	413	413	40 (IQR 30–60)	NA	STSC 80W Soft coag mode Erbe effect 4	6 months	0/30 (0%) 3/51 (5.9%)	12/48 (25%) 28/160 (17.5%)	0.002 0.041
Shahidi, 2021 [23]	Australia	Prospective cohort	No	No	1	817	817	35 (IQR 30–50)	72%	STSC 80W Soft coag mode Erbe effect 4	6 months	2/336 (0.6%)	82/481 (17.0%)	<0.001
Sidhu, 2021 [15]	Australia	Prospective cohort, no control group	No	No	6	1049	1049	35 (IQR 25–45)	54%	STSC 80W Soft coag mode Erbe effect 4	6 months	10/707 (1.4%)	NA	NA

APC, argon plasma coagulation; STSC, snare tip soft coagulation; NR, not reported; NA, not applicable.

¹ Comparison between APC and STSC. STSC reported as intervention group (IG) and APC as control group (CG)² Estimated mean + SD, calculated from reported size categories with frequencies



► **Fig. 2** Pooled data from included studies. IG, intervention group; CG, control group; RD, risk difference; STSC, snare tip soft coagulation; APC, argon plasma coagulation. *Not all included lesions in this study are ≥ 20 mm in size.

All studies included large colorectal polyps, but inclusion criteria differed between studies, with the size of lesions suitable for inclusion ranging from ≥ 10 mm to ≥ 20 mm.

Mean age and gender distribution between groups in the included studies were comparable. Furthermore, the included studies reported comparable size and location of lesions between intervention and control groups.

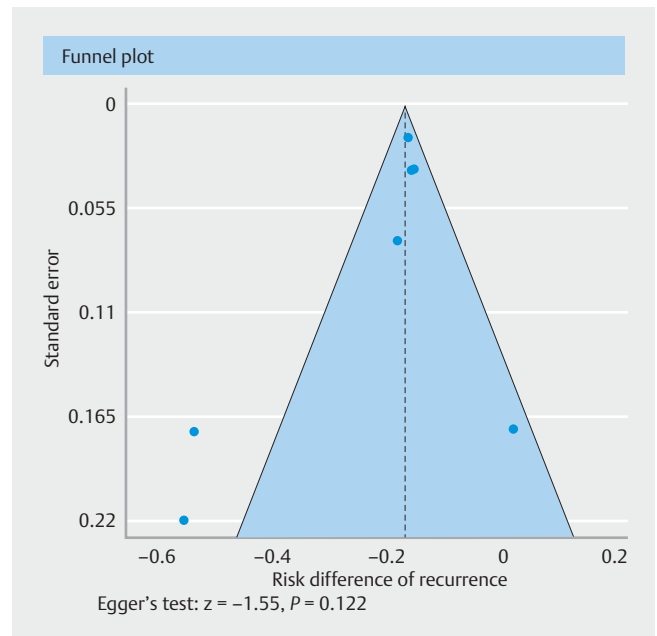
Quality assessment

Quality and risk of bias assessment according to the QUIPS tool for randomized trials is presented in **Supplementary Material, Table 1**. In addition, quality and risk of bias assessment according to the NOS for all included studies is presented in **Supplementary Material, Table 2**.

Adjuvant thermal ablative treatment

The main results of the effect of adjuvant STSC and APC on recurrence are presented in ► **Fig. 2**. Pooled estimates of the effect of any adjuvant treatment modality on recurrence yielded a statistically significant risk difference of -0.17 (95% CI -0.22 to -0.12) compared to no adjuvant treatment. Pooled estimates of the effect of STSC on recurrence yielded a statistically significant risk difference of -0.16 (95% CI -0.19 to -0.14), while the pooled effect of APC on recurrence yielded a non-significant risk difference of -0.26 (95% CI -0.80 to 0.28).

Risk of publication bias is presented in ► **Fig. 3**. The funnel plot shows two studies being outliers, but this was not significant (Egger's test $P=0.112$).



► **Fig. 3** Funnel plot of included studies.

Sensitivity analysis without the two studies including lesions from a size of ≥ 10 and ≥ 15 mm showed no difference in outcome, with an overall risk difference of -0.16 (95% CI -0.19 to -0.13).

Sensitivity analysis to account for possible case overlap in studies from the same research group did also not show any significant difference in outcome, with an STSC-specific risk difference ranging from -0.18 to -0.22 (95%-CI lower bound ranging from -0.25 to -0.34 and upper bound ranging from -0.09 to -0.12).

Comparing thermal ablation modalities

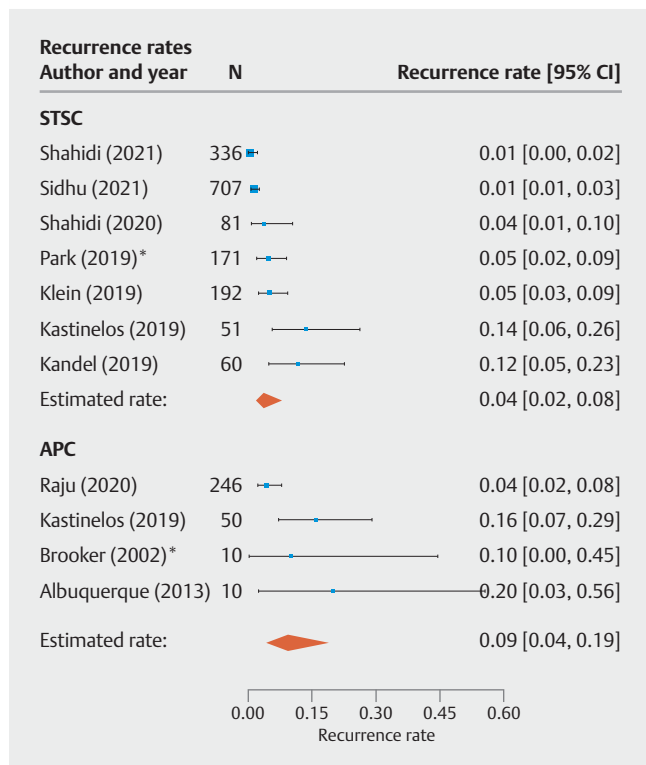
Pooled estimates of the recurrence rates after STSC and APC are presented in ► **Fig. 4**. Pooling studies reporting on STSC yielded a recurrence rate of 4% (95% CI 2% to 8%), while a recurrence rate of 9% (95% CI 4% to 19%) was seen for APC.

One of 10 included studies directly compared APC ($n=50$) and STSC ($n=51$) in a retrospective manner, and showed no significant difference in recurrence after APC vs. STSC (16% vs. 13.7%; $P=0.34$).

Discussion

This systematic review and meta-analysis of 10 studies shows that adjuvant thermal ablative treatment of mucosal defect margins reduces recurrence rate after endoscopic resection of large colorectal polyps (RD -17% ; 95% CI -22% to -12%). STSC showed a significantly reduced recurrence rate, while APC did not lead to a significant reduction in recurrence. Pooled recurrence rates showed 4% and 9% recurrence after STSC and APC, respectively.

Our findings are in accordance with recent studies on thermal ablation of mucosal defect margins that concluded that



► **Fig. 4** Pooled recurrence rates for STSC and APC after 6 to 12 months. *Not all included lesions in this study are ≥ 20 mm in size.

thermal ablation after endoscopic resection, also described as EMR-T, is an effective measure to reduce recurrence in large colorectal polyps [6, 15, 16]. In addition, a recent meta-analysis about endoscopic techniques to reduce recurrence rates after colorectal EMR also showed that treatment of the EMR resection margins significantly reduces recurrence [17]. However, this meta-analysis by Kemper et al. harbors some concerns. First, it did not include all currently available evidence regarding thermal ablation of resection margins. Kemper et al. evaluated thermal ablation in only four studies, together accounting for 529 lesions, whereas we evaluated thermal ablation in ten studies, together accounting for 3380 lesions. Second, in the effect analysis, they also included studies in which extended EMR and precutting was performed. This may have influenced the results. Third, they did not perform sensitivity analysis for size and case overlaps. Fourth, using only randomized controlled trials (RCTs) for their comparison between APC and STSC ruled out important observational studies. Especially for APC, the original RCTs are of questionable quality and applicability to current practice. Based on the data of this systematic review and meta-analysis, evaluating all currently available evidence on this subject, it can be concluded that thermal ablation of mucosal defect margins should be incorporated for all large (≥ 20 mm) colorectal polyps removed by piecemeal approach.

Two treatment modalities are available for thermal ablation, which both seem to reduce the risk of recurrence. However, in this meta-analysis, APC did not show a significant reduction when pooling studies, in contrast to STSC, which significantly

reduced recurrence risk. While pooled data are presented for STSC and APC separately, this information should be interpreted with caution. A couple of recent high-quality studies have been published on STSC, but the evidence on APC is of moderate quality. The number of lesions included in the APC studies is very small (Brooker et al. $n = 21$; Albuquerque et al. $n = 21$). Furthermore, the study by Brooker et al. showed a recurrence rate of 63.6% in the control group, which raises the question whether these data are representative for current practice [18, 19]. In addition to the studies by Brooker et al. and Albuquerque et al., an abstract by Chattree and Rutter (2015) also reported data on the effect of APC on recurrence. In this abstract, a total of 153 piecemeal EMR procedures were retrospectively analyzed, with 18% vs. 31% recurrence in APC group vs. non-APC group respectively ($P = 0.064$) [20]. Sensitivity analysis, including these abstract data, did not lead to a significant effect of APC. Consequently, at this point, the evidence on the effect of APC to reduce recurrence is of insufficient quantity and quality to make any firm statements.

In addition to risk reduction analysis, all available evidence (including observational studies without control group) was pooled to estimate recurrence rate after APC and STSC. The difference in pooled recurrence rate after APC and STSC was not statistically significant, given the overlapping CIs. Therefore, superiority of one of these modalities remains unknown at this time.

Settings used during thermal ablation of mucosal defect margins sometimes differ between operators. However, our data showed that operators in general agree about the settings for STSC. For STSC, universally, the soft coagulation mode is used with a current of 80 Watts and effect mode 4 on Erbe ENDO CUT Q [6, 15, 21–23].

Settings for APC show more variation between operators, with currents between 30–70 Watts and a gasflow of 0.8–2.0 liters per min [18, 19, 24, 25]. A recent study in porcine models evaluating the effects of STSC and APC showed that APC applied at 1.0L/min, 30W, was associated with islands of preserved mucosa [26]. Therefore, it appears that higher power in APC is necessary to achieve deeper thermal ablation. We advise using forced coag 60 Watts when applying APC.

En bloc EMR is associated with lower recurrence rates compared with piecemeal EMR (3% vs. 20%) [27]. However, en bloc resection by EMR is difficult for lesions ≥ 20 mm. Therefore, most large colorectal polyps are resected piecemeal when there is no suspicion for submucosal invasion. Of the included studies in this meta-analysis, only three made the distinction between en bloc and piecemeal resection [6, 21, 25], and only one of these three performed post-hoc analysis to evaluate the specific effects of EMR-T after en bloc and piecemeal resection separately [6]. In this study, there was no significant difference in recurrence rate after traditional en bloc EMR (0/23; 0%) compared to en bloc EMR-T (1/25; 4%). Therefore, it appears that the positive effects of EMR-T seen after piecemeal resection, are not seen in en bloc resections. Combining these data with the fact that recurrence rates after en bloc resection are already low, the added value of thermal ablation remains questionable. Prospective studies, with larger numbers are needed

to make firm statements about the value of thermal ablation after en bloc resection.

While large colorectal polyps without suspicion of submucosal invasion could be treated by EMR, the discussion remains ongoing whether some of these lesions should be removed en bloc by ESD [28,29]. The main argument for non-selective ESD on large colorectal polyps, is the fact that it is associated with lower recurrence rates compared to EMR [27,30,31]. In a systematic review and meta-analysis by Fuccio et al., recurrence rate after ESD was only 2.0% (95% CI 1.3% to 3.0%) [3]. However, with the emergence of EMR-T, recurrence rates after EMR can be significantly reduced to percentages as low as 1.3% [15], waiving this advantage of ESD over EMR. As thermal ablation of mucosal defect margins is not associated with a higher frequency of adverse events [15], it should be preferred over ESD for treatment of large colorectal polyps without suspicion for submucosal invasion. However, it is of utmost importance to perform a thorough selection of cases suitable for EMR. When there is any suspicion for submucosal invasion, one needs to perform an en bloc resection to obtain free resection margins (R0 resection), which enables pathologists to perform detailed pathological analysis [32,33]. EMR on superficially invasive colorectal cancers leads to suboptimal treatment outcomes, with low R0-resection rates [34]. Therefore, in case there is any doubt about potential submucosal invasion being present, an en bloc resection technique such as ESD is preferred.

Alternatives to EMR-T are present, such as (extra-)wide-field EMR (also known as extended EMR) or marking of the lesion prior to EMR. In (extra-)wide-field EMR, a wider excision is performed to excise at least 5 mm of normal-appearing tissue around the edges of the lesion. However, a large cohort study, comparing extended EMR with standard EMR did not show a reduction of recurrence after extended EMR [35]. Furthermore, a recent retrospective observational study by Emmanuel et al. showed that microscopic residual adenoma was detected at the apparently normal defect margins in 19% of cases after wide-field EMR [36]. These studies suggest that wide-field EMR is not the appropriate technique to secure that all microscopic adenomatous tissue is being resected and prevent recurrence.

Another recently evaluated alternative to EMR-T is margin marking before EMR. A single-center historical control study, performed by Yang et al., showed that margin marking before EMR reduced recurrence rates with 80% when compared with conventional EMR [37]. This technique may therefore provide an alternative to margin ablation. However, larger prospective or randomized studies might be desired to validate these outcomes. In the future, expanding the scope to not only treating defect margins, but also the base of resection, might be important to further reduce recurrence [36,38].

Our study has some limitations. First, some studies included in this meta-analysis were performed on a small number of patients. Especially in the studies concerning APC, the numbers of patients were limited, which leads to a higher heterogeneity when pooling studies and wider CIs. Heterogeneity was also caused by different duration of follow-up between studies.

Therefore, especially the data concerning APC should be interpreted with caution.

Second, this study does not allow us to perform sub-analyses based on specific risk profiles (e.g. piecemeal vs. en bloc; number of pieces; high-grade dysplasia; experience of endoscopist, local access to the lesion). Unfortunately, none of the included studies evaluated the relationship between the number of pieces and the additional value of thermal ablation. In other words, might thermal ablation only be of added value from a specific number of pieces onwards. This question therefore remains unanswered. Consequently, we are unable to make any firm statement about which specific lesions could benefit the most from thermal ablation.

Third, while it was not the primary goal of this systematic review, we could not detect a significant difference in effectivity between APC and STSC to reduce recurrence. However, only one comparative study of both treatment modalities exists, of which reliability and generalizability could be questioned because of the retrospective, single endoscopist design, small numbers and long time period of inclusion [24]. Because of these concerns, a prospective randomized controlled trial should be performed to determine whether there is a difference between APC and STSC in reducing the risk of recurrence. Despite the lack of evidence, one could argue that STSC is preferred over APC because of standard availability with EMR and the fact that for APC an additional APC probe is needed, which leads to additional costs [15]. Therefore, STSC is considered the most cost-effective modality and, consequently, suggested as primary thermal ablative treatment modality in most cases. Furthermore, a recent study in porcine models showed possible superiority of STSC over APC, demonstrated by less incomplete ablation with islands of preserved mucosa after STSC compared to APC [26].

Conclusions

Thermal ablation of mucosal defect margins significantly reduces the risk of recurrence after resection of large non-pedunculated colorectal polyps and should be used universally for piecemeal-resected large non-pedunculated colon polyps. Although evidence for superiority is lacking, STSC is preferred over APC because this is the most evidence-based and probably most cost-effective modality. Further (randomized) studies are needed to investigate the difference between APC and STSC efficacy in reducing recurrence after endoscopic resection of large non-pedunculated colorectal polyps.

Acknowledgments

The authors are grateful to Gregor Franssen, scientific information specialist, Maastricht University Medical Center, for his help defining the literature search.

Competing interests

Dr. Bogie was supported by an unrestricted educational grant from Pentax Medical B.V. Dr. Masclee was supported by a health care efficiency grant from ZON MW (Organization for Health Research and Development, The Netherlands), an unrestricted research grant from Will Pharma S.A., a restricted educational grant from Ferring B.V., research funding from Allegan and Grünenthal, gave scientific advice to Bayer, Kyowa Kirin, and Takeda, and received a research grant from Pentax Europe GmbH and the Dutch Cancer Society. Dr. Moons declares consultancy for Boston Scientific.

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