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ORIGINAL ARTICLE

Predictors for interval appendectomy in non-operatively treated complicated appendicitis

J. de Jonge[1] · M. D. M. Bolmers[1] · G. D. Musters[2] · C. C. van Rossem[3] · W. A. Bemelman[2] · A. A. W. van Geloven[1]

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Abstract

Purpose To determine the incidence rate and identify predictive factors for interval appendectomy after non-operatively treated complicated appendicitis.

Methods Single-center retrospective cohort study conducted between January 2008 and June 2017. Adult patients with acute appendicitis were identified. Patients with complicated appendicitis initially treated non-operatively were included. Outcomes included abscess rate on imaging, results of additional imaging during follow-up, incidence rate of and surgical indications for interval appendectomy, and outcomes of histological reports.

Results Of all adult patients with acute appendicitis ($n = 1839$), 9% (170/1839) was initially treated non-operatively. Median age of these patients was 55 years (IQR 42–65) and 48.8% (83/170) were men. In 36.4% (62/170) of the patients, an appendicular abscess was diagnosed. 62.4% (106/170) did not require subsequent surgery (no interval appendectomy group) and in 37.6% (64/170), an interval appendectomy was performed (interval appendectomy group). Median follow-up was 80 weeks (17–192) and 113 weeks (34–246), respectively. Most frequent reason to perform subsequent surgery was recurrent appendicitis (45% (29/64)). Increasing age was significantly associated with a lower risk of undergoing interval appendectomy (OR 0.7; CI 0.6–0.89); $p = 0.002$). In the interval appendectomy group, appendicular neoplasm was found in 11% (7/64) of the patients, in contrast to 1.5% (25/1669) of the patients that had acute surgery ($p < 0.001$).

Conclusions One out of three patients non-operatively treated for complicated appendicitis required an interval appendectomy. The incidence of appendicular neoplasms was high in these patients compared with those that had acute surgery. Therefore, additional radiological imaging following non-operatively treated complicated appendicitis is recommended.

Keywords Appendicitis · Inflammatory mass · Non-operative treatment · Interval appendectomy · Appendicular neoplasm

Introduction

The gold standard for acute appendicitis is acute appendectomy. In two to 7 % of the patients presenting with acute appendicitis, an appendicular inflammatory mass with or without abscess is diagnosed [1–3]. Because acute appendectomy can potentially be risky and harmful in the presence of an inflammatory mass or abscess, the primary treatment for

J. de Jonge and M. D. M. Bolmers contributed equally to this work.

✉ J. de Jonge
jdejonge@tergooi.nl

M. D. M. Bolmers
MDMBolmers@gmail.com

G. D. Musters
G.D.Musters@amc.nl

C. C. van Rossem
RossemC@maasstadziekenhuis.nl

W. A. Bemelman
W.A.Bemelman@amc.nl

A. A. W. van Geloven
AvanGeloven@tergooi.nl

[1] Department of Surgery, Tergooi Hospital Hilversum, P.O. Box 10016, 1201DA Hilversum, The Netherlands

[2] Department of Surgery, Amsterdam University Medical Center, University of Amsterdam, 22660, 1105AZ Amsterdam, The Netherlands

[3] Department of Surgery, Maasstad Hospital Rotterdam, 9100, 3007AC Rotterdam, The Netherlands

this entity is most often non-operatively. This non-operative treatment consists of intravenous antibiotics with or without drainage of an abscess which is successful in 93% of the patients [2]. According to the Dutch guideline for acute appendicitis, a standard interval appendectomy is not indicated in these patients [4]. Despite the high initial success rate, there is a reported risk of recurrent appendicitis from 5 to 27% [2, 3, 5, 6], which is the major reason to perform subsequent surgery [7, 8]. Recent studies suggest an elevated incidence of appendicular neoplasms of up to 12% in patients that had an interval appendectomy [9–13] compared with 1 % in acute appendectomies [14–16]. The Dutch guideline recommends to perform a colonoscopy in all patients over 50 years of age who were treated non-operatively. Cross-sectional imaging is often performed and seems warranted when imaging at first presentation at the emergency department revealed a suspected pathological appendix, particularly in patients who have persistent or recurrent abdominal pain during follow-up, regardless of their age. Little is known with respect to the results of additional imaging and the predictive factors for subsequent surgery in these patients. This study aimed to determine the incidence rate and identify predictive factors for interval appendectomy after non-operatively treated complicated appendicitis.

Methods

All adult (> 18 years of age) patients treated in one general community teaching hospital for acute appendicitis, between January 2008 and June 2017, were retrospectively identified. Patients were included when initially a non-operative approach was started for complicated appendicitis.

The choice for non-operative treatment was made by the attending emergency surgeon and was based on clinical assessment and laboratory results, combined with results of imaging. Complicated appendicitis was defined as an appendicular inflammatory mass (inflammatory phlegmon ± abscess) on radiological imaging.

This approach consisted of antibiotics, with or without percutaneous abscess drainage or solely clinical observation. Patients were clinically observed when symptoms were mild and existed for a longer period. Antibiotics that were used were in accordance with local protocol and consisted of Cefuroxime (750 mg three times daily) and Metronidazole (500 mg three times daily), administered intravenously for at least 3 days. Non-operative treatment was considered to be successful if the patients could be discharged from the hospital after cessation of antibiotics and/or removal of abdominal drain if applicable.

Patients were excluded when appendicitis occurred secondary to a colon malignancy or inflammatory bowel disease, when a prior history of an appendectomy was present or when an appendectomy was performed within first hospital admission. Dutch regulations did not require review by the medical ethical board or written informed consent.

Additional imaging during follow-up

All patients were seen at the outpatient clinic after hospital discharge. During follow-up, additional imaging (US, CT-scan, or colonoscopy) was performed when an inflammatory mass, abscess, or abnormal appendix (an appendix suspicious for a neoplasm) was seen on initial imaging at first presentation, or in patients with persistent or recurrent abdominal pain. Recurrent appendicitis was defined as appendicitis recurring after a period without any symptoms.

Interval appendectomy and surgical indications

An interval appendectomy was defined as an appendectomy performed subsequently during follow-up. In patients with an abnormal appendix (thickened and/or suspicious for a neoplasm at additional imaging), persistent abdominal pain or recurrent appendicitis an appendectomy was performed. The appendectomies were performed either laparoscopically or via a gridiron incision. All postoperative surgical complications within 30 days were assessed using Clavien-Dindo [17] grading system.

Histological evaluation and consequences

All appendices were sent for histological evaluation. Appendicular neoplasms were classified and staged according to the World Health Organization histological classification of tumors of the digestive system [18]. When additional resection was required based on the outcome of histological evaluation, a right-sided colectomy or ileocecal resection was performed. Adjuvant chemotherapy was administered for stage III malignancy according to oncologic guidelines.

Data extraction and outcome

Patients were separated into two groups: merely non-operatively treated without subsequent appendectomy (no interval appendectomy (NIA) group) and initial non-operatively treated followed by an interval appendectomy (IA group). Records were searched for patient demographics, radiological imaging details, and treatment characteristics. Operative reports were searched for surgical indication, approach (open, laparoscopic, or conversion), and complications. Histological reports were used to obtain histological evaluation of all appendices. Length of follow-up was from the first visit at emergency department to the last visit in the hospital. Outcomes included abscess rate on imaging, results of additional imaging during follow-up, the incidence rate of and surgical

indications for interval appendectomy, and the outcomes of histological reports. This study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Statistical analysis

Normally distributed data was presented as mean with standard deviation (SD) and non-normally distributed data as median with interquartile range (IQR). Continuous variables were analyzed with the Mann-Whitney-Wilcoxon test and categorical data were analyzed using the chi-square test or Fisher's exact test. For uni- and multivariable analysis of risk factors for interval appendectomy, binary logistic regression was used. Outcomes were presented with odds ratio, confidence intervals, and p values. $p < 0.05$ was considered statistically significant. Statistical analysis was performed using IBM SPSS statistics, version 22.0 (IBM Corp., Armonk, NY, United States).

Results

Between January 2008 and June 2017, 1839 adult patients were diagnosed with acute appendicitis of whom 90.8% (1669/1839) had an acute appendectomy. The remaining 9.2% (170/1839) were non-operatively treated. The median age of these patients was 55 years (IQR 42–65) and 48.8% (83/170) were men. Initial diagnosis on imaging was an appendicular inflammatory mass with abscess in 36.5% (62/170) and without abscess in 63.5% (107/170) of the patients. One patient was treated in another hospital and the initial diagnosis was unknown. Initial non-operative treatment consisted of antibiotics alone in 54.7% (93/170), antibiotics with percutaneous drainage of an abscess in 17.6% (30/170), and percutaneous drainage alone in 1.2% (2/170) of the patients. 19.4% (33/170) of the patients were clinically observed without antibiotics and in 7.1% (12/170) the initial treatment was unknown. All demographics are shown in Table 1, and Fig. 1 displays the flow diagram.

No interval appendectomy group versus interval appendectomy group

The median length of follow-up of all patients was 89 weeks (IQR 25–224). During follow-up, no subsequent appendectomy was done in 62.4% (106/170) and an interval appendectomy was performed in 37.6% (64/170) of the patients, the NIA group and the IA group, respectively (Table 1). Age, initial diagnosis on imaging, type of non-operative treatment, and recurrence rate differed significantly between these two groups. Almost one-fifth of the NIA patients (18.9%; 20/106) had recurrent appendicitis with mild symptoms or symptoms persisting longer than 5 days and/or complicated appendicitis was seen on radiological imaging. These patients underwent a second course of antibiotics. In 15 of these patients, additional imaging following the second course of treatment showed no persisting abnormalities. In the remaining five patients, the attending surgeon decided to not perform an interval appendectomy based on clinical judgment. In total, 2.9% (5/170) of the patients died, all in the NIA group, compared with none in the IA group ($p = 0.099$). None of these patients died due to a colon malignancy or causes related to non-operative treatment. Furthermore, no colon malignancy was diagnosed among the remaining patients in both groups.

Additional imaging and outcomes during follow-up

Table 2 shows all indications to perform imaging and/or a colonoscopy at the outpatient clinic following non-operatively treated appendicitis, in the two different treatment groups (NIA group and IA group). Additional radiological imaging was performed in 72.4% (123/170). In 13% (16/123), there was an appendix suspected for a neoplasm, in four patients on ultrasound, in ten patients on CT-scan, and in the last two patients on both imaging modalities. In 15 of these patients, an interval appendectomy was performed, one patient refused additional surgery. 38.8% (66/170) of the patients received a colonoscopy during follow-up. Overall, 26% (28/170) did not have any additional imaging (US, CT-scan, or colonoscopy) during follow-up.

Surgical indications and characteristics

Interval appendectomies were performed after a median follow-up of 19 weeks (IQR 9–34). Besides the 15 patients with an appendix suspected for a neoplasm on additional imaging, one other patient had a slightly thickened appendix and therefore an interval appendectomy was performed. Five of these patients had persistent abdominal pain after initial non-operative treatment. Other indications for surgery were abdominal pain in 28% (18/64) and recurrent appendicitis in 45% (29/64) of the patients (Table 2). In 80% (51/64) of the operated patients, a laparoscopic approach was used, a median operating duration of 44 min (IQR 33–60). Intraoperative complications occurred in 3% (2/64) of the patients. Complications within 30 days appeared in 6% (4/64), classified as grade IIIa (3/64) and grade IIIb (1/64) complications.

Predictive factors for interval appendectomy

In univariable analysis, increasing age was significantly associated with a lower risk of undergoing an interval appendectomy (OR 0.73; CI 0.6–0.89); $p = 0.002$). Recurrent appendicitis after non-operative treatment was significantly associated with undergoing subsequent surgery, as expected (OR 4.87;

Table 1 Patient and initial non-operative treatment characteristics ($n = 170$)

		Total ($n = 170$)	NIA group ($n = 106$)	IA group ($n = 64$)	p value
Sex, male (n, %)		83 (48.8)	52 (49.1)	31 (48.4)	0.99
Age, yrs. (med, IQR)		55 (42;65)	58 (47;69)	48 (34;61)	0.001
Comorbidity (n, %)	Abd. surgery	29 (17.1%)	19 (17.9)	10 (15.6)	0.15
	Diabetes	9 (5.3)	6 (5.7)	3 (4.7)	
	Respiratory	11 (6.5)	10 (9.4)	1 (1.6)	
	Cardiovascular	51 (25.5)	32 (30.2)	19 (29.7)	
ASA-classification (n, %)	I	53 (31.2)	29 (27.4)	24 (37.5)	0.59
	II	46 (27.1)	24 (22.6)	22 (34.4)	
	III	15 (8.8)	9 (8.5)	6 (9.4)	
	IV	2 (1.2)	2 (1.9)	0 (0)	
	Unknown	54 (31.8)	42 (39.6)	12 (18.8)	
Diagnosis on imaging (n, %)	Abscess	62 (36.5)	39 (36.8)	23 (35.9)	0.91
	No abscess	107 (62.9)	66 (62.3)	41 (64.1)	
	Unknown	1 (0.6)	1 (0.9)	0 (0)	
(Initial) non-operative treatment (n, %)	AB	93 (54.7)	65 (61.3)	28 (43.8)	< 0.001
	Drainage	2 (1.2)	2 (1.9)	0 (0)	
	AB and drainage	30 (17.6)	23 (21.7)	7 (10.9)	
	Observation only	33 (19.4)	13 (12.3)	20 (31.2)	
	Unknown	12 (7.1)	3 (2.8)	9 (14.1)	
Length of hospital stay, dys (med, IQR)		5 (4;7)	5 (4;8)	4 (3;6)	0.07
Persistent abdominal pain (n, %)		52 (30.6)	0 (0)	52 (81.3)	< 0.001
Recurrences (n, %)	1	45 (26.5)	15 (14.2)	30 (46.9)	< 0.001
	2	6 (3.5)	3 (2.8)	3 (4.7)	
	3	3 (1.8)	2 (1.9)	1 (1.6)	
Follow-up, wks (med, IQR)		89 (25;224)	79.5 (17;192)	113 (34;246)	0.09

n, number of patients in group; *yrs*, years; *IQR*, inter quartile range; *abd*, abdominal; *ASA*, American Society of Anaesthesiology; *SA*, simple appendicitis; *IM*, appendiceal inflammatory mass; *AB*, antibiotics; *wks*, weeks; *NIA*, no interval appendectomy; *IA*, interval appendectomy

CI 2.44–9.73; $p < 0.001$). Appendicular abscess was no indicator for future interval appendectomy (OR 0.96: CI 0.51–1.84; $p = 0.91$). In multivariable logistic regression analysis, increasing age remained a favorable factor (Table 3).

Histological evaluation following interval appendectomy

In 11% (7/64) of the patients that underwent an interval appendectomy, histological evaluation revealed an appendicular neoplasm, in contrast to 1.5% (25/1669) of the patients who underwent acute surgery ($p < 0.001$). Four patients had more than one neoplasm in the appendix; therefore, 11 neoplasms are mentioned in Table 4. In four of these seven patients, CT-scan showed an appendix suspected for malignancy, which was the reason to perform an interval appendectomy. In the remaining three patients, the indication for additional surgery was persistent abdominal pain. No suspicion of neoplasm was expressed in any colonoscopy. In 80% (51/64) of the patients, the diameter of the appendix was evaluated by the pathologist. The median diameter was 12 mm (IQR 9;15). Histological reports of the total IA group are shown in Table 4.

Appendicular neoplasms and additional surgery

Table 4 shows all tumor and surgical characteristics of the patients with an appendicular neoplasm in the IA group ($N = 7$). Initial diagnosis prior to non-operative treatment was an inflammatory mass with abscess in five out of seven patients. However, appendicular abscess was no indicator of appendicular neoplasm. In total, six out of seven patients had a malignant tumor. In two patients, the appendectomy was irradical and therefore a right-sided colectomy was performed. According to tumor size and based on the Dutch guideline, two more patients required additional resection. Pathology in one of the four colectomy specimens showed positive lymph nodes and this patient was therefore treated with adjuvant chemotherapy.

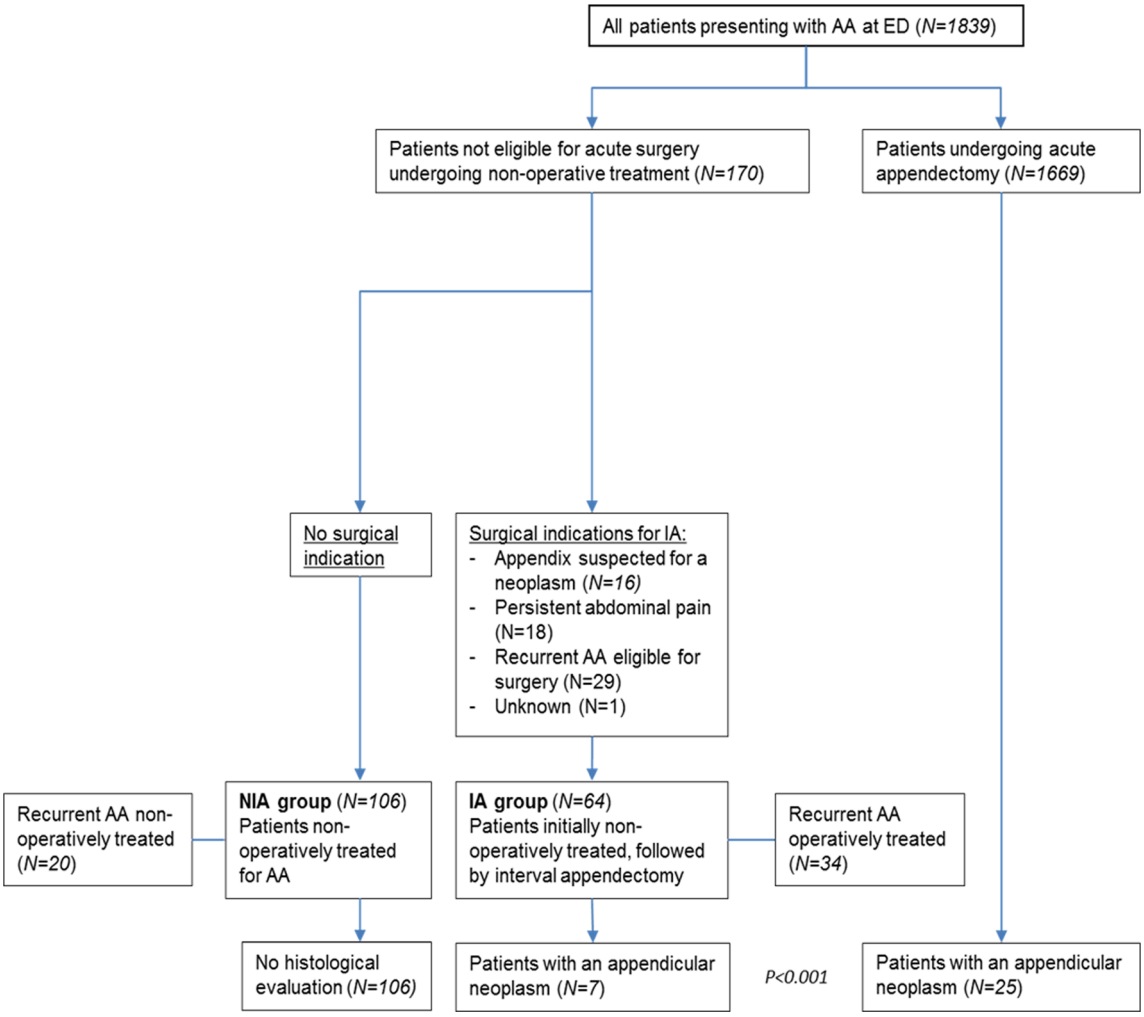

Fig. 1 Surgical indications and incidence of appendicular neoplasms

Discussion

In this single-center retrospective cohort study, patients with non-operatively treated complicated appendicitis were analyzed and potential predictive factors for an interval appendectomy were identified. The rate of interval appendectomies during follow-up proved to be high (37.6%) and was indicated predominantly due to persistent complaints.

Increasing age showed to be protective for interval appendectomy. An explanation for this finding could be that surgeons are more reluctant to perform an interval appendectomy in this patient category with higher perioperative risk. In this cohort, the risk of recurrent appendicitis following non-operatively treated complicated appendicitis was 31.8%. These recurrences were treated with a second course of antibiotics in 72.2% and with an appendectomy in 27.8%. The second course of antibiotics was successful in 51.3%. In the remaining patients, eventually an interval appendectomy was performed. These findings are in line with recent literature [19] confirming the substantial risk of additional surgery after non-operatively treated complicated appendicitis. No patients with suspicion of uncomplicated appendicitis were included in this study, as they were all acutely operated. In comparison to the current literature, a relatively large portion of patients with appendicitis in our study was initially treated non-operatively [1–3, 5, 8].

The incidence of appendicular neoplasms was high in the patients that had interval appendectomy compared with acutely operated patients (11% versus 1.5%). The main indication for interval appendectomy was persistent pain or recurrent appendicitis. In only four of the seven patients with an appendicular neoplasm, an appendix suspected for a neoplasm was seen on pre-operative imaging, the remaining three patients underwent subsequent surgery for persistent abdominal pain. This shows the value of both imaging and clinical evaluation following non-operatively treated appendicitis. None of the patients with a malignancy had an abnormal colonoscopy. Current guidelines recommend to perform a colonoscopy in elderly with a non-operatively treated inflammatory mass [4], to rule out an underlying right-sided colon malignancy [20].

Table 2 Diagnostic imaging modalities and indications following non-operatively treated complicated appendicitis

		NIA group (n = 106)	IA group (n = 64)
Diagnostic modality (n, %)	US	27 (25.5)	22 (34.4)
	CT-scan	29 (27.4)	19 (29.7)
	US + CT-scan	12 (11.3)	14 (21.9)
	Colonoscopy (total, ± radiology)	39 (36.8)	27 (42.2)
	Colonoscopy (− radiology)	10 (9.4)	–
Indication to perform colonoscopy (n, %)	Age > 50 yrs	33 (31.1)	18 (28.1)
	Discrepancies on imaging	2 (1.9)	4 (6.3)
	Persistent abdominal pain/recurrence(s)	4 (3.8)	5 (7.8)
	No colonoscopy	67 (63.2)	37 (57.8)
Indication to perform imaging (n, %)	Age > 50 yrs	–	1 (1.6)
	Abnormal appendix on initial imaging at ED	3 (2.8)	3 (4.7)
	Persistent abdominal pain/recurrence(s)	27 (25.5)	38 (59.3)
	Abnormal appendix and persistent pain	2 (1.9)	8 (12.5)
	Follow-up of inflammatory mass	36 (34.0)	5 (7.8)
	No imaging	38 (35.8)	9 (14.1)
No colonoscopy or imaging (n, %)		26 (24.5)	2 (3.1)

n, number of patients in group; *NIA*, no interval appendectomy; *IA*, interval appendectomy; *US*, ultrasound; *CT*, computed tomography; ±, with or without radiological imaging, *yrs*, years; *ED*, emergency department

Neuro endocrine tumors, which are most frequent, are often located at the tip or distal third of the appendix [12] and therefore not visible during colonoscopy. For this reason, additional imaging during follow-up is recommended in all non-operatively treated patients.

During follow-up of patients without subsequent interval appendectomy, and thereby without histological evaluation of their appendix, no colon malignancies were found among the patients that had additional imaging. Twenty-five percent of the patients were only clinically evaluated by their surgeon during follow-up. Although a suspicion for appendicular malignancy could be present during clinical judgment, right-sided colon malignancies are notorious for being asymptomatic [10, 15, 21], and neuro endocrine tumors often present without symptoms at all [22].

The increased risk of a malignancy in initially non-operatively treated complicated appendicitis is difficult to explain. Complicated appendicitis is a different entity than simple appendicitis but it has not been recognized as a risk factor for malignancy at its own. A large number of patients were initially diagnosed with appendicular abscess (36.5%) and only half of them were percutaneously drained. This is most likely because of the smaller size of the abscesses and position between small intestines. We showed that complicated appendicitis with an abscess is not a predictive or protective factor for a neoplasm or interval appendectomy. However, the delayed clinical presentation of a perforated appendix may be a consequence of a neoplasm obstructing the appendicular lumen. This could result in a more prolonged subclinical dilatation of the appendix [15, 16, 23, 24], than in the case of an acute obstruction. In our study, the diameter of the appendix was 16 mm in patients with appendicular neoplasm, compared with an appendix of 12 mm in the total IA group.

There are some limitations to this study, inherent to its retrospective design. A limited number of patients and variables were included in this study so further prospective

Table 3 Uni- and multivariable analysis of risk factors for an interval appendectomy after non-operatively treated complicated appendicitis

	Univariable analysis			Multivariable analysis		
	OR	95% CI	p value	OR	95% CI	p value
Age (per year)	0.73	0.6–0.89	0.002	0.7	0.56–0.87	0.001
Sex, male (vs female)	0.98	0.52–1.82	0.94	–	–	–
Appendicular abscess (vs no appendicular abscess)	0.96	0.51–1.84	0.91	–	–	–
Recurrence (vs no recurrence)	4.87	2.44–9.73	< 0.001	5.4	2.62–11.27	< 0.001

Table 4 Histological evaluation and appendicular neoplasms following interval appendectomy ($N = 64$)

Histological evaluation (*n*, %)	Normal appendix	3 (5)
	Acute appendicitis	13 (20)
	Chronic appendicitis	36 (56)
	Mucocele appendix	3 (5)
	Neoplasm	7 (11)
	Unknown	2 (3)
Number of appendicular neoplasms found in 7 patients (*n*)		11
Patients with > 1 appendicular neoplasm (*n*)		3
Type of appendicular neoplasm (*n*)	Serrated polyp	1
	LGMN	2
	NET grade 1	2
	Goblet cell carcinoid	2
	Adenocarcinoma	3
	Signet-ring cell carcinoma	1
pTNM-stage (*n*)	Stage 1	2
	Stage 2	3
	Stage 3	2
Additional procedure (*n*)	Right-sided colectomy	3
	Ileocecal resection	1
	None	3
Resected colon (*n*)	Tumor free	3
	Containing tumor cells	1

n, number of patients in group; *LGMN*, low grade mucinous neoplasm; *NET*, neuroendocrine tumor; *pTNM-stage*, pathological tumor staging according to WHO classification [18]. Stage 1 = T1,N0,M0. Stage 2 = T2 or T3. Stage 3 = T4, N0 or N1

research is needed to evaluate possible predictors for interval appendectomy and appendicular neoplasms in non-operatively treated patients. Furthermore, there was no hospital protocol during the study period for the IA following non-operative treatment. This individual decision of treating surgeon potentially introduced selection bias. Lastly, the duration of follow-up varied widely among all patients.

We identified a high rate of additional surgery in patients non-operatively treated for complicated appendicitis. Significantly more appendicular neoplasms were found in patients treated with an interval appendectomy after complicated appendicitis compared with immediately operated patients. We suggest that additional imaging is warranted in all patients with non-operatively treated complicated appendicitis. Colonoscopy should be used as a supplement to additional imaging in patients older than 50 years of age.

We recommend an interval appendectomy should be considered in patients with persistent abdominal pain and/or an appendix suspicious for malignancy on additional imaging during follow-up.

In conclusion, one out of three patients that had conservative management of their complicated appendicitis required interval appendectomy within 3–4 months mainly due to recurrent appendicitis. Additional imaging in these patients is recommended because of a high incidence of neoplasm.

Author contributions Drs de Jonge and Bolmers had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: all authors.
Acquisition, analysis, or interpretation of data: all authors.
Drafting of the manuscript: all authors.
Critical revision of the manuscript for important intellectual content: all authors.
Statistical analysis: de Jonge, Bolmers.
Administrative, technical, or material support: -
Study supervision: van Geloven, Bemelman.

Compliance with ethical standards

Dutch regulations did not require review by the medical ethical board or written informed consent.

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval The medical ethics committee approved the original study and no informed consent was necessary because of the observational design. Dutch regulations did not require review by the medical ethical board or written informed consent.

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