Risk of appendiceal neoplasm after interval appendectomy for complicated appendicitis: A systematic review and meta-analysis

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ABSTRACT

Background: Non-operative management is often the treatment of choice in cases of complicated appendicitis and routine interval appendectomy is not usually recommended. Actually, recent studies show an alarming number of appendiceal neoplasms following interval appendectomy. The aim of this study is to evaluate the prevalence of appendiceal neoplasms and their histological types after interval appendectomy for complicated appendicitis in adults.

Methods: A comprehensive literature search of the PubMed, Scopus and Web of Science databases was conducted according to the PRISMA statement. Studies reporting appendiceal neoplasm rates after interval appendectomy and histopathological characteristics were included. The most recent World Health Organization (WHO) classification of malignant tumours was considered. A pooled prevalence analysis for both prevalence and pathology was performed.

Results: A total of eight studies was included: seven retrospective series and one randomized controlled trial. The pooled prevalence of neoplasms after interval appendectomy was 11% (95% CI 7–15; $I^2 = 37.5\%$, $p = 0.13$). Appendiceal mucinous neoplasms occurred in 43% (95% CI 19–68), adenocarcinoma in 29% (95% CI 6–51), appendiceal neuroendocrine neoplasm in 21% (95% CI 6–36), globet cell carcinoma in 13% (95% CI -2-28), adenoma or serrated lesions in 20% (95% CI -0-41) of cases.

Conclusion: The risk of appendiceal neoplasm in patients treated with interval appendectomy for complicated appendicitis is 11%; mucinous neoplasm is the most common histopathological type. Further studies should investigate this association in order to clarify the biological pathway and clinical implications.

Introduction

Appendicitis is one of the most common causes of acute abdomen in adults[1] with an incidence of about 90–100 cases/100,000 inhabitants/year in developed countries[2]. Both mean age at diagnosis and incidence rate seem to increase over time[3,4], although a dissimilar epidemiologic trend was reported between perforated and non-perforated appendicitis suggesting a different pathophysiology of these diseases[5].

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Acute appendicitis can be defined as complicated when gangrenous or perforated appendix, with or without abscess formation, occurs [2,6]. Clinically, the result of a walled-off appendiceal perforation is an appendiceal mass represented by an inflammatory tumour, consisting of the inflamed appendix, its adjacent viscera and the greater omentum (phlegmon) or abscess[7]. There is therefore a considerable variability in defining "complicated appendicitis". The occurrence of periappendicular abscess may or not coexist with a perforated gangrenous appendicitis, and a clinically palpable mass may represent an advanced stage of the inflammatory process.

For cases of complicated appendicitis many surgeons successfully adopt a non-operative management (antibiotics with or without percutaneous abscess drainage) because the choice of an immediate surgical treatment often implies higher morbidity and overall complication rate as well as the need for a more extensive intestinal resection[8,9]. Furthermore, the need for interval appendectomy (IA), at distance from the acute inflammatory process, has been questioned by some authors who maintain that the performance of routine IA provides no benefit in terms of preventing recurrence[10-16]. However, an advantage of IA is that it might show a hidden neoplasm presenting with a complicated appendicitis case and it also provides an accurate histopathological diagnosis. A missed cancer diagnosis was detected in only 1.2% of appendiceal abscess or phlegmons after conservative treatment[8]. It is important to consider that many of the studies leading to this value are retrospective case series presenting high heterogeneity, with some of them having just a small sample size and including pediatric patients. Indeed, recent evidence[17,18] reported a rate of appendiceal tumors after interval appendectomy, especially in patients older than 40 years of age, not to be overlooked. This suggested to exclude malignancy by endoscopic or radiologic screening if IA was not performed in elderly patients with appendiceal mass[19-21] but it could also question whether to consider IA suitable for this kind of patients.

The aim of this systematic review is to evaluate the prevalence of appendiceal neoplasms and their hystological types in adult patients undergoing IA for complicated appendicitis by performing a meta-analysis of the reported data from original studies.

Materials and methods

Search strategy

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [22].

A systematic search of the literature was conducted on PubMed, Scopus and Web of Science databases to identify articles published from inception until April 2020, with no language restriction. A combination of the following key words: 'interval', 'delayed', 'appendectomy', 'appendicectomy', 'complicated appendicitis', 'perforated appendicitis', 'abscess', 'phlegmon', 'appendiceal cancer' were used separated by the Boolean operators. References of selected articles and relevant reviews were screened for potentially relevant articles. The full-search strategy is shown in the supplementary material (Supplemental Content S1).

Study selection

Two reviewers (RP and MDL) independently screened all titles and abstracts identified by the search. Subsequently, they also evaluated all full texts of the potentially relevant papers in order to assess eligibility according to predefined criteria. Disagreements between reviewers were resolved by consensus. Studies that investigated the outcomes after IA in terms of incidence rate of appendiceal neoplasm were considered eligible. The inclusion was restricted to the studies that exclusively reported quantitative and histopathological data in adult patients (over 16 years of age) undergoing IA for complicated appendicitis (abscess, phlegmon, perforation) and to those cases where it was defined as appendiceal inflammatory mass. Studies were excluded if they considered a pediatric study population rather than adults, or both. In addition, they were excluded if IA had been performed on indications different from any of the aforementioned.

Data extraction and outcome measures

Data were independently collected from each study by two authors (RP and MDL) using a dedicated template. Study type and period, patient number and characteristics (sex and age), preoperative diagnosis and mean time to IA were initially recorded. Then, total appendix neoplasm rates after all appendectomies and after IA were extracted along with histopathological findings. Prevalence rates of appendix neoplasms from each included study were considered to assess the oncological risk after IA for complicated appendicitis in adult patients. Data were presented as frequencies and percentages.

Pathological data were grouped into four categories: appendiceal mucinous neoplasm, appendiceal adenocarcinoma, appendiceal neuroendocrine neoplasm and adenoma or serrated lesions. According to the most recent World Health Organization (WHO) classification of malignant tumours[23], appendiceal mucinous neoplasms include low-grade appendiceal mucinous neoplasms (LAMN), high-grade appendiceal mucinous neoplasms (HAMN), mucinous adenocarcinomas and signet ring cell adenocarcinomas in mucin pools.

Assessment of the methodological quality of studies

All studies were assessed for methodological quality. For randomized studies, the validated score described by Moher et al.[24] was used. The scale consists of three items pertaining to descriptions of randomisation, masking, and dropouts and withdrawals in the report of an RCT. The scale ranges from 0 to 5, with higher scores indicating better reporting. The individual components assess the adequacy of reporting of randomisation, allocation concealment, and double-blinding and are described in detail elsewhere. High-quality trials scored more than 2 out of a maximum possible score of 5. Low-quality trials scored 2 or less out of a maximum possible score of 5. For the retrospective studies we used the Joanna

Briggs Institute (JBI) Prevalence Critical Appraisal Tool. The criteria address the following issues: Ensuring a representative sample, Ensuring appropriate recruitment, Ensuring an adequate sample size, Ensuring appropriate description and reporting of study subjects and setting, Ensuring data coverage of the identified sample is adequate, Ensuring the condition was measured reliably and objectively, Ensuring appropriate statistical analysis, Ensuring confounding factors/subgroups/differences are identified and accounted for. These questions can be answered with four possible responses: yes, no, unclear or not applicable[25]. Two reviewers (VC, RG) evaluated the risk of bias in each eligible study and disagreements between reviewers were resolved by consensus.

Statistical analysis

We used a systematic analytic approach to compute the pooled prevalence rates of appendix neoplasm after IA and EA surgery from all eligible studies. The standard deviation of each study was calculated according to the binomial distribution. In this study, Metaprop was used to perform meta-analyses of proportions close to or at the margins, 0% or 100%. Metaprop pools proportions and presents a weighted subgroup and overall pooled estimates with inverse-variance weights obtained from a random-effect model [26]. Heterogeneity of the included studies was examined by using the I-squared (I^2) statistic, to reflect the percentage of total variation across studies[27]. According to the Cochrane handbook, $I^2 >$ 50% reflects a substantial heterogeneity[28]. Therefore, a random effect model is used to combine data in the meta-analysis[29].

The possibility of publication bias in the present study was examined by using Begg's test and Egger's test[30]. All analyses were performed using Stata, version 14.1 (StataCorp, College Station, TX). A P value of 0.05 was used to determine the statistical significance for the test.

Results

Study selection

Seventy-six studies were identified through database searching (Fig. 1). After removing duplicates, two reviewers identified potentially eligible studies independently by titles and abstracts among fifty-one records; divergences, if any, were resolved by consensus. Reviews, correspondences and articles

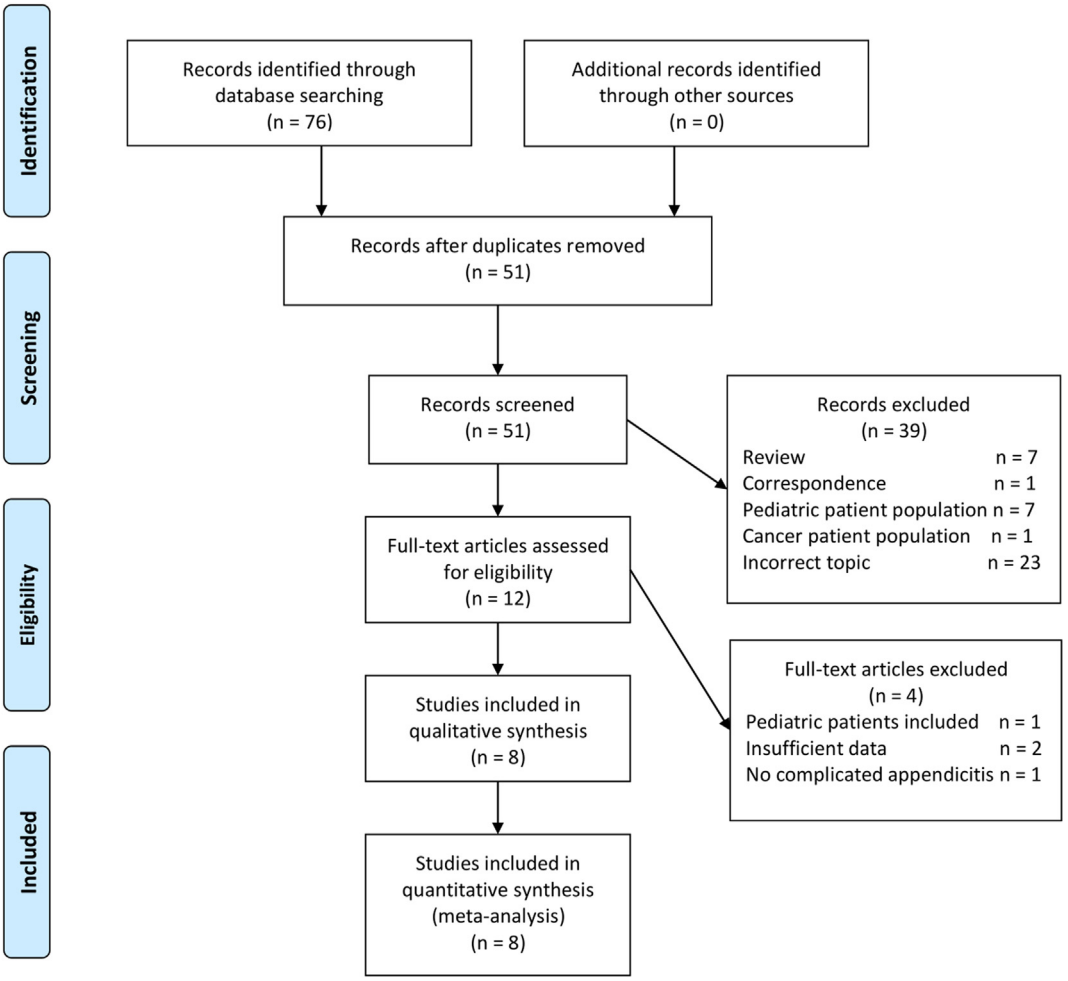

Fig. 1 – Literature search and selection process of studies included in analysis.

Table 1 – Baseline characteristics of included studies.[a] Randomized Controlled Trial;[b] Value reported in Median.[c] 91% of cases.

Author	Year	Study type	Study period	Preoperative diagnosis for IA	N. patients	Male (%)	Mean age ± SD	Percutaneous Abscess Drainage
Carpenter[17]	2012	Retro	2003–2007	Periappendicular abscess or perforation	18	11[61]	53 ± 16	Yes
Furman[18]	2013	Retro	2006–2010	Periappendicular abscess or phlegmon	17			No
Wright[36]	2015	Retro	2002–2013	Perforated appendicitis[c]	89	43[48]	51 ± 20	Yes
Mällinen[33]	2019	RCT[a]	2013–2016	Periappendicular abscess	25	16 (53.3)	49 (18–60)[b]	Yes
Al-Kurd[31]	2018	Retro	2000–2016	Periappendicular abscess or phlegmon	106	42 (39.6)	39.7 ± 16.2	Yes
Mima[34]	2019	Retro	2012–2018	Periappendicular abscess	50	23[46]		Yes
Son[35]	2020	Retro	2014–2018	Periappendicular abscess or phlegmon	111	58 (52.3)	54 ± 16.6	Yes
de Jonge[32]	2019	Retro	2008–2017	Abnormal appendix; persistent abdominal pain; recurrent appendicitis in patients with appendiceal mass (phlegmon ± abscess)	64	31 (48.4)	48[34–61b]	Yes

that did not meet the inclusion criteria were excluded. Twelve full-texts were assessed for eligibility and only eight of them were included in qualitative and quantitative analysis [17,18,31-6].

Study characteristics

Baseline characteristics of included studies are showed in Table 1. In all the articles preoperative diagnosis was a complicated appendicitis scenario. Seven retrospective studies[17,18,31,32,34-6] and one randomized controlled trial (RCT)[33] assessed neoplasm appendiceal rate after IA and histopathology (Table 2). Only in the RCT, patients who did not undergo IA were followed up with MRI imaging[33]. In addition, a qualitative synthesis from each study regarding age at the time of neoplasm diagnosis and mean time between acute episode and IA were reported in Table 3.

Quality assessment of studies

Figure 2 summarizes the quality assessment of included studies using the JBI Prevalence Critical.

Appraisal Tool. The risk of bias was considered low overall. The domains that showed a sustained unclear risk of bias were "data analysis conducted with sufficient coverage of the identified sample" and "standard criteria used for the reliability of measurement of the condition", probably due to dropouts, refusals or "not founds" amongst selected subjects and due to how the measurement of the condition was assessed. The methodological quality of the included RCT study was 4/5.

Prevalence rates of appendix neoplasm after IA and pathology

The total number of patients included in the analysis was 455 with a mean age of 49 ± 6.04 years. Overall, the pooled prevalence of neoplasm after IA was 11% (95% CI 7–15) with a heterogeneity of 37.5%, p = 0.13 (Fig. 3). The pooled prevalence of appendiceal mucinous neoplasms was 43% (95% CI 19–68) with a heterogeneity of 67.5%, p = 0.01; the pooled prevalence of appendiceal adenocarcinoma was 29% (95% CI 6–51) with a heterogeneity of 43.88%, p = 0.15; the pooled prevalence of

Table 2 – [a] Proportion not defined; [b]Incidence of neoplasm in interval group is higher also when compared to the subset of early appendectomy with complicated apendicitis (621/1902): 12.6% vs 2.2%.

Author	N. patients	Neoplasm Diagnosis after IA (%)	Appendiceal Mucinous Neoplasms	Subtypes of Mucinous Neoplasm	Appendiceal adenoca.	Appendiceal Neuroendocrine Neoplasm	Globet Cell carcinoma (carcinoid)	Adenoma or Serrated lesions
Carpenter[17]	18	5/18[28]	1	1 Mucinous Adenoca.	2	1		1
Furman[18]	17	5/17 (29.4)	5	Mucinous Adenoca.; Mucinous Cystoadenoma[a]				
Wright[36]	89	11/89 (12.3)	6		1	3	1	
Mällinen[33]	25	3/25[12]	2	1 LAMN; 1 LAMN and PMP				1
Al-Kurd[31]	106	6/106 (3.7)	5	1 Mucinous Cystoadenoma; 1 LAMN; 1 Mucinous Adenoca.; 2 Mucocele				1
Mima[34]	50	4/47 (8.5)	1	1 Mucinous Cystoadenoma	2	1		
Son[35]	111	14/111 (12.6)	14	2 Mucinous Adenoca.; 12 LAMN				
de Jonge[32]	64	7/64[11]	3	2 LAMN; 1 Signet-ring cell Carcinoma	3	2	2	1

Table 3 – Mean time to perform Interval Appendectomy (IA) and association between age and incidence of neoplasm for each study.

Author	Neoplasm Diagnosis after IA (%)	Mean time to IA	Age at neoplasm diagnosis
Carpenter[17]	5/18[28]	52.5 ± 31 days	The mean age of patients with complicated appendicitis and malignancy was 62y
Furman[18]	5/17 (29.4)	9[3–20] weeks	The mean age of all patients with appendiceal tumors was 49y (35–74)
Wright[36]	11/89 (12.3)	2.6 ± 1.9 months	The mean age of patients undergoing IA with appendiceal neoplasm was 60 ± 20y
Mällinen[33]	3/25[12]	16.2 weeks	The mean age of patients ondergoing IA with appendiceal neoplasm was 54y
Al-Kurd[31]	6/106 (3.7)	95 (32–619) days	The mean age of patients ondergoing IA with appendiceal neoplasm was 57.2 ± 8.7 (44–67)
Mima[34]	4/47 (8.5)	85 (68–101) days	The incidence of neoplasm in patient undergoing IA and > 70y was significally higher than that in patient < 70y (11% vs 6.9%)
Son[35]	14/111 (12.6)	10.2[1–23] weeks	The incidence of neoplasm in patient undergoing IA and > 40y was significally higher than that in patient < 40y (3.3% vs 0.1%)
de Jonge[32]	7/64[11]	19[9–34] weeks	

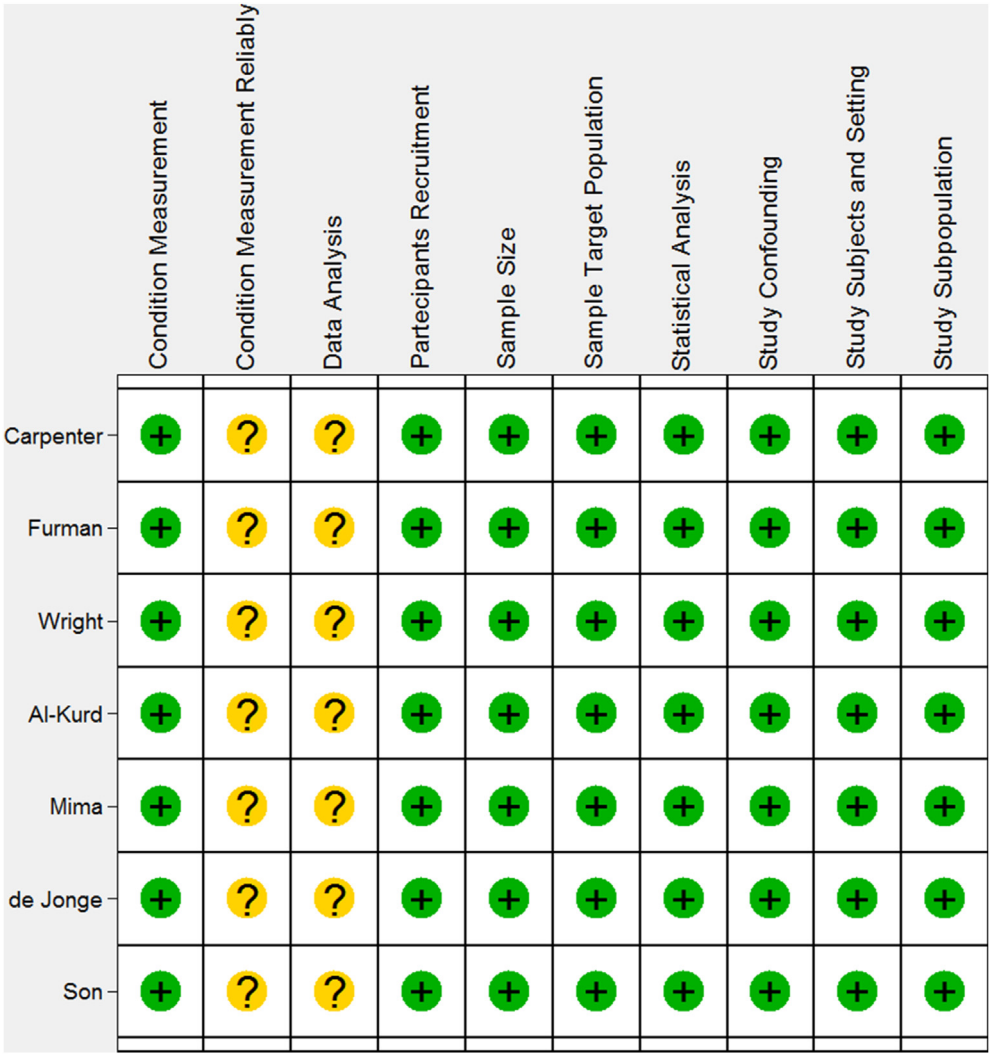

Fig. 2 – Quality assessment of the included studies using Joanna Briggs Institute (JBI) Prevalence Critical Appraisal Tool.

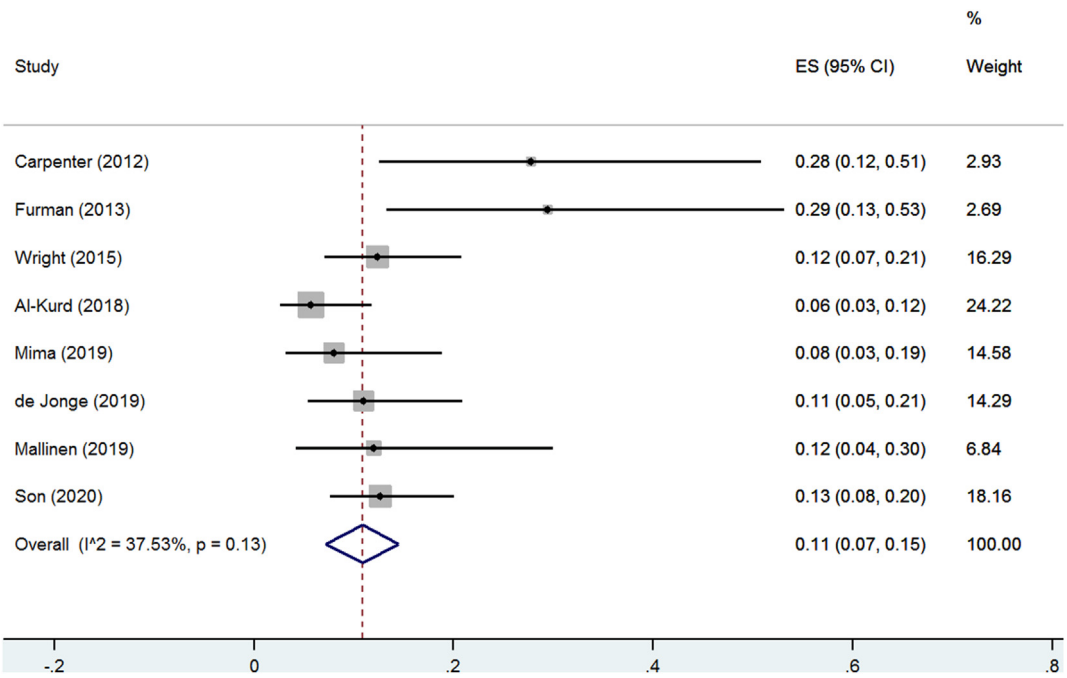

Fig. 3 – Pooled prevalence of neoplasm after Interval Appendectomy (IA).

appendiceal neuroendocrine neoplasm was 21% (95% CI 6–36) with no heterogeneity observed; the pooled prevalence of Globet cell carcinoma (carcinoid) was 13% (95% CI -2-28) with no heterogeneity observed and pooled adenoma or serrated lesions was 20% (95% CI -0-41) with no heterogeneity observed (Supplemental Content S2–S6).

In a subgroup analysis of two studies considering patients presenting with a periappendicular abscess, the pooled prevalence of neoplasm after IA was 9% (95% CI 3–16) with no heterogeneity observed (Fig. 4).

Potential bias

The funnel plots indicate the presence of bias in published studies that was significant for prevalence rate of neoplasms after IA (P = 0.009) (Supplemental Content S7).

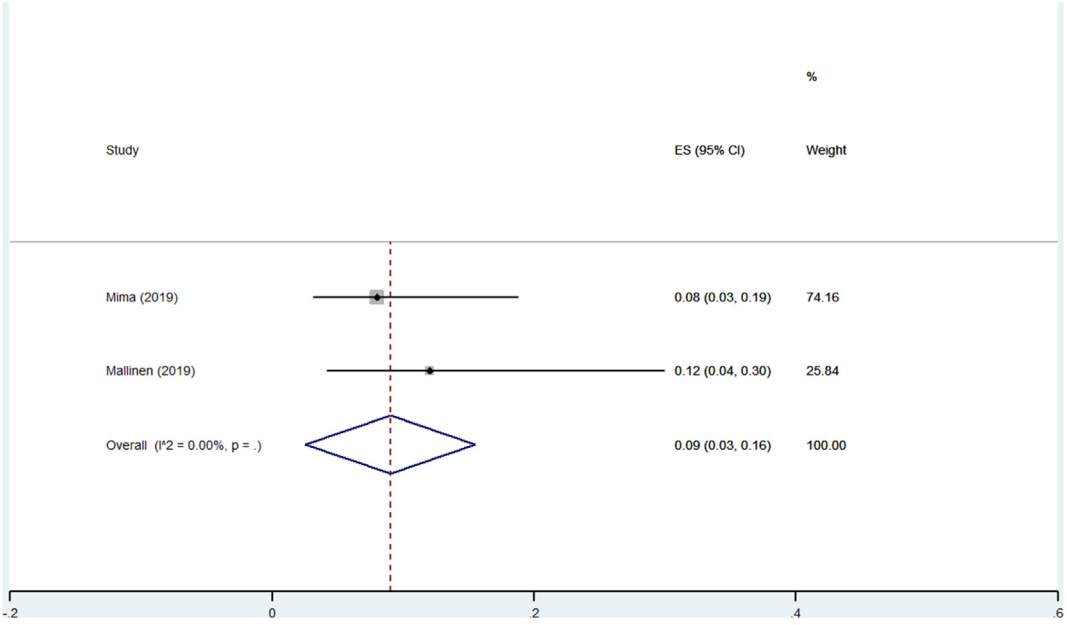

Fig. 4 – Pooled prevalence of neoplasm after Interval Appendectomy (IA) in a subgroup analisys: patients presenting with a periappendicular abscess.

Discussion

The optimal therapeutic approach of complicated appendicitis is still being debated. Non-operative management (NOM) consists of antibiotics with or without percutaneous drainage and it is adopted because inflamed tissue, distorted anatomy and difficult appendiceal stump closure occur in acute complicated settings. This can increase the risk of ileocecal resection or right hemicolectomy [8,37] and the morbidity rate after IA can rise up to 19.0%[10]. However, the surgical approach is also suggested as a first line option where an advanced laparoscopic expertise is available[19]. Recurrence rate after NOM for complicated appendicitis ranges from 7.4 to 25.5%[8,10]; however, routine IA is not recommended in order to avoid the possibility of recurrence[16,19].

In this review, the prevalence of appendiceal neoplasm in adult patients after IA for complicated appendicitis is evaluated in order to contribute to the therapeutic decision making process. Results show a rate of 11% of neoplasms after IA. This value is certainly higher than the 1.2% reported by Anderson[8] which included in the meta-analysis pediatric patients and heterogeneous studies. In contrast, the first two studies that addressed the topic [17,18] showed neoplasm rates more than twice higher than those found by the present pooled analysis, probably because of their small sample size. Furthermore, it was found that the prevalence rate of appendiceal neoplasms after IA is higher than that after early appendectomy reported in other studies between 0.7 and 2.5%[38-41]. Probably, this is because early appendectomy is mostly performed for uncomplicated acute appendectomy.

There was heterogeneity among the studies included in our analysis, in the same way as there is often heterogeneity among studies addressing prevalence and incidence. This is due to a number of reasons. Firstly, clinical heterogeneity may be present due to the measures used to determine the presence of a variable. Additionally, prevalence and incidence studies often look at specific populations at a specific point in time. Another consideration about the population is whether those considered at risk or eligible for the disease have been included[42]. However, despite the presence of a considerable amount of heterogeneity observed in this study, previous evidence showed that meta-analyses are the preferred options to narrative syntheses for interpreting results in reviews involving quantitative data[43]. Furthermore, the included studies demonstrated heterogeneity in defining cases of complicated acute appendicitis. Only two studies considered periappendicular abscess exclusively[33,34], while phlegmonous inflammation and perforated appendicitis complete the different forms of complicated appendicitis in the others studies.

A prevalence of 11% strengthens the correlation between complicated appendicitis and risk of neoplasm. This association is supported by retrospective analysis of histopathological data[44,45]. In addition, a Finnish nationwide population-based registry study showed a risk of appendiceal neoplasm significantly higher in patients with complicated rather than uncomplicated acute appendicitis[46]. For this reason, some authors suggest a screening program with colonoscopy and CT scan for patients treated non-operatively if older than 40 years of age [8,19,21] in order to find hidden pathologies. However, neoplasms of the appendix are rarely suspected before surgery and are discovered either intraoperatively or incidentally in the pathologic specimen[45,46]. The likelihood of finding early lesions of the appendix is rare using endoscopic[47] or radiologic[48] evaluation and no general consensus exists on the right time to perform investigations.

Neuroendocrine neoplasms account approximately for 30–80% of all appendiceal neoplasms and they are most often identified incidentally during surgery for appendicitis[49,50]. The surgical treatment is limited to appendectomy when the lesion is inferior to 1 cm. Only when the diameter reaches more than 2 cm or unfavorable histologic features occur, a right hemicolectomy should be performed[51]. In contrast, 70% of tumors after IA are mucinous neoplasms and adenocarcinomas of the appendix in the present study. Mucinous neoplasms are the most common after IA (40%). Within this group, LAMN and mucinous adenocarcinoma represent the most frequent subtypes. The prognosis of LAMN is highly stage-dependent. Patients with LAMN limited to the appendix, without perforation or peritoneal involvement, are safely treated with appendectomy alone. They have an excellent prognosis with negative resection margins. However, iatrogenic or spontaneous rupture of the appendix can convert the disease from localized to disseminated resulting in pseudomixoma peritonei[52,53]. In this case, citoreductive surgery with or without hyperthermic intraperitoneal chemotherapy (HIPEC) is indicated[23,51]. Therefore, neoplasms after IA need different clinical and therapeutic evaluations and could be associated to a poor prognosis.

What emerged from our study was a trend of asymmetry in funnel plot among studies for prevalence rate of neoplasm after IA, suggesting the presence of bias. Publication bias is a possible cause of funnel plot asymmetry. However, other possible sources are poor methodological quality, leading to spuriously inflated effects in smaller studies; true heterogeneity, in which the effects differ according to study size; and sampling variation, that can lead to an association between the effect and its standard error[27].

It is reasonable to assume that an association between clinically silent longstanding chronic inflammation and neoplastic modifications may exist when a complicated acute appendicitis is initially treated non operatively in some cases. Neoplastic pathologic changes can be not only pre-existing, but they could also develop over time in a chronic inflammation setting. This is already known for inflammatory bowel disease (IBD)[54] and hepatitis[55]. In addition, a qualitative synthesis of data from the included studies highlighted the correlation between the appendiceal neoplasm rate and age higher than 50 years of age in patients undergoing IA.

The pathological classification and terminology of appendiceal tumors has undergone numerous changes over the last decades both for neuroendocrine group of tumors[56,57] and for mucinous neoplasms with the introduction of LAMN and HAMN[58,59]. Furthermore, terms like ‘cystadenoma’, ‘mucocele’ and ‘mucinous cystoadenocarcinoma’ should no longer be in use[60-62]. Different terminology and classifications in the articles included represent one of the limitations of the study, although the present review refers to the most updated (WHO) classification of malignant tumors[23]. Other

limitations are represented by the retrospective nature of the studies included and the small study population size considered in same. Furthermore, a follow up of patients who did not undergo IA is missing, except for the study of Mällinen[33]: laparoscopic appendectomy was recommended to all the patients belonging to the follow up group. This study was prematurely terminated because of the high incidence of appendiceal tumors.

Conclusion

The appendiceal neoplasm rate of patients undergoing IA for complicated appendicitis is 11% and most are appendiceal mucinous neoplasms. These findings make the option of the management of complicated appendicitis in adult patients more viable when a non surgical approach is initially adopted. Further studies should aim to investigate the possibility of neoplastic transformation as a pathway deriving from chronic inflammation inputs. In addition to age, identifying other risk factors for appendiceal neoplasm in this category of patients could influence the choice of therapeutic strategy.

Research involving human participants and/or animals

This article does not contain any studies with animals performed by any of the authors.

Informed consent

The informed consent does not apply since this is a review study.

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Conflict of interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.surge.2021.01.010.

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