

# Post-EMR for colorectal polyps, thermal ablation of defects reduces adenoma recurrence: A meta-analysis \*



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## ABSTRACT

**Background and study aims** Adenoma recurrence is one of the key limitations of endoscopic mucosal resection (EMR), which occurs in 15% to 30% of cases during first surveillance colonoscopy. The main hypothesis behind adenoma recurrence is leftover micro-adenomas at the margins of post-EMR defects. In this systematic review and meta-analysis, we evaluated the efficacy of snare tip soft coagulation (STSC) at the margins of mucosal defects to reduce adenoma recurrence and bleeding complications.

**Methods** Electronic databases such as PubMed and the Cochrane library were used for systematic literature search. Studies with polyps only resected by piecemeal EMR and active treatment: with STSC, comparator: non-STSC were included. A random effects model was used to calculate the summary of risk ratio and 95% confidence intervals. The main outcome of the study was to compare the effect of STSC versus non-STSC with respect to adenoma recurrence at first surveillance colonoscopy after thermal ablation of post-EMR defects.

**Results** Five studies were included in the systematic review and meta-analysis. The total number patients who completed first surveillance colonoscopy (SC1) in the STSC group was 534 and in the non-STSC group was 514. The pooled adenoma recurrence rate was 6% (37 of 534 cases) in the STSC arm and 22% (115 of 514 cases) in the non-STSC arm, (odds ratio [OR] 0.26, 95% confidence interval [CI], 0.16–0.41,  $P=0.001$ ). The pooled delayed post-EMR bleeding rate 19% (67 of 343) in the STSC arm and 22% (78 of 341) in the non-STSC arm (OR 0.82, 95%CI, 0.57–1.18).

**Conclusions** Thermal ablation of post-EMR defects significantly reduces adenoma recurrence at first surveillance colonoscopy.

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## Introduction

Polypectomy during colonoscopy reduces colon cancer by approximately 50% [1]. Small polyps are routinely resected during endoscopic intervention. However, resection of large polyps (>20 mm) becomes more intricate and complicated. Among colonic polyps detected during endoscopy, 5% were lateral

spreading lesions (LSLs) that can manifest considerable growth along the bowel wall before progression to more invasive malignancy. Moreover, large LSLs are recognized precursors of colorectal cancer but fortunately can be treated with endoscopic mucosal resection (EMR) [2]. EMR is a standard technique for removal of large, sporadic, and laterally spreading colorectal polyps. Previously, larger lesions would be an indication for surgery, but endoscopic intervention has proven more effective in terms of significantly lowering healthcare costs and lessening hospitalization days [3, 4]. Unfortunately, EMR has a major drawback of adenoma recurrence. Despite complete EMR of such lesions via the piecemeal approach, rates of adenoma reappearance at first surveillance colonoscopy range from 15% to 30% [5]. The theory is that there exist unseen microadenomas at the margins of EMR, which steadily grow to sizable adenomas given a month to year. Subsequently, adenoma recurrence is one of the key limitations of EMR.

Snare tip soft coagulation (STSC) is a unique method initially used to control bleeding [6], but the technique was later applied as adjuvant ablation at post-EMR margins following standard resection of all visible adenoma islands. Klein et al [7] demonstrated efficacy in a randomized trial of adjuvant thermal ablation of post-EMR mucosal defect margins via reduction of polyp recurrence rates. Likewise, that result was later confirmed in a large multicenter study by Sidhu et al [8] illustrating the superior efficacy of adjuvant thermal ablation in real-world settings. Currently, the literature regarding colon EMR with adjuvant thermal ablation consists of three large studies—two multicenter RCTs and one large multicenter cohort study along with a few retrospective studies [7–12]. Our meta-analysis will prompt a broader examination of the efficacy of STSC as an adjuvant ablation method to post-EMR defects with regard to reduction in adenoma reappearance.

## Methods

### Literature search and search strategy

This review is in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) [13] (**Supplement 1**) with the studies reporting endoscopic mucosal resection of colorectal lesions and adenoma recurrence decreasing technique by STSC of margins of EMR defect. Electronic databases such as PubMed and the EMBASE (OVID) library were used for systematic literature search (**Supplement 2**). Comprehensive literature search was assisted by an experienced librarian. The search included key terms such as endoscopic mucosal resection, colorectal lesions, ablation technique-snare tip soft coagulation, and adenoma recurrence. The search was run in December 2021 and restricted to articles published in English. Ethical approval was not sought as analysis included dataset (**Table 1**) [7, 9–12].

### Inclusion and exclusion

Our meta-analysis included studies of human subjects published in English that addressed an adenoma recurrence technique called STSC on post-EMR defect margins in polyps >20 mm. The comparator arm consisted of polyps resected by

EMR without treatment with STSC. Included were randomized controlled trials (RCTs) and observational studies. Conference abstracts were also included in the study if they contained usable data. Adenoma recurrence data on first surveillance colonoscopy (SC1) had to be reported to be eligible. Resection of malignant polyps, polyps <20 mm, non-English studies, and studies including pediatric age groups (<18 years) were excluded.

### Study selection

Study eligibility was assessed by (MH and DY) by going through study titles, full text, and conference abstracts. Any discrepancies between reviewers were resolved by discussion with a third reviewer (PK).

### Outcome

The primary outcome of the study was the adenoma recurrence rate at first surveillance colonoscopy (SC1) with the use of STSC at the margins of mucosal defect compared to standard EMR. Both histology and endoscopic diagnosis were performed for adenoma recurrence assessment. Endoscopic diagnosis of adenoma recurrence is also highly accurate [14] for recurrence assessment. Data on post-procedure complications such as delayed bleeding (post-EMR bleeding) were collected as a secondary outcome (**Table 2**) [7, 9–12].

### Statistical analysis

We calculated the risk ratio (RR) for adenoma recurrence comparing STSC of margins of mucosal defect compared to standard EMR, non-STSC. The ORs of individual studies were pooled in this meta-analysis using RevMan software (version 5) with a random effects model. Random effects models are used to estimate an average effect. The variability of the effects represented by their average may have consequences for the clinical interpretation of the findings [15]. Therefore, prediction interval was included in the forest plot. The heterogeneity of studies was assessed using  $I^2$  (inconsistency) statistic. Heterogeneity values 25%, 50%, and 75% indicate low, moderate, and high level of heterogeneity [16] based on a previously published validated tool. In addition, we also calculated the OR of post-EMR delayed bleeding in the STSC group and non-STSC standard EMR group. Statistical analysis was conducted with Review Manager version 5.3.5 and JMP software version 14.

### Risk-of-bias assessment

Observational studies differ from controlled trials in regard to validity problems and can be prevented by the study design, e.g., by randomization, concealed allocation, and masking [17]. We have acknowledged limitations of non-randomized studies compared to the gold standard randomized studies. Studies were selected through meticulous search to avoid selection bias. There is always a risk of misclassification of groups/data in a meta-analysis. To prevent that, we included the most accurate measurement of available data and carefully categorized data according to the proper group. Sensitivity analysis was conducted only for randomized trials and non-randomized studies were excluded. The risk of bias (ROB) for each

► **Table 1** Baseline characteristics included in the studies.

Author, year	Study designs, country	Size	STSC				Non-STC			
			Pa-tient (n)	Age (mean)	Female (n)	Polyp size, SD, rage (mm)	Patient (n)	Age (mean)	Female (n)	Polyp size, SD, range (mm)
Senada, 2020 (abs)	RCT multi-center, USA	>20 mm	73	65.5	40	30 ± 11.1	75	66.6	40	33.3 ± 16.7
Wehbeh, 2020 (abs)	Retrospective, USA	>20 mm	148	66.6 (10.8)	70	32.5 (13.7)	140	66.6 (10.8)	61	30.4 (10.9)
Perez, 2021 (abs)	Retrospective, USA	>20 mm	43	65 (11)	23	NR	33	66 (9)	23	NR
Klein, 2019	RCT multi-center, Australia	>20 mm	210	66.1 ± 11.6	109	30 (25–40)	206	67.0 ± 13.1	104	30 (25–45)
Kandel, 2019	Retrospective, USA	>20 mm	60	66 (49–81)	35	28 ± 11; 25 (20–60)	60	65 (45–83)	29	28 ± 11; 25 (20–60)

STSC, snare tip soft coagulation; SD, standard deviation; RCT, randomized controlled trial.

► **Table 2** Outcomes data.

Author, year	STSC		Non-STSC	
	Adenoma recurrence (n)	Post-EMR bleeding (n)	Adenoma recurrence (n)	Post-EMR bleeding (n)
Senada, 2020 (abs)	9	9	23	19
Wehbeh, 2020 (abs)	9	NR	21	NR
Perez, 2021 (abs)	2	NR	16	NR
Klein, 2019	10	49	37	47
Kandel, 2019	7	9	18	12

STSC, snare tip soft coagulation.

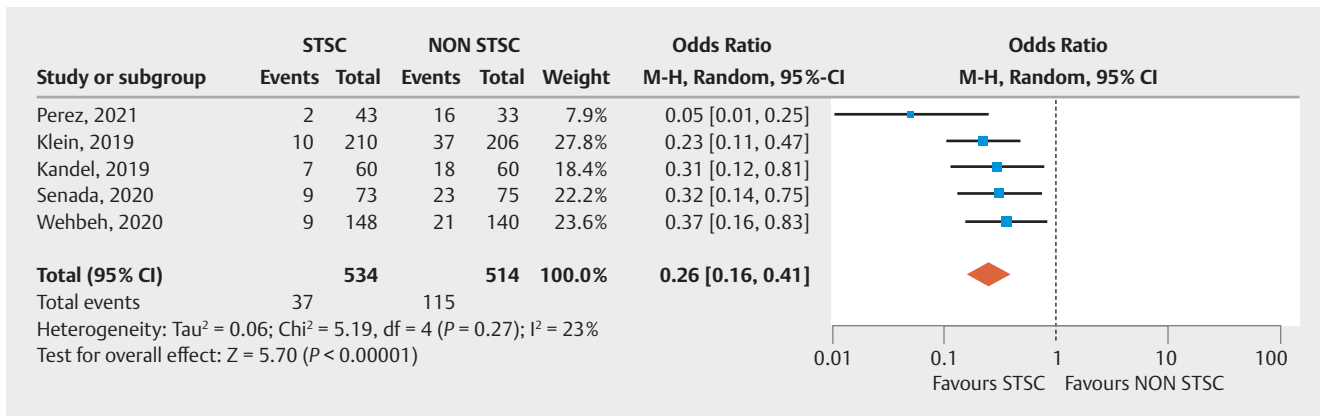
► **Table 3** Risk-of-bias assessment.

Author, year	Design	No. in interven-tion group (STSC)	No. in control group (non-STSC)	Risk of bias for ade-noma recurrence	Risk of bias for delayed bleeding
Senada, 2020 (abs)	RCT	73	75	Low	Low
Wehbeh, 2020 (abs)	Retrospective	148	140	Some concerns	Some concerns
Perez, 2021 (abs)	Retrospective	43	33	Some concerns	Some concerns
Klein, 2019	RCT	210	206	Low	Low
Kandel, 2019	Retrospective	60	60	Low	Low

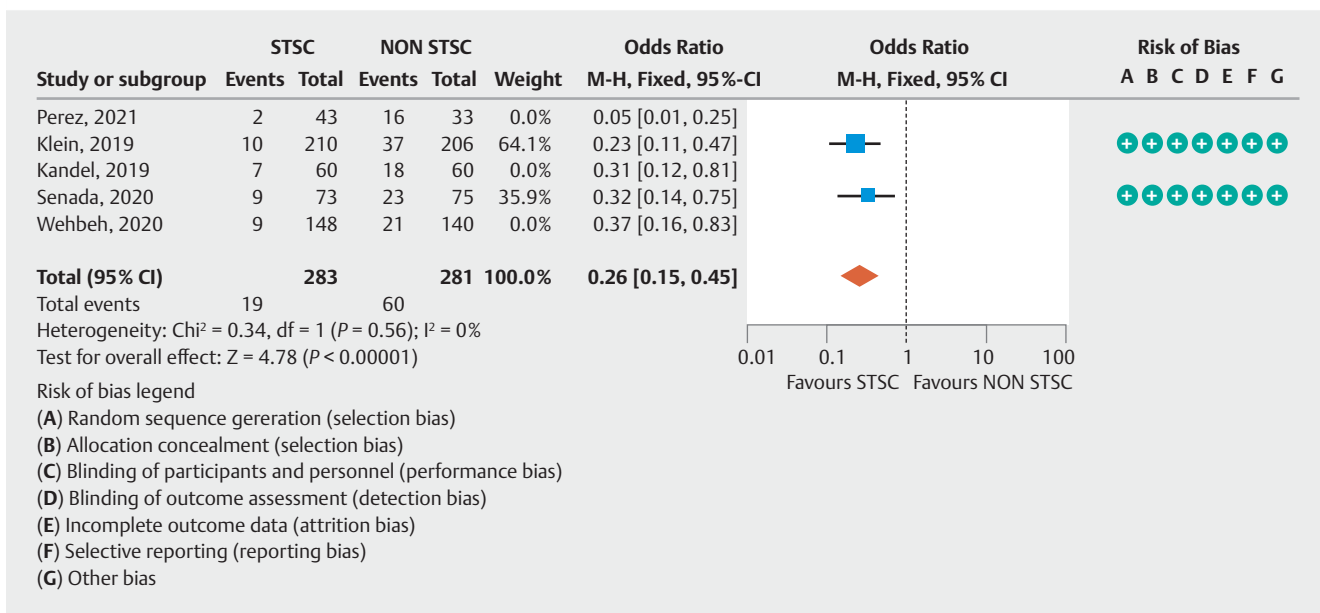
STSC, snare tip soft coagulation; RCT, randomized controlled trial.

study outcome was assessed using existing validated tools (► **Table 3**) [7,9–12]. For RCTs, we used a revised Cochrane risk-of-bias tool for the RCT checklist (ROB 2) [18] and the methodical index for non-RCTs (MINORS) checklist [19]. For RCTs, the outcomes were assessed as a low and high ROB using

the ROB algorithm. For non-RCTs, the MINORS checklist was used providing scores ranging from 0 to 24. Scores of 0 to 8 were considered high ROB, 9 to 16 were considered of some concern, and 17 to 24 as low ROB. For publication bias we used a funnel plot to evaluate asymmetry. However, given the small



► Fig. 1 Adenoma recurrence [7, 9–12].



► Fig. 2 Adenoma recurrence (RCT only) [7, 9–12].

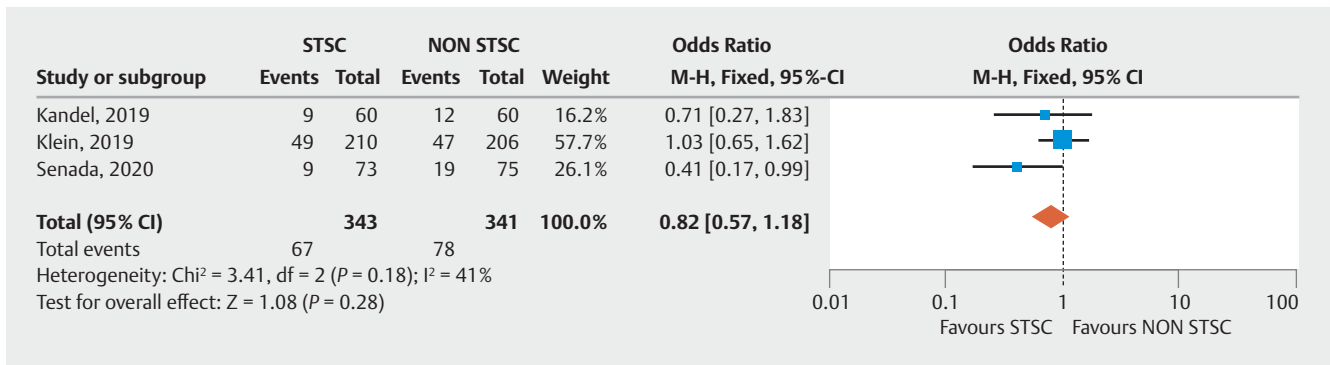
number of included studies, proper additional statistical analysis was not performed [20].

## Results

A total of 534 patients completed the first surveillance colonoscopy (SC1) and were included in the meta-analysis (► Table 1). We included five studies (Kandel [9], Kelin [7], Senada [12], Wehbeh [10], Perez [11]) for meta-analysis, all of which used STSC at mucosal defect margins after EMR as an intervention and adenoma recurrence as the primary outcome at first surveillance colonoscopy (SC1). Two studies were multicenter RCTs. The remaining three were retrospective cohort studies. First surveillance colonoscopy interval (SC1) ranged up to 12 months. Size of polyps included was >20mm in both groups. Mean age was >60 years. The total number of patients in the STSC group was 534 and in the non-STSC group was 514. The adenoma recurrence rate at SC1 in the STSC group was 6%

(confidence interval [CI], 5%–9%) and 22% (CI 18%–26%) in the non-STSC group. Overall pooled OR for adenoma recurrence in the STSC group was 0.26 (95% CI, 0.16–0.41) compared to the non-STSC group (► Fig. 1) [7, 9–12]. Heterogeneity between included studies was assessed with I<sup>2</sup> = 23%, which is considered as low. The heterogeneity decreased to zero, I<sup>2</sup> = 0 when only randomized trials were included (► Fig. 2) [7, 9–12].

Only three studies reported post-procedural delayed bleeding as a complication. The rate of delayed bleeding in the STSC group was 19% (CI, 15%–24%) and 22% (CI, 18%–27%) in the non-STSC group. The overall pooled odds ratio (OR) for delayed post-EMR bleeding in the STSC group was 0.82 (95% CI, 0.57–1.18) compared to the non-STSC group (► Fig. 3) [7, 9, 12]. The heterogeneity between included studies was assessed with I<sup>2</sup> = 40%, which is considered as low.



► Fig. 3 Post-EMR delayed bleeding [7, 9,12].

## Discussion

To the best of our knowledge, we present the first meta-analysis showing the effectiveness of EMR with adjunctive STSC at margins of mucosal defects to reduce adenoma recurrence. This meta-analysis demonstrated that use of STSC of post-EMR mucosal defects decreases adenoma recurrence in first surveillance colonoscopy. Among patients who had undergone EMR and had STSC as an adjunctive treatment of mucosal defect margins, 74% were less likely to have adenoma recurrence. There was no difference in rates of post-EMR delayed bleeding, suggesting that use of STSC as an adjunctive treatment is safe.

The field of endoscopy has undergone multiple advances that ultimately have reduced the prevalence of colorectal cancer (CRC). CRC has minimal lymph node metastases as the colonic mucosa lacks lymphatic vessels; thus, endoscopic resection of malignant tissue is essentially curative [21]. Consequently, EMR is an established therapeutic modality that can be performed on an outpatient basis and garner outstanding long-term results. In the treatment of large colorectal lesions, the rate of adenoma recurrence is as high as 30% and remains a major hindrance to EMR [2]. The CARE study mirrored similar results: a 23.3% rate of biopsy-proven residual adenomas in incompletely resected lesions measuring 15 to 20 mm [22]. Along with lesion size >40 mm, there are various other risk factors for adenoma recurrence, such as utilization of argon plasma coagulation (APC) to ablate malignant tissue, histological evidence of high-grade dysplasia, insufficient submucosal lifting leading to incomplete resection, and intraprocedural bleeding [23–25].

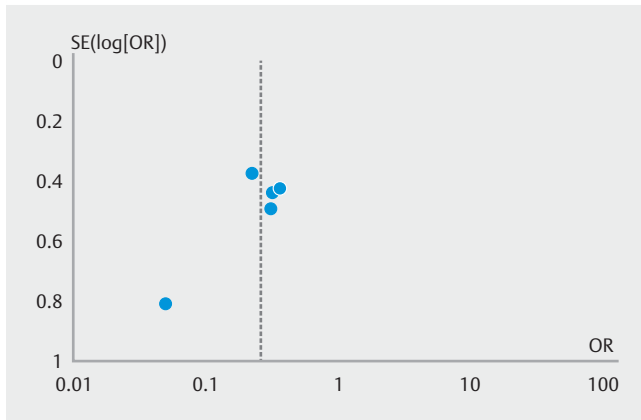
The past school of thought was to extend the EMR margin several millimeters within normal-appearing mucosa with the objective of eliminating neoplasia. Unfortunately, a multicenter study described no difference in terms of adenoma recurrence between typical and extended EMR [26]. This was an important finding in EMR because there exist unseen residual neoplastic cells at the margins of the snare trajectory. Intuitively, other interventions targeting the EMR margins have also been introduced in endoscopy practice along with extended EMR [26], such as precutting EMR [27], APC [28, 29], and STSC [7, 9]. In general, these interventions decrease recurrence rates by as much as 63% [30], with APC and STSC demonstrating superior

efficacy in recurrence reduction compared to extended EMR and precutting EMR as per subgroup analysis. This corresponds with a large retrospective multicenter cohort study in 2019 with only 4.5% recurrence in APC [31], and only 5.2% [7] and 12% [9] recurrence in STSC. Between the two cauterization techniques, however, STSC was associated with decreased recurrence at 7.8% compared with 10% regarding the APC group [32]. Regarding the current transmission from catheter to tissue, there is a heavy reliance on fluctuating arching and it is thus operator dependent. Arching is variable, sporadic, and is very challenging to visualize when confirming eradication of tissue [9]. In addition, there is always an increase in cost with the use of APC due to the need for a special generator and catheter. Adverse events (AEs) such perforation occur in approximately 0.5% if cases with APC, although they are rare [33, 34]. Thus, STSC seems to improve outcomes with EMR compared to APC.

The Australian cohort performed the first-ever large multicenter RCT assessing the efficacy of post-EMR thermal ablation with STSC. It showed a 4-fold reduction in adenoma recurrence at SC1 (5.8% in the STSC group versus 20.2% in the non-STSC arm) [7]. Those results were confirmed by a multicenter trial from the United States [12]. There was significant reduction in adenoma recurrence in the STSC group compared to the non-STSC group (12% STSC group vs 34% non-STSC group,  $P=0.001$ ).

Moreover, a smaller non-randomized controlled trial regarding an educational intervention of STSC demonstrated 12% recurrence rate in the STSC group versus 30% in the non-STSC group [9]. These results show superior efficacy in a controlled setting. In addition, results recently have been published of a large cohort study from the same group (Australia), which showed that thermal ablation of post-EMR defect mucosal margins was achieved in 95.4% of cases ( $n=989$  large nonmalignant colorectal polyps, LNPC). Ninety-four percent ( $n=755$ , LNPC) underwent SC1 (median time 6 months), and only 1.4% had adenoma recurrence on follow up [8]. Thus, STSC remained more precise because the application distance is standardized and garnering consistent results.

Our meta-analysis demonstrated a pooled adenoma recurrence rate 6% in the STSC arm compared to 22% in the non-STSC arm. These results were statistically significant with a nar-



► **Fig. 4** Funnel plot of comparison 1 STSC vs non-STSC, outcome 1.1 adenoma recurrence.

row CI, underscoring the exceptional effectiveness in STSC. Most adenoma recurrences are identified within 6 months post-EMR [23, 28,35]; thus, that timeframe was selected for surveillance colonoscopy (SC1) across all our studies. Subsequently, the study endpoints were homogenous with an  $I^2 = 23\%$ , indicating low heterogeneity. Likewise, baseline demographic characteristics and polyp size were similar across studies, thus minimizing avenues of confounding bias. In addition, a funnel plot seems symmetric, suggesting no publication bias (► **Fig. 4**).

Only three studies had reported delayed bleeding as a complication. Numerical results were similar; however, the wide CIs suggest statistical insignificance (RR 0.82; 0.57, 1.18). Although statistically insignificant, STSC has a clear benefit in prevention of delayed bleeding. Delayed bleeding is one of the most common complications post-EMR [36–39]. Delayed bleeding is defined as any bleeding occurring within a month after completion of the procedure and that requires Emergency Department presentation, hospitalization, or reintervention (repeat endoscopy, angiography, or surgery) [37]. Along with the reduction in adenomas, there are logistical and financial benefits associated with STSC. For example, STSC can be performed with the same snare that was used for resection, hence it does not significantly lengthen procedure times. Thus, STSC remains an extremely safe procedure with minimal AEs.

We acknowledge that our meta-analysis had limitations. First, our study only included five studies including abstracts, which can be interpreted as not quite adequate. However, we were able to include the usable data in the meta-analysis. Second, there was variation among studies in recording morphology of polyps such as NBI and Paris classification. If that information was available, we would have included it in the study. Third, the generator settings were not available for all studies. However, STSC effect in terms of adenoma recurrence is similar among all studies. This further validates that STSC is effective, despite use of different generator settings.

## Conclusions

In conclusion, our study illustrates that thermal ablation of post-EMR defects with STSC significantly reduces adenoma recurrence at first surveillance colonoscopy. This safe and simple technique can improve outcomes in such patients and should be integrated into routine EMR practice. With lower rates of adenoma recurrence, follow-up intervals post-EMR potentially can be prolonged, which can gradually lessen the burden on overall healthcare resources.

## Competing interests

The authors declare that they have no conflict of interest.

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