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Title:
Efficacy and safety of endoscopic resection of appendiceal lesions. A Spanish multicenter study

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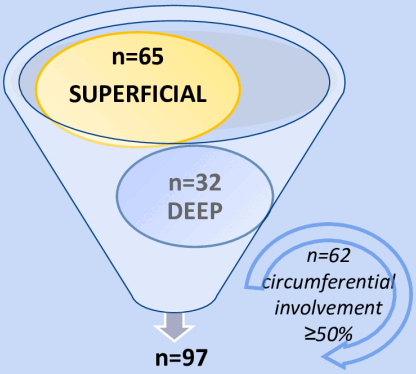
EFFICACY AND SAFETY OF ENDOSCOPIC RESECTION OF APPENDICEAL LESIONS: A SPANISH MULTICENTRIC STUDY

APPENDICEAL LESIONS (n=97)

INTRA-APPENDICULAR EXTENSION

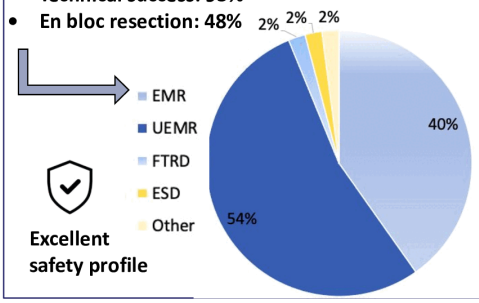


METHODS

RETROSPECTIVE, OBSERVATIONAL and MULTICENTRIC STUDY (8 Spanish referral centers). January 2016-July 2023.

SHORT-TERM OUTCOMES

- **Technical success: 93%**
- **En bloc resection: 48%**



Excellent safety profile

LONG-TERM OUTCOMES

- **RECURRENCE RATE** 25%
  -All after piecemeal resection.
  -Endoscopic follow-up ≥12m in 51 patients.
  -Median time to recurrence: 10 months (IQR 9-20)
- **NEED FOR SURGERY** n=12
  -Incomplete resection =7
  -Patient's preference (pT1a)= 1
  -Persistent residual adenoma=2
  -Delayed appendicitis=2
  (at 11 and 56 months post-resection).

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Efficacy and safety of endoscopic resection of appendiceal lesions. A Spanish multicenter study

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Key words: Appendiceal lesions. Endoscopic resection. UEMR.

List of abbreviations

- Appendiceal Orifice (AO)
- Endoscopic Mucosal Resection (EMR)
- Underwater Endoscopic Mucosal Resection (UEMR)
- Endoscopic submucosal dissection (ESD)
- Endoscopic Full-Thickness Resection (EFTR)
- Spanish Group of Endoscopic Resection (GSEED)
- Cap Suction pseudopolyp formation (CAP-UEMR)
- Standard Deviation (SD)
- Interquartile range (IQR)
- Computed tomography (CT)

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ABSTRACT

Aims: To determine the efficacy and safety of endoscopic resection of appendiceal orifice (AO) lesions. Primary endpoints were recurrence rate and the need for additional interventions during a clinical follow-up of at least 12 months and/or one surveillance colonoscopy.

Methods: Retrospective analysis of consecutive endoscopic resection of appendiceal lesions performed at eight centers in Spain between January 2016 and July 2023. Endoscopic resection techniques included endoscopic mucosal resection, underwater EMR (UEMR), endoscopic full-thickness resection, or endoscopic submucosal dissection.

Results: A total of 97 lesions were treated (median size 18 mm), 32 showing deep intra-appendicular involvement, and 62 having ≥50% circumferential involvement. UEMR was used in 52% of cases. Technical success was 93% (48% en-bloc resection). There were 6 intraprocedural and 1 postprocedural bleeding and 1 intraprocedural perforation managed endoscopically, but no cases of early post-resection appendicitis. During a median endoscopic follow-up of 23 months (n=51), 13 recurrences (25%) were identified (median time 10 months[IQR]=9-20). Piecemeal resection was significantly associated with recurrence (univariate). Deep AO extension, size ≥2cm and previous manipulation were significantly associated with piecemeal resection (multivariate). Surgery was required in 12 cases due to incomplete resection (n=7), malignancy (n=1), residual adenoma (n=2) and delayed post-resection appendicitis (n=2; at 11- and 56-months post-resection).

Conclusions: Endoscopic management of AO lesions is effective and safe. However, recurrence risk emphasizes the need for long-term follow-up. Further research is required to assess delayed appendicitis risk and the optimal management of deep extension AO lesions.

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Conflict of interest statement

H. Uchima is Proctor and teaching activities for ERBE Spain and Olympus Iberia. Consultant Olympus EMEA. E. Rodríguez de Santiago: Olympus (educational activities and advisory), Norgine (educational activities and congress fees), Erbe and Apollo Endosurgery(educational activities), 3D Matrix (speaker fee and research grant), Adacyte therapeutics (advisory), Izasa (speaker fee).

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The remaining authors have no conflicts of interest to declare.

Institutional Review Board Statement

The study protocol was approved by the Ethics Committee of Hospital Universitari Germans Trias i Pujol in November 2023 (reference number: PI-23-165). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research committee.

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Declaration of data availability

Data supporting the study findings are available from the corresponding author upon request

Artificial intelligence

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The authors declare that they did not use artificial intelligence (AI) or any AI-assisted technologies in the elaboration of the article.

Author contributions

HU, LGR and RMG contributed to conception and design, analysis and interpretation of the data, drafting of the article and critical revision of the article for important intellectual content.

ED and ERS also contributed to drafting and critical revision of the article for important intellectual content.

MFL, JTT, ER, JCB, BOF, HC, IMLS, AC, EV, MR, JR, PRR, VMV, PMG and AT contributed to data collection and contributed to drafting.

All authors gave their final approval of the article.

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INTRODUCTION

Endoscopic resection offers comparable efficacy to surgery for complex colorectal polyps while significantly reducing healthcare costs, hospitalization stay and morbidity, making it the preferred first-line treatment in specialized centers [1-6].

However, anatomical constraints of the appendiceal orifice (AO), including its narrow opening and extension, increase risks of incomplete resection, recurrence, and adverse events like perforation and appendicitis [2-3]. Consequently, lesions involving or occluding the AO are often referred for surgical resection [4-6].

In the past decade, advances in techniques such as Endoscopic Mucosal Resection (EMR), endoscopic submucosal dissection (ESD) and Endoscopic Full-Thickness Resection (EFTR), along with increased expertise, have made endoscopic management of AO lesions feasible and a promising minimally invasive alternative [7-10].

Efficacy has been reported mostly in retrospective studies with a limited follow-up [10-14]. Furthermore, long-term data on recurrence and adverse events are scarce and current guidelines lack specific recommendations for managing AO lesions.

This study aims to determine the long-term outcomes of endoscopic resection for AO lesions, focusing on efficacy and safety, including recurrence rate and need for surgery due to adverse events like delayed appendicitis.

METHODS

Study design

Retrospective, observational and multicenter study conducted at eight Spanish referral centers, including all consecutive AO lesions endoscopically resected between January

2016 and July 2023), with ≥12months follow-up. Patients under 18 years old or with prior appendectomy were excluded.

Study Endpoints

The objective of this study was to evaluate the efficacy and safety of the endoscopic resection of lesions involving the AO during a clinical follow-up of at least 12 months and/or at least one surveillance colonoscopy.

Primary endpoint:

- Recurrence rate, detected at any time during surveillance colonoscopy.

Secondary endpoints:

- Need for additional intervention.
- Technical success rate (complete visible resection, including any adjunctive treatment).
- Adverse events rates (intraprocedural, postprocedural within 30 days and late onset appendicitis).
- Outcome comparison by AO lesion depth (superficial versus deep) and technique (UEMR versus EMR).
- Factors linked to technical failure, piecemeal resection and recurrence.

Variables and definitions

Technical failure was defined as incomplete macroscopic resection and recurrence as the presence of histologically confirmed neoplastic lesions at resection site. Previous manipulation included biopsies or prior resection attempts. Adjunctive treatment included any additional endoscopic interventions for resection completeness [15]. Post-procedural bleeding was defined as bleeding occurring within 30 days requiring unplanned medical care. Post-procedural perforation was defined as a perforation occurring within 30 days after the procedure that required unplanned medical attention

[16].

Short-term outcomes were defined as any event occurring within 30 days after the procedure, including immediate complications and technical success, while long-term referred to events beyond 30 days, such as recurrence or late complications.

Lesions were classified by AO extension (Figure 1): superficial (visible margin) versus deep (margin not visible prior to resection). A further comparison was made between the two techniques most frequently employed in the cohort: UEMR and EMR.

Circumferential AO involvement was classified as <50%, 50–89%, or 90–100% according to each endoscopist's judgement. Cecal involvement was classified as present (cecal extension) or absent ("pure" AO lesion).

Lesion evaluation, endoscopic procedure and surveillance

Lesions were evaluated with white light imaging and image-enhanced endoscopy to exclude deep submucosal invasion. CT scan or imaging techniques were performed at the operator's discretion if the deep margin was unclear.

Procedures were performed by experienced endoscopists members of the Spanish Group of Endoscopic Resection (GSEED) with documented expertise in the management of intraprocedural adverse events and a minimum of 30 EMR [17]

Endoscopic resection techniques included EMR, UEMR (including cap suction pseudopolyp formation, CAP-UEMR), EFTR or ESD depending on the operator's preference.

Single-dose periprocedural antibiotic was given at operator discretion. Biopsies of the resection base were taken if completeness was uncertain. Surveillance colonoscopy was performed at 4-6 months for piecemeal resection and at 12 months for en-bloc resection. Residual or recurrent lesions were removed and scars were biopsied according to operator's preference.

Statistical analysis

Data were analyzed using SPSS Statistics software (Version 25.0, IBM).

Quantitative variables are presented as mean and standard deviation (SD) or median and interquartile range (IQR). Normality assessed by Kolmogorov-Smirnov test and variance 'homogeneity by Levene's test. Categorical variables are presented as counts and proportions. Technical success, en-bloc and piecemeal rates were calculated using Wilson's method to estimate the 95% confidence intervals (95%CI). Sample size for recurrence estimate based on 20% recurrence rate [18], 10% margin and 95%CI yielding 62 patients. Chi-squared, ANOVA, Student's t-test and Mann-Whitney U used as appropriate. All tests were two sided and significance set at P <0.05. Logistic regression was performed for variables statistically significant in univariate analysis.

RESULTS

A total of 97 AO lesions were included. Mean age was 68 years (SD 9.9), 43% were female. Median lesion size was 18 (IQR 10-29mm), 20% had prior manipulation. Sixty-two lesions (64%) involved ≥50% circumference. Baseline characteristics according to AO extension are detailed in Table 1.

Imaging

Pre-resection imaging was performed in 13 cases, revealing relevant findings in 5. One CT showed mural enlargement that resolved post-resection, another showed a hyperdense cecal image with no follow-up imaging, and one revealed an appendicular mass later diagnosed as pT2, treated surgically. Two ultrasound studies showed cecal enlargement but lacked follow-up.

Short term outcomes

Technical success rate was 93% (95% CI 88-98%), with 48% en-bloc (95% CI 38-58%) and 52% piecemeal (95% CI 41-62%) resections. Adjunctive endoscopic treatment was needed in 20 cases (21%): cold avulsion in 13, hot avulsion in 5 and cold avulsion with snare-tip soft coagulation in 2. UEMR was performed in 52 (54%) cases (42% of which were CAP-UEMR); EMR in 39 (40%). EFTR and ESD were performed in two cases each. Two combined approaches (EMR+EFTR, UEMR+EFTR) and two cold snare resections were also performed.

Histology after complete resection showed malignancy in 2: One pT1a lesion resected by piecemeal that finally underwent surgery due to the patient's preference (no residual tissue in the surgical specimen) and one low-risk pT1a (R0 resection) with no recurrence after 30 months.

Seven cases presented technical failure at first attempt. Four with deep AO involvement which were referred to surgery: one pT2, two high-grade dysplasia (pT3 on the surgical specimen), and one tubular adenoma. The other three underwent a second endoscopic attempt but ultimately required surgery (two serrated lesions with dysplasia and one tubular adenoma). These were excluded from follow-up (Figure 2).

Complications included 6 intraprocedural bleeding and one post-procedural bleeding 48h after resection, all managed successfully endoscopically.

A single perforation occurred during EMR of a 50mm (≥50% circumferential involvement), successfully managed by complete resection with EFTR and defect closure. Histology revealed high-grade dysplasia without recurrence. No post-procedural perforations or early post-resection appendicitis were detected.

Comparative outcomes by AO extension appear in Table 2.

UEMR-treated lesions were more likely ≥2cm, with deep AO extension and ≥50% circumferential involvement. Only size≥2cm remained significant in the multivariate analysis [OR 3.12 IC95%(1.1-8.8); p=0.027]. Efficacy and safety data are shown in Table 3.

Factors Associated with Technical Failure and Piecemeal Resection

Univariate analysis linked lesion size ≥2cm and deep AO extension with technical failure, but no significant associations were identified in multivariate analysis (Table 4). Piecemeal resection was independently associated with depth of AO extension, lesion size ≥2cm and prior manipulation (Table 5).

Long-term outcomes

Long-term outcomes were available for analysis in 84 cases (Figure 2). Clinical follow-up lasted ≥12 months (median duration:27months (IQR 16-43). Among these, 72 had

endoscopic follow-up including 17 with scar biopsies (24%).

Long-term follow-up with a surveillance colonoscopy ≥ 12 months after index endoscopic resection was available in 51 (71%) with a median follow-up of 23 months (IQR 16-34).

Recurrence

Thirteen recurrences (25%; 95% CI 13.1%-36.9%) were detected among 51 patients with long-term colonoscopy follow-up; 7 (54%) had deep AO extension. Median time to recurrence was 10 months (IQR 9-20). Twelve cases were re-treated endoscopically (Figure 2).

Two patients eventually required surgery due to the persistence of residual tissue detected at further follow-up colonoscopy. Both cases were discussed in a multidisciplinary team meeting. Surgical specimens showed low-grade adenomas.

Exploratory analysis found only piecemeal resection significantly associated with recurrence ($p<0.001$), as all occurred after piecemeal resection.

Need for surgery

Two patients required surgery due to delayed post-resection appendicitis. One had residual dysplasia detected in biopsies at index resection. Although surgery was recommended by a multidisciplinary team, the patient initially declined it and 11 months' post-resection developed appendicitis (surgical specimen revealed low-grade dysplasia). The second patient developed appendicitis at 56 months' post-resection (surgical specimen showed no dysplasia or malignancy). Twelve surgeries (12%) were performed in the entire cohort (Figure 2), none for acute complications.

Four cases (4%) of malignancy were detected: followed incomplete endoscopic resection and required surgery (pT2 and a pT3 with index histology showing high-grade dysplasia) and two were pT1a, previously described.

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DISCUSSION

This multicenter study provides valuable insights into the long-term efficacy, safety and recurrence of endoscopic resection for AO lesions. Overall, endoscopic management achieved a high technical success rate with low complications, supporting its role as a minimally invasive alternative to surgery in selected patients.

Most cases in this cohort were treated using EMR-based techniques, predominantly UEMR (54%). The overall technical success rate of 93% is consistent with previous series, like Tate et al. and Binmoeller et al., reporting success rates between 89-93% for AO lesions treated with EMR or UEMR [9,16]. As expected, technical success and en-bloc resection were significantly more frequent in lesions with superficial AO extension, highlighting the importance of lesion anatomy in procedural planning. Surprisingly, en-bloc resection rates were lower in the UEMR group, likely due to larger lesion sizes influencing technique choice, which may have acted as a potential cofounder.

Recurrence occurred in 25% of lesions with long-term endoscopic follow-up, a rate higher than that reported in earlier studies (1.6-15.6%) [11-13,19-20]. This difference is likely explained by the longer follow-up in the present cohort and the inclusion of complex lesions with deep AO extension and large circumferential involvement. Importantly, all recurrences occurred after piecemeal resection, reinforcing prior evidence that en-bloc resection is a key determinant of durable outcomes after EMR [18]. The wide 95%CI (13.1%–36.9%) around the recurrence estimate reflects the need for cautious interpretation.

Lesion size ≥2cm, deep AO extension, circumferential involvement ≥50% and prior manipulation were associated with piecemeal resection in univariate analyses. In

multivariate analysis, deep AO extension, lesion size≥2cm and previous manipulation remained independently associated with piecemeal resection, suggesting that these factors should be carefully considered during pre-procedural assessment. The findings are in line with previous reports identifying lesion size and appendiceal extension as predictors of incomplete resection [6-7,21-22].

Post-resection appendicitis remains a relevant concern when managing AO lesions, with rates varying from 0% to 50% according to the literature [13-14, 23-26]. While no cases of early post-resection appendicitis were observed, two patients developed delayed appendicitis at 11 and 56 months after resection. The underlying mechanism is unclear and may involve manipulation, swelling or clip-related obstruction [23-24]. In one, residual adenoma was detected in biopsies obtained at the resection site. This suggests that residual tissue after resection may contribute to late complications and that biopsies of AO defect scars might help detect early recurrence. However, given the small number of events, no conclusions can be drawn and further research is needed to determine the true utility and cost-effectiveness of this approach.

The safety profile in this study was favorable. All bleeding events and the single intraprocedural perforation were managed endoscopically. These findings are consistent with previously published series and support the feasibility of endoscopic resection of selected AO lesions in experienced centers [6, 10-12, 19].

This study has several strengths, including its multicenter design, involvement of experienced endoscopists, and long-term follow-up with clinical data available for 87% of patients and endoscopic surveillance extending beyond 12 months in a substantial proportion of cases. However, several limitations must be acknowledged. The retrospective design and limited sample size, particularly for deep AO lesions, restrict the power of subgroup analyses, including the inability to run multivariate analysis on recurrence. In addition, the absence of a surgical control group -given the descriptive nature of the study- precludes direct comparison between endoscopic and surgical management strategies.

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In conclusion, endoscopic resection is effective and safe for superficial AO lesions, particularly for lesions with superficial AO involvement. and a potential alternative in selected deep cases of deep extension into the AO. However, recurrence and appendicitis risks highlight the need for long-term follow-up. Pre-resection imaging, AO defect biopsy and tailored strategies for deep AO lesions warrant further research. Larger prospective studies, including comparisons with surgical approaches, are needed to better define the role of endoscopic resection in lesions with deep AO extension.

KEY POINTS BOX

- Endoscopic resection of appendiceal lesions shows favorable efficacy and safety outcomes for non-invasive lesions.
- Endoscopic follow-up is crucial, especially after piecemeal resection, due to a higher risk of recurrence.
- Further research including comparative studies and longer cohorts are needed to better determine the most appropriate management of challenging cases involving deep AO extension.

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TABLES

Table 1. Baseline patient and lesion characteristics according to AO extension.

INTRA-APPENDICULAR EXTENSION	**Superficial (n=65)**	**Deep (n=32)**	**p-value**
Age *years,mean (SD)*	66.4 (8.9)	71.5 (11.2)	0.018
Female, n(%)	31 (48%)	11 (35%)	0.213
Antithrombotic			0.420
Anticoagulants	9 (13%)	6 (19%)	
Antiplatelet	12 (18%)	7 (22%)	
Lesion size, median *mm(median[IQR])*	15 (7-20)	30 (16-49)	<0.001
Size category			0.001
<20mm	41 (63%)	9 (28%)	
≥20mm	24 (37%)	23 (72%)	
Circumferential involvement			<0.001
<50%	31(48%)	4(13%)	
50-89%	28(43%)	17(53%)	
90-100%	6(9%)	11(34%)	
Paris classification			0.822
0-Ip	3(5%)	0(0%)	
0-Is	19(29%)	11(34%)	
0-IIa	35(53%)	14(45%)	
0-IIb	1(2%)	0(0%)	
0-IIa + Is	4(6%)	7(23%)	
0-IIa + IIc	3(5%)	0(0%)	
Previous manipulation			0.788
Previous biopsies	10(15%)	7(22%)	
Previous incomplete resection	2(3%)	0(0%)	

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Histology			0.086
Serrated without dysplasia	22(34%)	4(13%)	
Serrated with dysplasia	5(8%)	4(13%)	
Low-grade dysplasia adenoma	28(43%)	13(40%)	
High-grade dysplasia adenoma	9(14%)	9(28%)	
pT1	1(1%)	1(3%)	
pT2	0(0%)	1(3%)	

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Table 2. Comparison of short-term outcomes based on AO extension

INTRA-APPENDICULAR EXTENSION	**Superficial (n=65)**	**Deep (n=32)**	**p-value**
Technical success, n(%)	62(97%)	27(84%)	0.037
En bloc resection, n(%)	40(62%)	7(22%)	<0.001
Complications	4(6%)	4(12%)	0.672
Intraprocedural bleeding	4	2	
Post-procedural bleeding	0	1	
Intraprocedural Perforation	0	1	
Delayed Perforation	0	0	
Early post-resection appendicitis	0	0	

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Table 3. Comparison of short-term outcomes based on technical procedure (n=91)

Technical procedure	**EMR (n=39)**	**UEMR (n=52)**	**p-value**
Technical success, n(%)	35(90%)	49(94%)	0.45
En bloc resection, n(%)	24(62%)	17(33%)	0.004
Complications	2(5%)	4(8%)	0.99
Intraprocedural bleeding	2	3	
Post-procedural bleeding	0	1	
Intraprocedural Perforation	0	0	
Delayed Perforation	0	0	
Early post-resection appendicitis	0	0	

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Table 4. Factors associated with technical failure of appendiceal lesions.

Factors	**Category**	**Technical success**	**Technical failure**	**Univariate analysis (p-value)**	**Multivariate analysis OR (IC 95%)**
Age	-	67.6(9.9)	74.1(8.9)	**0.096**	0.96 (0.88-1.04); p=0.33
Cecal involvement	Present	46(92%)	4(8%)	1.00	
	Absent	44(94%)	3(6%)		
Intra-appendicular extension	Superficial	63(97%)	2(3%)	**0.037**	3.25(0.53-19.78); p=0.20
	Deep	27(84%)	5(16%)		
Lesion Size	<2cm	49(98%)	1(2%)	**0.054**	4.33(0.46-40.86); p=0.20
	≥2cm	41(87%)	6(13%)		
Circumferential involvement	<50%	34(97%)	1(3%)	0.416	
	≥50%	56(90%)	6(10%)		
Previous manipulation	No	73(94%)	5(6%)	0.622	
	Yes	17(89%)	2(11%)		

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Factors	**Category**	**En-bloc resection**	**Piecemeal resection**	**Univariate analysis (p-value)**	**Multivariate analysis OR (IC 95%)**
Age	-	66.5(9.5)	69.6(10.3)	0.123	
Cecal involvement	Present	22(44%)	28(56%)	0.365	
	Absent	25(53%)	22(47%)		
Intra-appendicular extension	Superficial	40(62%)	25(38%)	**<0.001**	**3.64(1.22-10.85); p=0.02**
	Deep	7(22%)	25(78%)		
Lesion size	<2cm	34(68%)	16(32%)	**<0.001**	**3.20(1.22-8.50); p=0.01**
	≥2cm	13(28%)	34(72%)		
Circumferential involvement	<50%	23(66%)	12(34%)	**0.011**	1.63(0.58-4.55); p=0.35
	≥50%	24(39%)	38(61%)		
Previous manipulation	No	43(55%)	35(45%)	**0.011**	**3.75(1.04-13.49); p=0.04**

Table 5. Factors associated with piecemeal resection of appendiceal lesions.

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FIGURE LEGENDS

Figure 1. Representative cases of AO lesions.

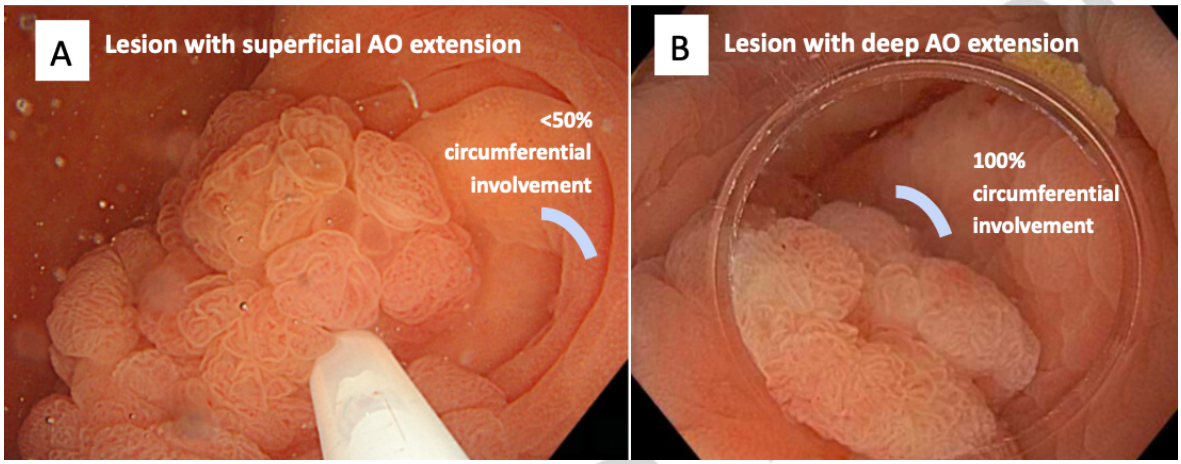

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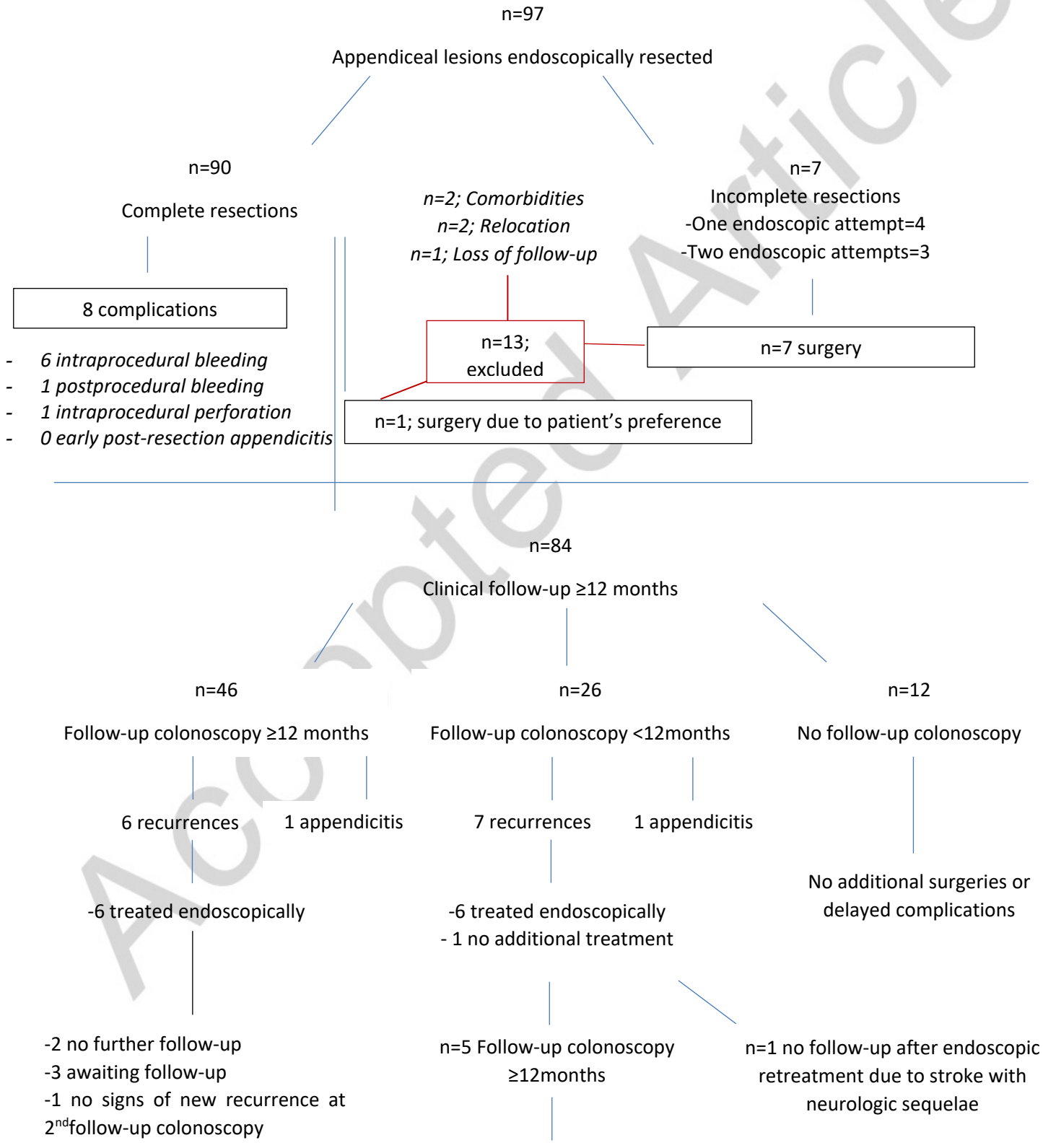
Figure 2. Flowchart of lesions involving AO included in the study.



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3 no signs of recurrence
2 persistent residual tissue

n=4 additional surgeries
-2 delayed appendicitis
-2 persistent residual tissue