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Full-thickness resection device for management of lesions involving the appendiceal orifice: Systematic review and meta-analysis

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ABSTRACT

Background and study aims Endoscopic resection of lesions involving the appendiceal orifice is technically challenging and is commonly referred for surgical resection. However, post-resection appendicitis is a concern. Many studies have varying rates of post-procedure appendicitis. We aim to report the rate of post-resection appendicitis by performing a systematic review and meta-analysis.

Methods Studies that involved the use of a full-thickness resection device (FTRD) for management of appendiceal polyps were included. The primary outcome was appendicitis after FTRD and a subgroup analysis was performed on studies that only included FTRD performed at the appendiceal orifice.

Results Appendicitis was encountered in 15% (95%CI: [11]–[21]) of the patients with 61% (95% CI: [44]–[76]) requiring surgical management. Pooled rates of technical success, histologic FTR, and histologic R0 resection in this subgroup (n = 123) were 92% (95% CI: [85]–[96]), 98% (95% CI: [93]–[100]), and 72% (95% CI: [64–84%]), respectively. Post-resection histopathological evaluation revealed a mean resected specimen size of 16.8 ± 5.4 mm, with non-neoplastic pathology in 9 (7%), adenomas in 103 (84%), adenomas + high-grade dysplasia (HGD) in nine (7%), and adenocarcinoma in two (2%). The pooled rate for non-appendicitis-related surgical management (technical failure and/or high-risk lesions) was 11 % (CI: 7–17).

Conclusions FTRD appears to be an effective method for managing appendiceal lesions. However, appendicitis post-resection occurs in a non-trivial number of patients and the R0 resection rate in appendiceal lesions is only 72%. Therefore, caution should be employed in the use of this technique, considering the relative risks of surgical intervention in each patient.

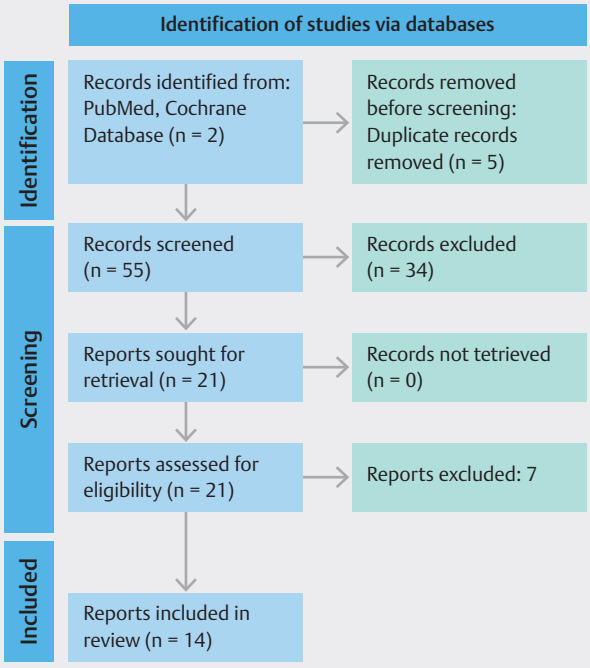
Introduction

Endoscopic removal of polyps involving the appendiceal orifice is technically challenging, and thus, it is not uncommon for these cases to be referred for surgical resection. Available techniques include snare resection, endoscopic mucosal resection (EMR), and endoscopic submucosal dissection (ESD) [1, 2, 3]. These techniques have been deemed alternatives to surgical resection but are often difficult when lesions have deep extension into the appendiceal orifice because they are associated with technical failures and higher risk of adverse events (AEs) [1, 2, 3]. One other technique that has shown promise is endoscopic

full-thickness resection (EFTR) [4], and more specifically, the Full-Thickness Resection Device (FTRD), which allows EFTR in one step. The efficacy and safety of (FTRD) for managing such lesions have been reported in multiple studies, mostly retrospective, which show acceptable rates of en bloc resection and R0 pathologic resection [5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18].

Safety, specifically post-resection appendicitis, has been an increasing concern in these studies, leading to the question of whether direct referral for surgery is superior to FTRD and potential urgent appendectomies. Post-resection appendicitis likely stems from the obstruction of the appendiceal orifice, which can induce inflammation. And to date, no steps to mitigate the risk of appendicitis have been used in major studies other than prophylactic antibiotics. From the available data, there are no large, controlled studies that are available that demonstrate the use of prophylactic antibiotics is helpful and reduces the risk of appendicitis.

The rate of reported appendicitis has been heterogenous between multiple studies, ranging from as low as 0% to 50% [9, 10, 19, 20]. The varying rate is likely due to the definition of post-FTRD appendicitis, sample size variation, and operator experience. Many of the studies do not report whether a patient had a previous appendectomy, potentially lowering the actual rate of appendicitis [21]. Therefore, we performed a systematic review and meta-analysis of existing studies to shed light on the rate of post-FTRD appendicitis and subsequently performed a subgroup analysis on studies that only included FTRD performed at the appendiceal orifice.



▶ **Fig. 1** PRISMA flowchart for chosen articles. From: *Page MJ, McKenzie JE, Bossuyt PM* et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372: n71.

Methods

Literature Search and Study Selection

A comprehensive literature search strategy was employed by the authors of this paper based on the Preferred Reporting Items for Systematic Reviews and meta-analysis (PRISMA) guidelines for two electronic databases: PubMed, Cochrane from January 2010 to January 2021 (▶ **Fig. 1**) [22]. Due to authors' previous experience and expertise in publishing on this topic, it was known to authors that a limited amount of studies are available on this topic. The goal was to find studies related to the FTRD that included lesions at the appendiceal orifice and rates of appendicitis. The following keyword and search terms that were used included: "Full-thickness resection device, appendicitis, appendiceal orifice, EFTR, FTRD". Only English language articles were included and the bibliographies of the articles chosen were then reviewed to find any additional studies that were of interest/relevant. Review of literature did not identify any relevant studies published in languages besides English, although this is limited by the language barrier.

Inclusion and exclusion criteria

Inclusion criteria were determined by two investigators (MO, YI) and any conflict that emerged was decided by a third investigator (MA). The studies were eligible if they met the following criteria: (1) original articles that assessed the use of FTRD for lesions including the appendiceal orifice; (2) studies that were performed in humans; (3) studies that included the rate of appendicitis; (4) studies that were published in English; and (5) studies that were published from 2010 to 2021. Studies that were excluded were: (1) published in a language other than English; (2) had EFTR/FTRD performed on animals; (3) case reports with less than five patients; (4) abstracts that did not have a corresponding study and that were not peer-reviewed were excluded; and (5) any studies with patients under the age of 18 years were excluded.

Data collection process and listed items

From each study, the investigators retrieved the following information: (1) country; (2) multicenter/single-center; (3) design of study; (4) study period; (5) total number of patients in the index study; (6) total number of patients with lesions involving the appendiceal orifice; (7) method of EFTR and details of procedure; (8) sex; (9) age; (10) prior surgical history of appendectomy; (11) number of lesions; (12) lesion size; (13) number of lesions with prior biopsy; (14) mean total procedure time; (15) number of patients who received peri-operative antibiotics; (16) total number of EFTRs with technical success/en bloc resection; (17) total number of FTRD with technical failures; (18) AEs; (19) median resected specimen size; (20) histologic FTR status; (21) pathology of resections; (22) and follow-up of the patients after the procedures. The information was taken from each study by an investigator and the data was rechecked by a second investigator. Technical success of FTRD was defined

▶ **Table 1** Main characteristics of included studies [4, 5, 6, 7, 9, 11, 16, 18, 19, 20, 21, 23, 24].

Author	Country	Study design	Study period (month/year to month/year)	Total number of patients with colorectal lesions	Total number of patients with appendiceal lesions	Age (mean/median)	Largest measured diameter (median) (mm)
Schmidt Et Al 2015 [17]	Germany	Multicenter/retrospective	7/12–7/14	25	5	70	24
Al-Bawardy et al 2017 [18]	USA	Multicenter/retrospective	6/14–10/15	9	2	63	8
Aepli Et Al 2018 [5]	Switzerland	Multicenter/retrospective	5/15–11/16	33	2	65.9	27
Schmidt et al 2018 [4]	Germany	Multicenter/prospective	2/15–4/16	181	34	65	
Valli Et al 2017 [9]	Switzerland	Single-center/retrospective	6/12–10/16	60	4	68	24
Bronzwaer et. al 2018 [19]	Netherlands	Single-center/prospective	11/16–12/17	7	7	64	8.25
Andrisani et al. 2019 [7]	Italy	Multicenter/retrospective	1/15–3/18	114	2	68	20
Albrecht et al. 2019 [6]	Germany	Multicenter/retrospective	11/14–12/17	70	2	79.5	23
Ichkhanian et al. 2020 [20]	USA	Multicenter/retrospective	10/27–12/18	95	11	65.6	20
Krutzenbichler, I. et al. 2020 [21]	Germany	Multicenter/retrospective	11/14–6/19	229	9	69.29	16.3
Zwager et al 2020 [22]	Netherlands	Multicenter/prospective	7/15–10/18	362	17	69	23
Velegraki et al. 2019 [23]	Greece	Multicenter/retrospective	10/15–12/18	17	2	59.7	14
Schmidbaur et al 2021 [11]	Germany	Multicenter/retrospective	2014–2019	50	50	65.8	18.3
Ichkhanian et al. 2021 [16]	USA/Canada/Europe	Multicenter/retrospective	11/16–8/20	66	66	64.3	16.8

as success with targeting the lesion and deploying the FTRD clip with successful resection. Histologic full-thickness resection was defined as complete success of procedure and proof of histologic resection of all three layers. Histologic R0 resection was defined as resection that achieves absolute resection with negative microscopic and macroscopic margins on pathology.

Risk of bias in individual studies

Given prior exposure to the literature, the authors anticipated the majority of the literature to be retrospective studies; thus, the Newcastle-Ottawa Scale (NOS) was selected for analysis of bias. Of the studies, three were excluded from the scale because they were prospective.

Outcomes

The primary outcome of the study was rate of post-FTRD appendicitis. A subgroup analysis was subsequently performed on studies that only included FTRD performed at the appendiceal orifice. Secondary outcomes included the rate of surgically managed appendicitis, rate of technical success (en bloc resection), histologic FTR, and histologic R0 resection (negative microscopic and macroscopic margins).

Statistical analysis

Data on the primary and secondary outcomes relevant to this study were included when available. Missing information that was needed was obtained by contacting the primary authors of selected studies through personal communication, if necessary and available; all relevant information was available in the

▶ **Table 2** New Castle-Ottawa Scale analysis adjusted for the purposes of systemic review.

Study	Case definition adequate	Representativeness of cohort	Demonstration that outcome of interest was not present at start of study	Ascertainment of exposure	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow-up of cohorts
Schmidt et al 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Al bawardy Et al 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Aepli et al 2018	Yes	Yes	Yes	Yes	Yes	no	no
Schmidt et al 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Vali Et al 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bronzewater et al 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Adrisani et al 2019	Yes	Yes	Yes	Yes	Yes	Yes	No
Albrecht et al 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ichkhanian et al 2020	Yes	Yes	Yes	Yes	Yes	No	No
Krutzenbicher et al 2020	Yes	yes	Yes	Yes	Yes	Yes	No
Velegraki et al 2019	Yes	yes	Yes	Yes	Yes	Yes	Yes
Schmidbaur et al 2021	Yes	yes	Yes	Yes	Yes	No	No
Ichkhanian et al 2021	Yes	yes	Yes	Yes	Yes	Yes	No

publications and no authors were contracted for supplemental information. Weighted pooled rate with 95% confidence interval (CI) was calculated for the primary outcome of interest and secondary outcomes; rate of appendicitis, technical success, and r0 resection rate. An I^2 value of more than 50% with a corresponding P <0.1 resulting from Cochrane Q test was considered as an indication of the presence of heterogeneity. A subgroup analysis with studies that were exclusively at the appendiceal orifice was conducted with similar methods. The statistical analysis in this meta-analysis was performed by a statistician employed by Henry Ford Hospital.

Results

The 14 studies included in this review and meta-analysis are detailed in ▶ **Table 1** along with pertinent study characteristics [5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18]. Eleven studies were conducted in Europe, two studies were conducted in the United States, and one study was international (United States/Canada/Europe). Eleven studies (79%) were retrospective whereas three studies (21%) were prospective. Twelve studies were multicenter (86%) whereas two studies (14%) were single-center. Across the included studies, a total of 1319 colorectal polyps underwent resection with FTRD, of which 205 (15.5%) involved the appendiceal orifice. All studies provided comprehensive data on the primary outcome and secondary outcomes.

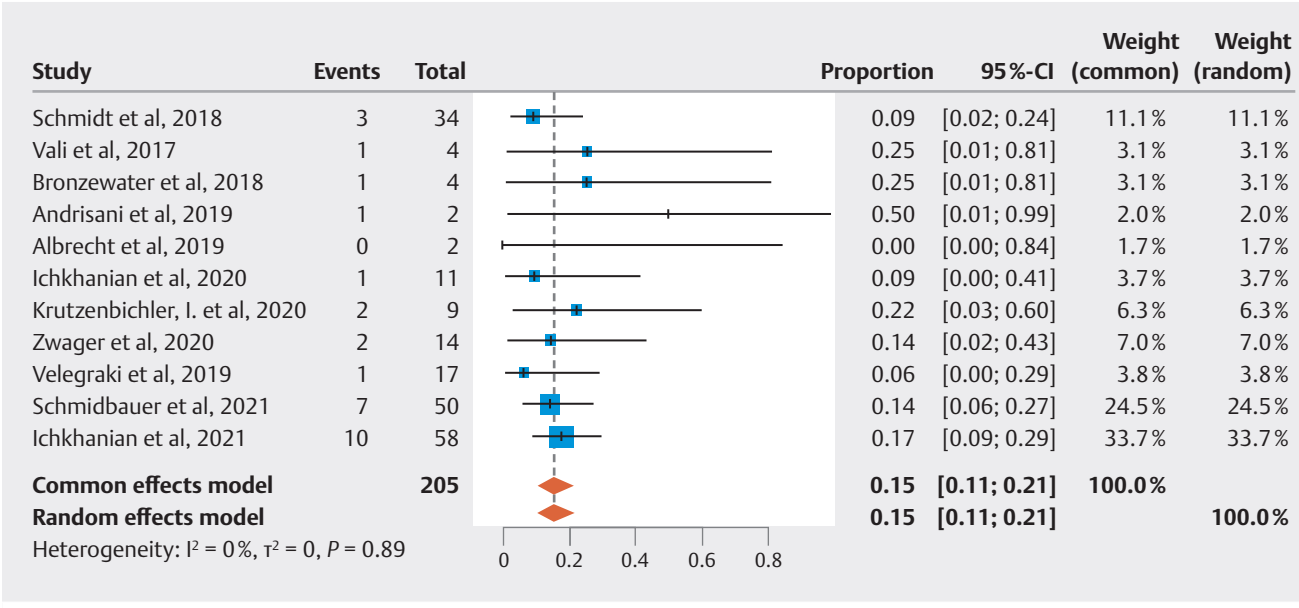
Risk of bias

▶ **Table 2** also shows the studies and their appropriate NOS results. The studies have an acceptable risk of bias. The studies that were included in the scale were considered high risk of bias due to the lack of control and lack of randomization due to the nature of the studies being retrospective with small sample sizes [23]. Many of the studies did not have a control group, so other aspects of the NOS were measured and are shown in ▶ **Table 2**.

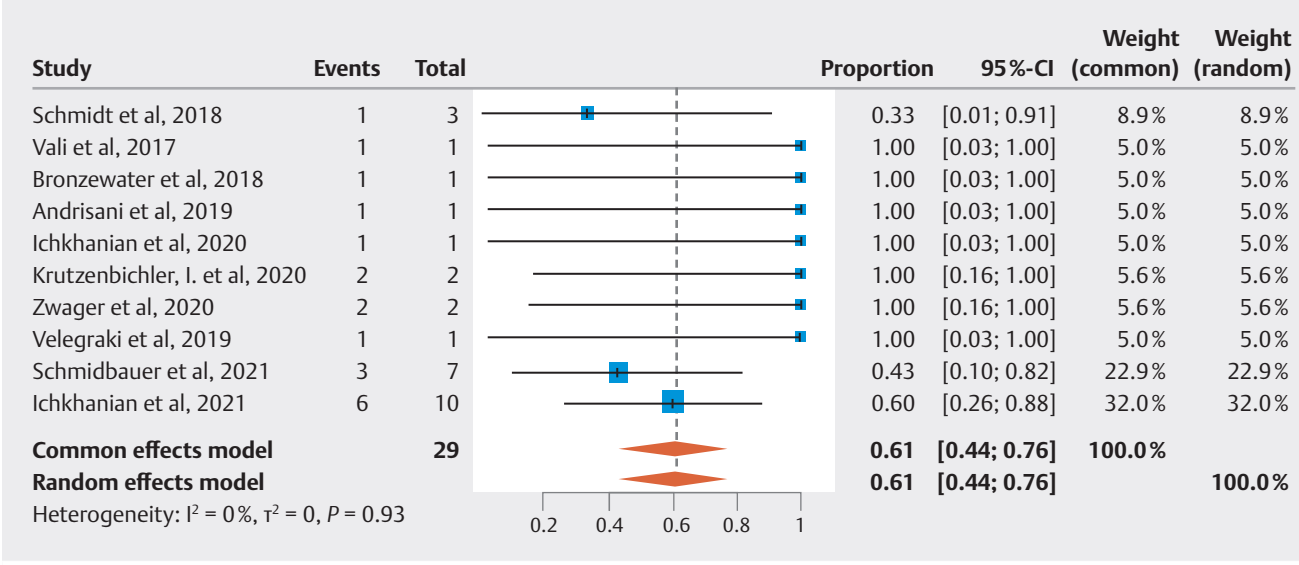
Primary outcome

The primary outcome, defined as the rate of post-procedural appendicitis in patients who underwent FTRD, was determined to be 15% (95% CI: [11–21%]) as seen in ▶ **Fig. 2**. This value was derived from 29 events of appendicitis across 205 patients. This pooled primary outcome had an I^2 value of 0% ($P = 0.89$), indicating that minimal clinically relevant heterogeneity exists.

Among the 29 patients who developed post-procedural appendicitis, 19 patients underwent surgical management of this complication at a rate of 61% (95% [CI: 44–76%]), as seen in ▶ **Fig. 3**. This pooled secondary outcome demonstrated minimal clinically relevant heterogeneity as indicated by the I^2 value of 0% ($P = 0.93$). The remaining 10 patients were managed medically with antibiotics.



▶ **Fig. 2** Pooled rate of appendicitis after FTRD. Shows the rate of appendicitis after the procedure was performed.



▶ **Fig. 3** Surgery requirement in appendiceal polyps with no prior history of appendectomy.

Secondary outcomes

Technical success

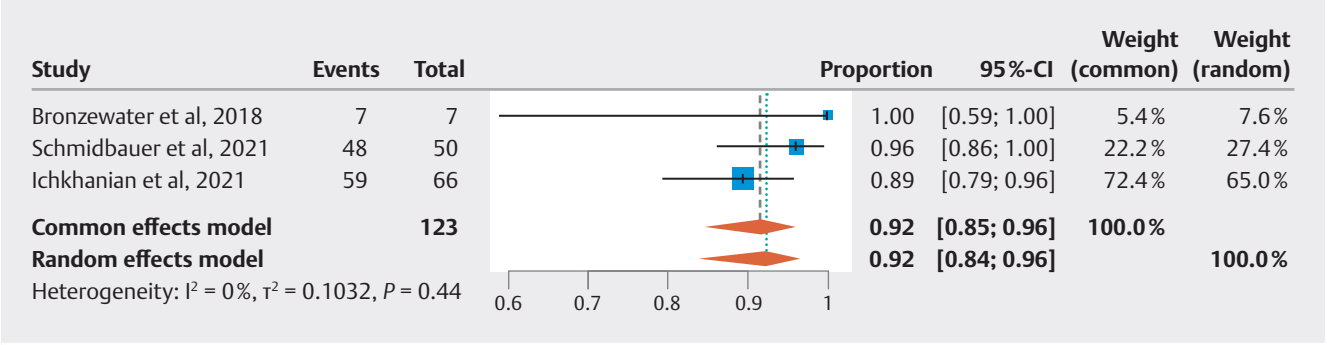
This subgroup analysis was limited to three studies that only included lesions at the appendiceal orifice, as that is the procedure of interest for this study [10, 14, 15]. Of the 123 cases that met these criteria, 114 demonstrated technical success at a rate of 92% (95% CI: [84–96%]) as seen in ▶ **Fig. 4**. This pooled secondary outcome demonstrated minimal clinically relevant heterogeneity as indicated by the I^2 value of 0% (P = 0.44).

Histologic full-thickness resection

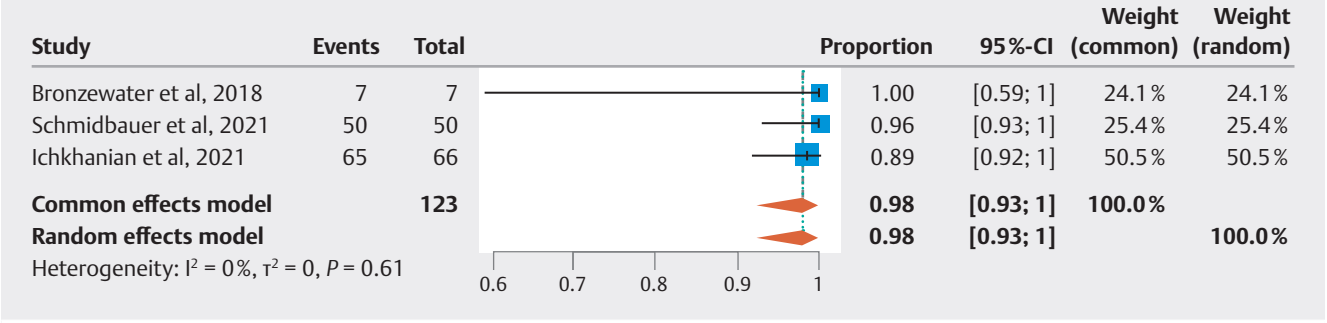
This subgroup analysis was limited to three studies that only included lesions at the appendiceal orifice [10, 14, 15]. Of the 123 cases that met these criteria, 122 achieved histologic full-thickness resection at a rate of 98% (95% CI: [93–100%]) as seen in ▶ **Fig. 5**. This pooled secondary outcome demonstrated minimal clinically relevant heterogeneity as indicated by the I^2 value of 0% (p = 0.61).

Histologic R0 resection

This subgroup analysis was limited to three studies that only included lesions at the appendiceal orifice [10, 14, 15]. Of the 123 cases that met these criteria, 90 achieved histologic R0 resec-



▶ **Fig. 4** Technical success of FTRD procedure in studies that were only performed at the appendiceal orifice.



▶ **Fig. 5** Full-thickness resection rates in studies that performed at the appendiceal orifice.

tion at a rate of 72% (95% CI: [64–80%]), as seen in ▶ **Fig. 6**. This pooled secondary outcome demonstrated and had moderate clinically relevant heterogeneity as indicated by the I2 value of 45% (P = 0.16).

Appendiceal orifice lesions in patients with no prior history of appendectomy requiring surgical management after FTRD

Of the 203 patients with no prior history of appendectomy who were found to have lesions at the appendiceal orifice, 19 required surgical intervention after FTRD at a rate of 11% (95% CI [7–17%]) as seen in ▶ **Fig. 7**. This pooled secondary outcome demonstrated minimal clinically relevant heterogeneity, as indicated by the I2 value of 0% (P = 0.48).

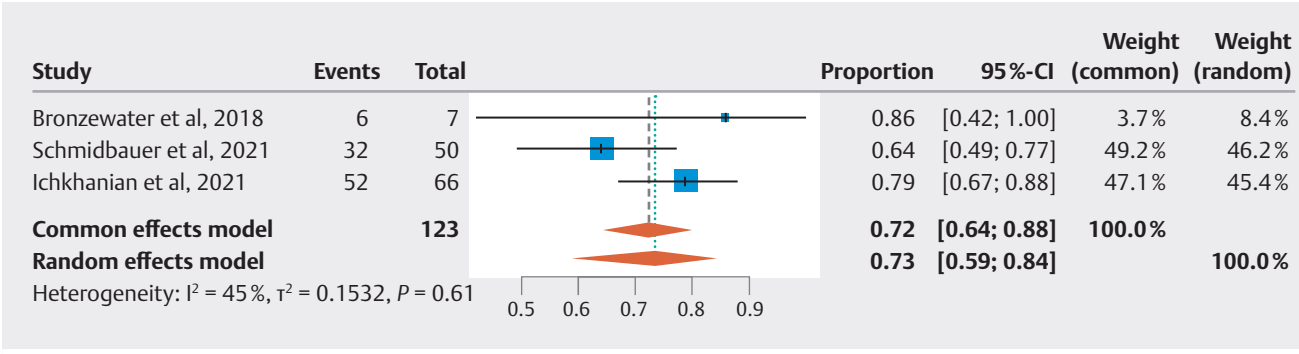
Discussion

We believe this study represents the first systematic review and meta-analysis specifically on the use of FTRD for appendiceal lesions. The purpose of the study was to analyze the risk of appendicitis because it is a potential complicating factor of the procedure. With the estimated incidence of these primary appendiceal neoplasms at approximately 0.3%, there are a sizable number of neoplasms that may need intervention, highlighting the importance of calculating the AEs [24]. The type of management of these lesions is important as the different procedures may affect quality of life and may limit the progression to malignant.

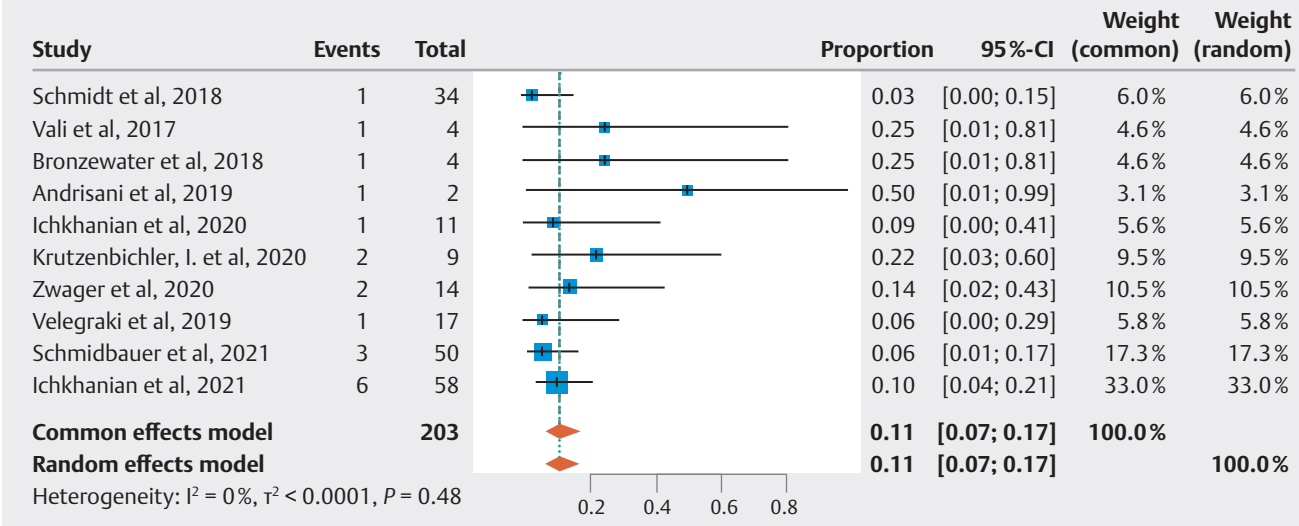
As has been previously mentioned in other studies, we have found that FTRD appears to be a fairly effective method for managing appendiceal lesions [11]. In our review, three studies exclusively focused on appendiceal lesions as the primary indication for FTRD and we measured this subgroup separately (▶ **Fig. 4, Fig. 5, Fig. 6**). The technical success and histologic FTR were all above 90%; however, the R0 resection rate was only 72% for lesions at the appendiceal orifice. The characteristics of these lesions showed that the majority of lesions were adenomas (84%) and the minority were high-grade dysplasia or adenocarcinoma (9%). This highlights the needs to be able to reach these lesions effectively before they progress further. However, the primary endpoint of this study is the rate of the appendicitis and surgical complications.

In this meta-analysis, we found that appendicitis post-resection is occurring in a non-trivial number of patients. Appendicitis was seen in 15% of patients, 61% of whom required surgery. This adds crucial information to practitioners prior to prescribing the FTRD for appendiceal adenomas. First, the physician has a responsibility to discuss the risks and benefits of a procedure and must add appendicitis as a non-trivial risk. In addition, some patients may not be able to tolerate an appendectomy and/or have contraindications, making the clinical decision more difficult with alternatives needing exploration.

In the studies included, it was common to include prophylactic antibiotic administration and it was observed in 95% of patients who underwent resection at the appendiceal orifice. Because 95% of the patients received some form of antibiotics,



▶ **Fig. 6** R0 resection in studies performed at the appendiceal orifice.



▶ **Fig. 7** Appendiceal orifice lesions in patients with no prior history of appendectomy requiring surgical management after FTRD.

it is difficult to decipher the effect of the medication. While there is a theoretical benefit to antibiotics prior to and after surgery, further trials would be needed to discern a true benefit. No other AEs or mortality related to FTRD were significant in our study. It is also important to note that the rates of AEs, including appendicitis, measured in our study were in the immediate timeframe of the procedure rather than months or years after. Many of the studies had patients lost to follow-up and/or had a minimal duration for follow-up. With the clip remaining in place, there is a theoretic risk of appendicitis, and longer-duration follow-up and larger studies would be needed to make a claim that there is no chance of appendicitis in the long term.

In the modern age of medicine, endoscopic procedures are seen as alternatives for patients who are high-risk surgery candidates, but in this case, the complication of appendicitis may require emergent surgery, rendering that point moot. Although there are no studies on these data and the population chosen, we would agree with Dr. Schmit that it is better to have an elective surgery that is high risk rather than an emergent surgery in a patient who is high risk [21]. Therefore, one must note the patient population before prescribing this procedure. Of note, 11% of the patients studied required surgical management anyway due to technical failure and/or high-risk lesions. This again highlights that there is a non-trivial chance of surgical intervention after the FTRD for an appendiceal adenoma that can stem from a variety of reasons.

It is difficult to ascertain why some patients' procedures are complicated by appendicitis and others are not. Given the nature of our meta-analysis, we were unable to discern the risk factors for appendicitis due to the unclear criteria for patient selection for FTRD in each study. Further studies are required to differentiate the risk factors. Ichkanian et al previously noted that male sex and failure to achieve histologic FTR were associated with a higher risk of appendicitis, but they had a limited sample size as well as a concern for confounders [11]. In regard to the actual pathophysiology, it has been hypothesized that obstruction of the orifice is what causes appendicitis due to closure via the clip and there may be novel approaches to preventing appendicitis. One novel approach to managing this poten-

tial complication is prophylactic appendiceal retrograde intraluminal stent placement (PARIS) [19]. Keane et al reported a case in which temporary stent placement likely maintained drainage of the appendix and likely limited the risk of appendicitis. This provides an interesting addition to the FTRD that may provide benefit in limiting appendicitis but larger trials and training for physicians are needed before attempting this novel approach.

Answering the true question about whether the FTRD benefits outweigh the risks of appendicitis requires a discussion of the alternatives. Of course, the most common alternative is surgical resection, which is naturally more invasive and often requires colectomy with significant recovery time. Another alternative includes EMR and ESD, which have been associated with technical difficulties and incomplete resection [1, 2, 3]. There also has been difficulty with attempting endoscopic resection with deep luminal extension or large lesions occluding the orifice, which make up a significant part of the lesions seen at the orifice. In one study in Japan, some of the side effects were intraoperative perforation and postoperative appendicitis, which highlights that these procedures are not without complication and further studies and comparisons are needed [2].

Limitation of this study may affect the conclusions drawn and influence its applicability in a clinical setting. FTRD is a novel and specialized intervention that requires significant operator skills and experience; endoscopists with less exposure to this procedure would be expected to have poorer outcomes. With many of these studies being some of the initial FTRD attempts, endoscopists may have gained more experience. Secondary outcome analysis was limited to three studies with 123 patients, of the total 14 studies, as the remainder did not publish further data; the studies included are more likely to have occurred in specialized centers with experienced endoscopists, which will skew the data. An additional limitation of this study was the small sample sizes (<10 patients) for five of the included studies, which led to the large range in the individual study rates but was not reflected in the heterogeneity tests.

Conclusions

In conclusion, FTRD remains a generally safe and effective procedure for removing appendiceal lesions; however, there is a significant chance that a patient may develop appendicitis. This is important to discuss with patients prior to the procedure and clinicians should be aware of this non-trivial risk. We do not recommend FTRD at the appendiceal lesion for patients who are high-risk surgical candidates as an alternative, given the real risk that patients may need emergent surgery. Further studies are needed to focus on limiting the risk of appendicitis and/or evaluating risk factors in patients who develop appendicitis.

Conflict of Interest

T. Zuchelli: Consultant for Boston Scientific. C. Piraka: Research support from US Endoscopy and Aries; speaker for US Endoscopy. S. Singla: Consultant for Boston Scientific. All other authors disclosed no financial relationships.

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