



Click here to view linked References

## Appendiceal Neoplasm Risk Associated with Complicated Acute Appendicitis – a Population Based Study

Elina Lietzén<sup>1, 2</sup>, M.D., Juha M Grönroos<sup>1, 2</sup>, M.D., Ph.D., Jukka-Pekka Mecklin<sup>3, 4</sup>, M.D., Ph.D., Ari Leppäniemi<sup>5, 6</sup>, M.D., Ph.D., Pia Nordström<sup>7, 8</sup>, M.D., Ph.D., Tero Rautio<sup>9, 10</sup>, M.D., Ph.D., Tuomo Rantanen<sup>11, 12, 13</sup>, M.D., Ph.D., Juhani Sand<sup>14</sup>, M.D., Ph.D., Hannu Paajanen<sup>15</sup> M.D., Ph.D., Anne Kaljonen<sup>16</sup>, MSc and, Paulina Salminen<sup>1, 2\*</sup>, M.D., Ph.D.

<sup>1</sup> Division of Digestive Surgery and Urology, Department of Digestive Surgery, Turku University Hospital, Turku, Finland

<sup>2</sup> University of Turku, Turku, Finland

<sup>3</sup> Department of Surgery, Jyväskylä Central Hospital and Sport and Health Sciences, Jyväskylä, Finland

<sup>4</sup> University of Jyväskylä, Jyväskylä, Finland

<sup>5</sup> Department of Gastrointestinal Surgery, Helsinki University Central Hospital, Helsinki, Finland

<sup>6</sup> University of Helsinki, Helsinki, Finland

<sup>7</sup> Division of Surgery, Gastroenterology and Oncology, Tampere University Hospital, Tampere, Finland

<sup>8</sup> University of Tampere, Tampere, Finland

<sup>9</sup> Department of Surgery, Division of Gastroenterology, Oulu University Hospital

<sup>10</sup> University of Oulu, Oulu, Finland

<sup>11</sup> Department of Surgery, Seinäjoki Central Hospital, Seinäjoki

<sup>12</sup> Department of Surgery, Kuopio University Hospital, Kuopio, Finland

<sup>13</sup> University of Kuopio, Kuopio, Finland

<sup>14</sup> Health and Medical Services, Päijät-Häme Joint Authority for Health and Wellbeing, Lahti, Finland

<sup>15</sup> Department of Surgery, Mikkeli Central Hospital, Mikkeli, Finland

<sup>16</sup> The Department of Biostatistics, University of Turku, Turku, Finland

Funding / support: This study was supported by a Turku University Hospital Government Research Grant (TYKS EVO Foundation), Paulo Foundation, and Constitution of The Gastroenterological Research Foundation.

Conflicts of interest: Dr Salminen has received personal fees for lectures from Merck, Lilly, and Orion Pharma.

Word count for the text: 3334, for the abstract: 250.

\* Correspondence:

Elina Lietzén, M.D.

The Division of Digestive Surgery and Urology

Kiinanmyllynkatu 4-8, 20520 Turku, Finland

Tel. +358-2-3135918

Fax. +358-2-2612284

E-mail: [elina.lietzen@tyks.fi](mailto:elina.lietzen@tyks.fi)

## ABSTRACT

**PURPOSE:** Appendiceal tumors are rare, but high neoplasm rates have been reported at interval appendectomy after periappendicular abscess. Non-operative management of uncomplicated acute appendicitis has shown promising results. The data on appendiceal tumor incidence and presentation among acute appendicitis patients is limited, especially in patient cohorts differentiating between uncomplicated and complicated acute appendicitis. Objective was to assess appendiceal tumor incidence and tumor association to appendicitis in patients with uncomplicated and complicated acute appendicitis.

**METHODS:** This nationwide population based registry study was conducted from 2007 to 2013. The Finnish Cancer Registry and the National Institute for Health Registry were used to combine data on all appendiceal tumors and acute appendicitis diagnosis with medical reports evaluated at eight study hospitals.

**RESULTS:** Altogether 840 appendiceal tumors were identified and out of these, 504 patient reports were reviewed including 472 patients in this study. Tumor was diagnosed at appendectomy for suspected acute appendicitis in 276 patients (58%). In the whole study, histologically acute appendicitis and tumor were both present in 53% (n=250) and out of these 41% (n=102) were complicated and 59% (n=148) uncomplicated acute appendicitis. The associated tumor risk was significantly higher in complicated acute appendicitis compared with uncomplicated cases (3.24% vs. 0.87%,  $p<0.001$ ). Overall tumor prevalence among acute appendicitis patients was 1.24%.

**CONCLUSIONS:** Appendiceal tumor prevalence in acute appendicitis was low. Tumor risk was significantly higher in complicated acute appendicitis compared with uncomplicated acute appendicitis. The risk of missed appendiceal tumors related to antibiotic therapy of uncomplicated acute appendicitis is very low.

**Key words:** acute appendicitis, uncomplicated acute appendicitis, complicated acute appendicitis, non-operative treatment, appendectomy, appendiceal neoplasm

**Abbreviations:** CT, computed tomography; HIPEC, Hyperthermic Intra Peritoneal Chemotherapy; ICD-10, International Classification of Disease version 10; FCR, Finnish Cancer Registry; MANEC, mixed adeno-neuroendocrine carcinoma; MRI, magnetic resonance imaging; NET, neuroendocrine tumor; NIHW, National Institute for Health and Welfare; WHO, World Health Organization

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

## INTRODUCTION

1  
2  
3 The treatment paradigm of uncomplicated acute appendicitis may be changing as promising results  
4  
5 with antibiotic therapy have been reported and operative treatment may be unnecessary for the  
6  
7 majority of uncomplicated acute appendicitis patients[1-3]. In order to optimize and tailor the  
8  
9 treatment for acute appendicitis, precise and accurate diagnostic tools such as computed  
10  
11 tomography (CT) are required. As CT has high sensitivity in diagnosing acute appendicitis, it has  
12  
13 become the golden standard in right lower quadrant abdominal pain differential diagnosis[4].  
14  
15 Uncomplicated acute appendicitis may also resolve spontaneously without even antibiotics let alone  
16  
17 surgery[5]. Non-operative management of uncomplicated acute appendicitis has also been shown to  
18  
19 reduce treatment costs[6]. In cases of complicated acute appendicitis with a formation of a  
20  
21 circumscribed abscess, the need for interval appendectomy after initial successful conservative  
22  
23 treatment has also been questioned as the risk of appendicitis recurrence is quite low between 5-  
24  
25 20%[7]. However, there are some more recent studies reporting an alarming rate of appendiceal  
26  
27 neoplasms detected at interval appendectomy in patients with previous periappendicular abscess[8,  
28  
29 9], especially regarding patients over the age of 40 years[8, 10].

30  
31  
32 Appendiceal tumors are rare, usually incidental findings most often detected at histological  
33  
34 evaluation of the removed appendix. Appendiceal neoplasm rate varies from 0.7% to 2.5% of  
35  
36 appendectomy specimens in several large appendectomy series[7, 11-13]. With the development of  
37  
38 precise diagnostic capabilities like CT, appendiceal tumors may increasingly be suspected on  
39  
40 CT[14, 15]. However, most of the CT signs related to appendiceal tumors are unspecific and  
41  
42 preoperative diagnosis of an appendiceal tumor on CT can be obscured by signs of acute or  
43  
44 secondary inflammation[14]. Appendiceal tumors are a heterogeneous group of diseases ranging  
45  
46 from typical neuroendocrine tumors (NET) to adenocarcinomas including all the varieties within  
47  
48 this spectrum. The pathological classification and terminology of appendiceal tumors has undergone  
49  
50 major changes over the last decades[16-18]. In addition, most studies on appendiceal tumors are  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1 retrospective case report compilations further contributing to possible diagnostic, therapeutic and  
2 also prognostic uncertainty related to neoplasms of the appendix. Further, the majority of  
3 appendiceal tumor data has previously been based on retrospective single-center studies of low  
4 patient numbers with limited generalizability. In an attempt to overcome these limitations, we  
5 assessed appendiceal tumors through a population based study relying on combining the national  
6 cancer surveillance and surgical procedures data with actual patient medical records enabling  
7 assessment at both population and patient level. To our knowledge, there is only a limited number  
8 of recent population-based registry studies published on appendiceal tumors[16, 18-27].  
9

10 The aim of this study was to evaluate both the incidence of appendiceal tumors among acute  
11 appendicitis patients and the possible tumor association to both uncomplicated and complicated  
12 acute appendicitis using both national population-based cancer surveillance and surgical procedure  
13 data.  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

## METHODS

1  
2  
3 A nationwide population based registry study was performed to assess all diagnosed appendiceal  
4 tumors in Finland from 2007 to 2013. This study was approved by Turku University Hospital  
5 ethical committee. Diagnoses were categorized according to the World Health Organization  
6 International Classification of Disease year 2010 classification (ICD-10)[28]. The study population  
7 of appendiceal primary tumors was collected from the Finnish Cancer Registry (FCR), which is  
8 responsible for maintaining a nationwide database on all cancer cases in Finland. All hospitals and  
9 laboratories are required by law to provide the FCR with information on all new diagnosed cancers.  
10 The accuracy of FCR is very reliable as it covers over 99% of all solid tumors diagnosed in Finland.  
11 From the patient population diagnosed with a histologically proven appendiceal primary tumor, we  
12 collected hospital medical record data on patients treated at eight study hospitals: all five university  
13 hospitals (Helsinki, Tampere, Turku, Kuopio and Oulu) and three larger central hospitals  
14 (Jyväskylä, Mikkeli and Lahti). These eight hospitals were included in the study for practical data  
15 retrieving reasons in order to be able to collect adequate nationwide data comprising the majority of  
16 the study population. The population of these study hospitals represented 70.1% (study hospital  
17 population 3 843 871/ population of the whole country 5 487308) of the whole population in  
18 Finland. In all patients the medical record data collection included patient demographics, tumor  
19 diagnosis, related imaging and operative findings, tumor histology and associated treatments.  
20 Operative findings and histological reports were reviewed in order to reliably differentiate  
21 uncomplicated and complicated acute appendicitis diagnosis. Complicated acute appendicitis was  
22 defined as perforation or a periappendiceal abscess. Unclear cases were assessed by another senior  
23 surgeon with blinded evaluation. Some of the medical records were not available due to lack of  
24 common hospital district databases at the time of the study and patients with unavailable data were  
25 excluded from the study. All included patients had complete medical data records available and all  
26 patient information contained in these datasets was non-identifiable at analysis.  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1 All eligible patients with available data were divided into three groups based on how the  
2 appendiceal tumor was diagnosed. In group 1 the appendiceal tumor was detected at or after  
3 (histology) surgery for suspected acute appendicitis (emergency appendectomy or interval  
4 appendectomy), in group 2 the appendiceal tumor was diagnosed at or after (histology) surgery  
5 performed for other indications (incidental appendectomy), and in group 3 the appendiceal tumor  
6 was diagnosed at preoperative imaging.  
7  
8  
9  
10  
11  
12  
13

14 In order to assess the true prevalence of appendiceal tumors among all acute appendicitis patients,  
15 we collected information from the National Institute for Health and Welfare (NIHW) registry to  
16 gather data on both acute appendicitis diagnosis and appendectomies during the study period. Dates  
17 of admission and discharge, discharge diagnosis, surgical procedure, and demographic data of the  
18 patient are by law recorded in NIHW registry for every hospitalized patient nationwide. In  
19 analyzing the patients in the NIHW registry, no additional tumors not presented in FCR were  
20 identified underlining the almost perfect coverage of appendiceal tumors in the FCR database.  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33

### 34 **Statistical methods**

35  
36 The differences in background variables between the three groups (Group 1: appendiceal tumor was  
37 detected at or after (histology) surgery for suspected acute appendicitis, Group 2: at surgery  
38 performed for other indications, Group 3: at preoperative imaging) were tested for a numeric  
39 variable (age) with one-way analysis of variance and for categorical variables using Chi-Square test.  
40  
41 The risk of having appendiceal tumor was calculated using the Chi-square test and Odds Ratio with  
42 95% Confidence Limits. ~~For the incidence of tumor among appendicitis patients, the follow-up time~~  
43 ~~was calculated for tumors from appendicitis to tumor diagnosis, and for non-tumors from~~  
44 ~~appendicitis diagnosis to the end of follow-up (31.12.2013).~~ All of the statistical analyses were  
45 performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA).  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

## RESULTS

1  
2  
3 A total of 840 appendiceal primary tumor patients were identified from FCR database and 504  
4  
5 (60%) patients were treated in the hospital districts of the eight study hospitals. Altogether 472  
6  
7 appendiceal tumor patients with available diagnostic and clinical data were included in this study  
8  
9 (Figure 1). In the whole study group preoperative imaging was performed for 58% (n=293/472) of  
10  
11 the patients and the main imaging modality (n=231) was contrast enhanced CT scan. Out of these  
12  
13 472 patients, the appendiceal tumor was diagnosed at surgery either for suspected acute appendicitis  
14  
15 or interval appendectomy after primary conservative treatment of periappendicular abscess in 276  
16  
17 (58%) patients (group 1) at a mean age of 46 years, at abdominal surgery for other indications in  
18  
19 142 (30%) patients (group 2) at a mean age of 60 years, or at any preoperative imaging in 54 (11%)  
20  
21 patients (group 3) at a mean age of 59 years. Detailed patient demographics, clinical and diagnostic  
22  
23 findings, histology and additional treatments according to these study groups 1-3 are presented in  
24  
25 Table 1.  
26  
27  
28  
29  
30  
31  
32

33 Patients undergoing surgery for suspected acute appendicitis (group 1), 92% (n=254/276)  
34  
35 underwent appendectomy and 7% (n=20/276) underwent a more extensive bowel resection. The  
36  
37 majority of the patients (87%, 241/276) underwent an emergency operation. Out of these 276  
38  
39 patients, 86% (n=235) had acute appendicitis at histology resulting in a negative appendectomy rate  
40  
41 of 14 %. In group 1 53% (n=145) underwent diagnostic imaging and none of the tumors were  
42  
43 suspected on preoperative imaging. At surgery a tumor was macroscopically suspected in 11%  
44  
45 (n=29) of the operations and 12 of these 29 cases were interval appendectomies.  
46  
47  
48  
49  
50

51 In group 2 undergoing surgery for other indications than suspected acute appendicitis, 77%  
52  
53 (n=110/142) of the patients underwent elective surgery. Out of these 74 patients for gynecological  
54  
55 indications (72 for suspicion of a gynecological tumor and 2 for suspected pelvic endometriosis). In  
56  
57 addition there were four emergency gynecological operations due to suspected pelvic inflammation.  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Four patients undergoing elective surgery were diagnosed with a periappendicular abscess and complicated acute appendicitis at surgery and histology. Three out of these four patients were operated on due to suspicion of gynecological tumor and one for suspected caecal tumor. Out of the 32 emergency procedures in this group seven of the patients had acute appendicitis at surgery and histology. In the whole patient group 2, 66% (n=94) underwent preoperative imaging and none of the appendiceal tumors were suspected preoperatively.

In group 3 with tumor suspicion on preoperative imaging, 91% of the patients (n=49/54) underwent elective surgery. Out of all 54 patients, only four (7%) had acute appendicitis. In preoperative imaging 74% (n=40) of group 3 patients were accurately diagnosed with a tumor. In two patients the imaging over-estimated and in 9 patients under-estimated the tumor staging, when compared to operative and histological findings. In three patients the disease was disseminated and no operation was performed, in two patients appendiceal tumor histology was obtained by radiological tumor biopsy and in one patient at autopsy.

During the study period, there were altogether 19976 patients with acute appendicitis diagnosis but without appendiceal tumor identified in the eight study hospitals and the NIHW registry (Figure 1) resulting in an appendiceal tumor prevalence of 1.24% ( $p < 0.001$ ) in the acute appendicitis patient population. The grand mean of follow-up time was 3.3 years per patient and the incidence of tumor on our data (66861 follow-up years and 245 tumor cases; 5 cases missing due to lack of follow-up information) was thus 0.0037 per one living year. There were altogether 250 patients with both acute appendicitis and an appendiceal tumor based on both histology and surgical finding (Figure 1.). Out of these, 102 (41%) patients had complicated acute appendicitis and 148 (59%) had uncomplicated acute appendicitis. The complicated acute appendicitis cases included 66 patients with a periappendiceal abscess and 36 perforated acute appendicitis cases. Out of the 66 patients with periappendiceal abscess, 29 patients underwent an interval appendectomy and 37 patients were operated on in an acute care setting. The appendiceal tumor risk was significantly higher in

1 complicated acute appendicitis compared with uncomplicated acute appendicitis (3.24% vs. 0.87%,  
2 p<0.001). The odds ratio (OR) for having an appendiceal tumor in complicated acute appendicitis  
3 was 3.83 (CI 95% 2.96-4.93). A separate subgroup analysis of tumor risk associated with  
4 periappendiceal abscess patients (n=66) also showed a significantly higher tumor risk compared  
5 with uncomplicated acute appendicitis (4.99% vs. 0.87%, p<0.001). The odds ratio (OR) for having  
6 an appendiceal tumor in complicated acute appendicitis presenting as periappendicular abscess was  
7 6.01 (CI 95% 4.47-8.08). These comparisons are presented in detail in Table 2. The mean age of all  
8 acute appendicitis patients without a tumor in NIHW database was 37 years (SD ±19.1), in  
9 uncomplicated acute appendicitis 35 years (SD ±17.9) and in complicated acute appendicitis 44  
10 years (SD ±43.8).  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23

24  
25 In the whole patient cohort of 472 appendiceal tumor histology, 49% (n=232) were NETs, 11%  
26 (n=52) mixed adeno-neuroendocrine carcinomas (MANEC) or goblet cell tumors, 14% (n=65)  
27 mucinous tumors or pseudomyxomas, and 26% (n=123) adenocarcinomas. In the whole patient  
28 population 49% of tumors were NETs, but in patients operated on for suspected acute appendicitis  
29 (group 1), the NET proportion was higher (61%). In group 1, 39% (109/276) of patients had a more  
30 malignant tumor histology other than NET. Of these 109 patients, 57% (n=62) of the patients had  
31 complicated acute appendicitis, 35 patients had uncomplicated acute appendicitis, 11 patients had  
32 no inflammation of the appendix and in one patient the appendicitis could not be histologically  
33 determined. In group 1, 14% of patients (n=34) did not have acute appendicitis at histology; 82%  
34 (n=28) out of these tumors were NETs, 15% (n=5) were adenocarcinomas and one patient had  
35 pseudomyxoma. According to histology or surgical finding, 78% (42/54) of group 3 patients had a  
36 local lymph node metastasis or disseminated disease, whereas metastatic disease was present in  
37 19% in group 1(51/276) and in 53% in group 2 (75/142).  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

## DISCUSSION

1  
2  
3 In this study the overall appendiceal tumor prevalence of 1.24% among patients with acute  
4 appendicitis was low. Of all patients with both acute appendicitis and an appendiceal tumor, 41%  
5 (n=102) were complicated and 59% (n=148) were uncomplicated acute appendicitis cases. The risk  
6 of an appendiceal tumor was statistically significantly higher in patients with complicated acute  
7 appendicitis compared to uncomplicated acute appendicitis (3.24% vs. 0.87%). The risk was even  
8 higher in a subgroup analysis comparing complicated acute appendicitis presenting with  
9 periappendiceal abscess to uncomplicated acute appendicitis (4.99% vs. 0.87%).  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20

21 Tumors of the appendix are incidental and rare. In many retrospective patient cohorts evaluating  
22 histopathology of the appendectomy specimens, the reported appendiceal tumor rate varies between  
23 0.7-1.7%[29-31]. These retrospective patient series do not differentiate the two different forms of  
24 acute appendicitis. Tumor rate in the randomized APPAC trial[1] comparing appendectomy and  
25 antibiotic therapy in the treatment of uncomplicated acute appendicitis was 1.5% in accordance with  
26 large histopathological appendectomy series[31]. According to a systematic review[7] the rate of  
27 malignant tumors diagnosed with acute appendicitis and an inflammatory mass was similar to tumor  
28 rates in uncomplicated acute appendicitis series[1]. However, contradictory alarming rates of  
29 appendiceal neoplasms have been reported in patients presenting with an appendiceal inflammatory  
30 mass varying from 10% to 29%[8-10, 12]. These results are in line with our study as the tumor risk  
31 for complicated acute appendicitis was significantly higher compared with patients with  
32 uncomplicated acute appendicitis. Tumor risk was even more prominent in patients with acute  
33 appendicitis presenting with periappendiceal abscess. According to two systematic reviews and  
34 meta-analysis[7, 32], initial non-operative management of periappendiceal abscess patients is  
35 superior with decreased complication and reoperation rates compared with emergency  
36 appendectomy. There is still major controversy regarding the necessity of an interval appendectomy  
37 after successful non-operative treatment of periappendicular abscess[7, 32]. However, there are  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1 some recent studies reporting significant rate of appendiceal neoplasms detected at interval  
2 appendectomy in patients with previous periappendiceal abscess, especially regarding patients over  
3  
4 40 years [8-10, 12]. These and our study results highlight the need for accurate differential  
5  
6 diagnosis between uncomplicated and complicated acute appendicitis and consideration of interval  
7  
8 appendectomy after initial non-operative treatment of periappendiceal abscess.  
9

10  
11  
12 Based on epidemiological studies[33] and accumulating data[1, 3] we now know that  
13  
14 uncomplicated and complicated acute appendicitis are two different diseases and this is also evident  
15  
16 when evaluating appendiceal tumor incidence in acute appendicitis patient population[12].  
17  
18 Approximately 25% of acute appendicitis cases present as complicated acute appendicitis[33].  
19  
20 Increasing evidence from randomized trials suggests that the majority of patients with  
21  
22 uncomplicated acute appendicitis can be treated safely with antibiotics with low tumor rates  
23  
24 avoiding unnecessary surgery resulting in decreased morbidity and cost savings[1, 3, 6]. The  
25  
26 markedly lower tumor rate associated with uncomplicated acute appendicitis is of vital clinical  
27  
28 importance as non-operative management of uncomplicated appendicitis is one its way of becoming  
29  
30 one of the treatment options for uncomplicated acute appendicitis [1, 3, 34] as the appendiceal  
31  
32 tumors are not generally suspected preoperatively[30, 35]. This is in line with our results as none of  
33  
34 the tumors in this study were suspected preoperatively in patients operated on for suspected acute  
35  
36 appendicitis and in only 11% of cases the tumor was suspected macroscopically during operation.  
37  
38  
39  
40  
41  
42  
43  
44

45 Clinical identification of appendiceal tumor patients preoperatively seems to be very challenging,  
46  
47 even though some risk factors have been identified such as advanced age, multiple comorbidities,  
48  
49 atypical presentation and complicated appendicitis.[13] In a large retrospective patient cohort[30],  
50  
51 80% of appendiceal tumors presented with a periappendicular abscess. The lack of preoperative  
52  
53 diagnostic tools for detecting appendiceal tumors further emphasize the role of preoperative  
54  
55 imaging as the differential diagnosis between uncomplicated and complicated acute appendicitis is  
56  
57 essential in both evaluating the treatment options and also regarding the tumor risk. Differential  
58  
59  
60  
61  
62  
63  
64  
65

1 diagnosis between these two forms acute appendicitis without imaging is not feasible[35]. There is  
2 a need for determining CT criteria that could help reliably identify complicated acute  
3 appendicitis[4] and also incidental appendiceal neoplasms to ensure their surgical resection[36].  
4  
5 Several CT features suggestive of coexisting appendiceal tumor have been described, but frequently  
6  
7 the radiographic appearance is one of acute appendicitis[36-38]. Sensitivity of tumor diagnosis with  
8  
9 CT increases with greater appendiceal diameter and with secondary tumor findings, i.e. metastasis,  
10  
11 which[15] is in concurrence with this study as 11% of tumor patients had a preoperative diagnosis  
12  
13 and 78% out of these had metastatic disease at presentation.  
14  
15  
16  
17  
18  
19

20 The pathological types and behavior of appendiceal tumors are diverse with both confusing  
21  
22 classification and terminology. Recognizing the difference in the clinical presentation and the  
23  
24 prognosis of primary appendiceal tumors is essential when evaluating risk of misdiagnosis among  
25  
26 acute appendicitis patients. The World Health Organization (WHO) classifies appendiceal tumors in  
27  
28 two main groups: NETs and appendiceal carcinomas. The overall survival rate is associated with  
29  
30 the histologic subtype[39]. The appendiceal NETs belongs to a sub-group of neoplasms, where  
31  
32 about 80% of diagnosis are incidental among patients treated due to acute appendicitis or  
33  
34 appendectomy performed for other reasons[28]. NETs are the most common primary tumors of the  
35  
36 appendix[17, 28] and in most cases prognosis is excellent[12]. The more malignant NETs are mixed  
37  
38 phenotype tumors include goblet cell tumors and MANECs reported to represent less than 5% of  
39  
40 primary appendiceal tumors[19]. In this whole patient population 49% of tumors were NETs. This  
41  
42 proportion was higher (61%) in patients operated on for suspected acute appendicitis (group 1) and  
43  
44 39% (109/276) of patients in group 1 had a more malignant tumor histology other than NET. Of  
45  
46 these 109 patients, 57% (n=62) of the patients had complicated acute appendicitis further  
47  
48 supporting the results of this population-based study and the higher tumor risk of complicated acute  
49  
50 appendicitis compared with uncomplicated acute appendicitis.  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

This study has several strengths. To our knowledge, this study is to date the most extensive comparison of appendiceal tumor risk between uncomplicated and complicated acute appendicitis patients. The use of population based data enhances the generalizability of the findings compared to case reports from single institutions with a defined population. Another strong element of the study is the evaluation of the appendicitis severity by combining appendectomy finding with histology instead of solely relying on registry data. A limitation of this study is that we included only patients in eight study hospitals instead of the whole FCR registry data. However, our study hospitals include all university hospitals and largest central hospitals in Finland thus representing the majority (70.1%) of both the Finnish population and also the registry data (60%) patient population. The minor discrepancy between the proportion of the tumors found at these eight hospitals and the proportion of the Finnish population in these hospital districts most likely has no impact on the study results as the FCR database is very reliable. There is no reason to expect that the excluded patients would differ significantly from those included in the study; the practical reason was based only on the feasibility of the patient medical record collection.

## CONCLUSION

In conclusion, the prevalence of appendiceal tumor among patients with acute appendicitis was low. Tumor risk was significantly higher in complicated acute appendicitis, especially in patients with periappendicular abscess. However with the very low incidence of appendiceal tumors associated with uncomplicated acute appendicitis, the risk of missing an appendiceal tumor related to non-operative antibiotic treatment of uncomplicated acute appendicitis is extremely low.

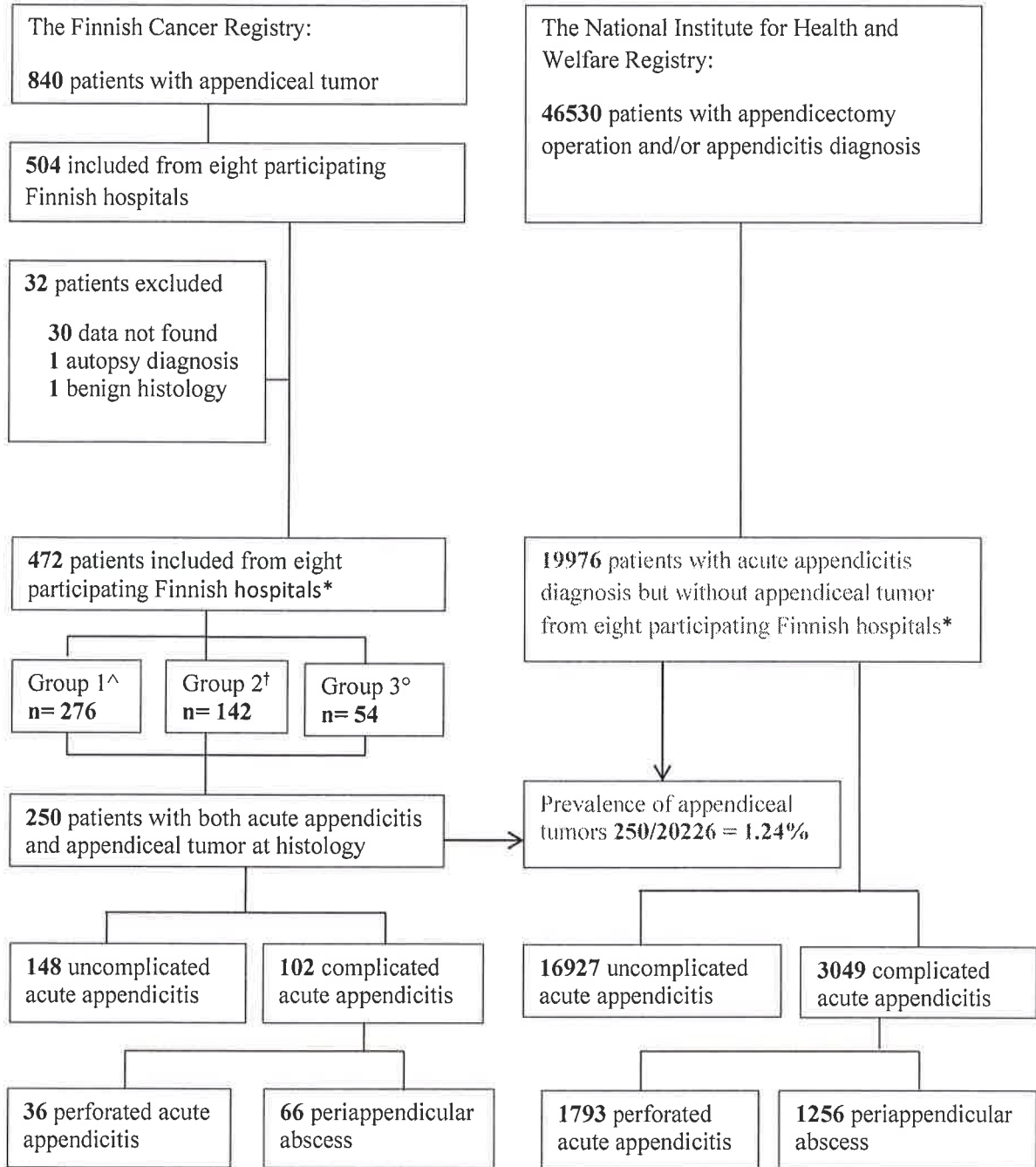
## REFERENCES

1. Salminen P, Paajanen H, Rautio T, Nordstrom P, Aarnio M, Rantanen T, et al. Antibiotic Therapy vs Appendectomy for Treatment of Uncomplicated Acute Appendicitis: The APPAC Randomized Clinical Trial. *JAMA*. 2015;313(23):2340-8.
2. Sallinen V, Akl EA, You JJ, Agarwal A, Shoucair S, Vandvik PO, et al. Meta-analysis of antibiotics versus appendectomy for non-perforated acute appendicitis. *Br J Surg*. 2016;103(6):656-67.
3. Vons C, Barry C, Maitre S, Pautrat K, Leconte M, Costaglioli B, et al. Amoxicillin plus clavulanic acid versus appendectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. *Lancet*. 2011;377(9777):1573-9.
4. Kim HY, Park JH, Lee YJ, Lee SS, Jeon JJ, Lee KH. Systematic Review and Meta-Analysis of CT Features for Differentiating Complicated and Uncomplicated Appendicitis. *Radiology*. 2017;171260.
5. Park HC, Kim MJ, Lee BH. Randomized clinical trial of antibiotic therapy for uncomplicated appendicitis. *Br J Surg*. 2017;104(13):1785-90.
6. Sippola S, Gronroos J, Tuominen R, Paajanen H, Rautio T, Nordstrom P, et al. Economic evaluation of antibiotic therapy versus appendectomy for the treatment of uncomplicated acute appendicitis from the APPAC randomized clinical trial. *Br J Surg*. 2017;104(10):1355-61.
7. Andersson RE, Petzold MG. Nonsurgical treatment of appendiceal abscess or phlegmon: a systematic review and meta-analysis. *Ann Surg*. 2007;246(5):741-8.
8. Wright GP, Mater ME, Carroll JT, Choy JS, Chung MH. Is there truly an oncologic indication for interval appendectomy? *Am J Surg*. 2015;209(3):442-6.
9. Furman MJ, Cahan M, Cohen P, Lambert LA. Increased risk of mucinous neoplasm of the appendix in adults undergoing interval appendectomy. *JAMA Surg*. 2013;148(8):703-6.
10. Carpenter SG, Chapital AB, Merritt MV, Johnson DJ. Increased risk of neoplasm in appendicitis treated with interval appendectomy: single-institution experience and literature review. *Am Surg*. 2012;78(3):339-43.
11. Murphy EM, Farquharson SM, Moran BJ. Management of an unexpected appendiceal neoplasm. *Br J Surg*. 2006;93(7):783-92.
12. Teixeira FJR, Jr., Couto Netto SDD, Akaishi EH, Utiyama EM, Menegozzo CAM, Rocha MC. Acute appendicitis, inflammatory appendiceal mass and the risk of a hidden malignant tumor: a systematic review of the literature. *World J Emerg Surg*. 2017;12:12.
13. Loftus TJ, Raymond SL, Sarosi GA, Jr., Croft CA, Smith RS, Efron PA, et al. Predicting appendiceal tumors among patients with appendicitis. *J Trauma Acute Care Surg*. 2017;82(4):771-5.
14. Whitley S, Sookur P, McLean A, Power N. The appendix on CT. *Clin Radiol*. 2009;64(2):190-9.
15. Pickhardt PJ, Levy AD, Rohrmann CA, Jr., Kende AI. Primary neoplasms of the appendix manifesting as acute appendicitis: CT findings with pathologic comparison. *Radiology*. 2002;224(3):775-81.
16. Shaib W, Krishna K, Kim S, Goodman M, Rock J, Chen Z, et al. Appendiceal Neuroendocrine, Goblet and Signet-Ring Cell Tumors: A Spectrum of Diseases with Different Patterns of Presentation and Outcome. *Cancer Res Treat*. 2016;48(2):596-604.
17. Hsu C, Rashid A, Xing Y, Chiang YJ, Chagpar RB, Fournier KF, et al. Varying malignant potential of appendiceal neuroendocrine tumors: importance of histologic subtype. *J Surg Oncol*. 2013;107(2):136-43.
18. Brathwaite S, Yearsley MM, Bekaii-Saab T, Wei L, Schmidt CR, Dillhoff ME, et al. Appendiceal Mixed Adeno-Neuroendocrine Carcinoma: A Population-Based Study of the Surveillance, Epidemiology, and End Results Registry. *Front Oncol*. 2016;6:148.
19. McGory ML, Maggard MA, Kang H, O'Connell JB, Ko CY. Malignancies of the appendix: beyond case series reports. *Dis Colon Rectum*. 2005;48(12):2264-71.
20. Benedix F, Reimer A, Gastinger I, Mroczkowski P, Lippert H, Kube R, et al. Primary appendiceal carcinoma--epidemiology, surgery and survival: results of a German multi-center study. *Eur J Surg Oncol*. 2010;36(8):763-71.

21. McCusker ME, Cote TR, Clegg LX, Sobin LH. Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973-1998. *Cancer*. 2002;94(12):3307-12.
22. Smeenk RM, van Velthuysen ML, Verwaal VJ, Zoetmulder FA. Appendiceal neoplasms and pseudomyxoma peritonei: a population based study. *Eur J Surg Oncol*. 2008;34(2):196-201.
23. Maggard MA, O'Connell JB, Ko CY. Updated population-based review of carcinoid tumors. *Ann Surg*. 2004;240(1):117-22.
24. Mullen JT, Savarese DM. Carcinoid tumors of the appendix: a population-based study. *J Surg Oncol*. 2011;104(1):41-4.
25. Marmor S, Portschy PR, Tuttle TM, Virnig BA. The rise in appendiceal cancer incidence: 2000-2009. *J Gastrointest Surg*. 2015;19(4):743-50.
26. van den Heuvel MG, Lemmens VE, Verhoeven RH, de Hingh IH. The incidence of mucinous appendiceal malignancies: a population-based study. *Int J Colorectal Dis*. 2013;28(9):1307-10.
27. Shaib WL, Goodman M, Chen Z, Kim S, Brucher E, Bekaii-Saab T, et al. Incidence and Survival of Appendiceal Mucinous Neoplasms: A SEER Analysis. *Am J Clin Oncol*. 2015.
28. Pape UF, Niederle B, Costa F, Gross D, Kelestimur F, Kianmanesh R, et al. ENETS Consensus Guidelines for Neuroendocrine Neoplasms of the Appendix (Excluding Goblet Cell Carcinomas). *Neuroendocrinology*. 2016;103(2):144-52.
29. Tchana-Sato V, Detry O, Polus M, Thiry A, Detroz B, Maweja S, et al. Carcinoid tumor of the appendix: a consecutive series from 1237 appendectomies. *World J Gastroenterol*. 2006;12(41):6699-701.
30. Lee WS, Choi ST, Lee JN, Kim KK, Park YH, Baek JH. A retrospective clinicopathological analysis of appendiceal tumors from 3,744 appendectomies: a single-institution study. *Int J Colorectal Dis*. 2011;26(5):617-21.
31. Charfi S, Sellami A, Affes A, Yaïch K, Mzali R, Boudawara TS. Histopathological findings in appendectomy specimens: a study of 24,697 cases. *Int J Colorectal Dis*. 2014;29(8):1009-12.
32. Simillis C, Symeonides P, Shorthouse AJ, Tekkis PP. A meta-analysis comparing conservative treatment versus acute appendectomy for complicated appendicitis (abscess or phlegmon). *Surgery*. 2010;147(6):818-29.
33. Livingston EH, Fomby TB, Woodward WA, Haley RW. Epidemiological similarities between appendicitis and diverticulitis suggesting a common underlying pathogenesis. *Arch Surg*. 2011;146(3):308-14.
34. Hansson J, Körner U, Ludwigs K, Johnsson E, Jönsson C, Lundholm K. Antibiotics as first-line therapy for acute appendicitis: evidence for a change in clinical practice. *World J Surg*. 2012;36(9):2028-36.
35. Lietzen E, Mallinen J, Gronroos JM, Rautio T, Paaajanen H, Nordstrom P, et al. Is preoperative distinction between complicated and uncomplicated acute appendicitis feasible without imaging? *Surgery*. 2016;160(3):789-95.
36. Sagebiel TL, Mohamed A, Matamoros A, Taggart MW, Doamekpor F, Raghav KP, et al. Utility of Appendiceal Calcifications Detected on Computed Tomography as a Predictor for an Underlying Appendiceal Epithelial Neoplasm. *Ann Surg Oncol*. 2017;24(12):3667-72.
37. Bennett GL, Tanpitukpongse TP, Macari M, Cho KC, Babb JS. CT diagnosis of mucocele of the appendix in patients with acute appendicitis. *AJR Am J Roentgenol*. 2009;192(3):W103-10.
38. Hines JJ, Paek GK, Lee P, Wu L, Katz DS. Beyond appendicitis; radiologic review of unusual and rare pathology of the appendix. *Abdom Radiol (NY)*. 2016;41(3):568-81.
39. Turaga KK, Pappas SG, Gamblin T. Importance of histologic subtype in the staging of appendiceal tumors. *Ann Surg Oncol*. 2012;19(5):1379-85.

Figure

**Figure 1.** Patient inclusion from The Finnish Cancer Registry (FCR) and The National Institute for Health and Welfare Registry (NIHW) between years 2007-2013.



\*Eight participating Finnish hospitals: University hospitals of Helsinki, Tampere, Turku, Kuopio, and Oulu, Central hospitals of Jyväskylä, Mikkeli, Lahti

Appendiceal tumor was found: ^Group 1: at surgery for suspected acute appendicitis,

†Group 2: at surgery done for other indications and °Group 3: at preoperative imaging

Table

Table 1. The Finnish Cancer Registry (FCR) database from 8 participating hospitals (n=472), patient demographics, clinicopathological characteristics and treatment regimens.

	Group 1 n=276	Group 2 n=142	Group 3 n=54	p
<b>Age, years</b>				<0.001
mean	45.7 ± 18.7	59.6 ± 15.2	59.2 ± 12.7	
range	9-94	11-97	27-85	
<b>Gender</b>				<0.001
Men	120 (43%)	40 (28%)	33 (61%)	
Women	156 (57%)	102 (72%)	21 (39%)	
<b>Preoperative imaging</b>	n=145 (53%)	n=94 (66%)	n=54 (100%)	<0.001
CT with iv contrast	105	78	48 (89%)	
CT without contrast	1	4	1 (2%)	
ultrasound	38	3	1 (2%)	
MRI	1	1	4 (7%)	
X-ray	-	7	-	
<b>Surgery</b>	n=276	n=142	n=51	<0.001
elective	35 (13%)	110 (77%)	49 (91%)	
emergency	241 (87%)	32 (23%)	2 (4%)	
no surgery	-	-	3 (5%)	
<b>Macroscopic tumor suspicion</b>	n=276	n=142	n=54	<0.001
no	244 (89%)	71 (50%)	6 (11%)	
yes	29 (11%)	65 (46%)	45 (83%)	
unclear*	3 (1%)	6 (4%)	3 (6%)	
<b>Operation</b>	n=276	n=142	n=51	<0.001
appendectomy	176 (64%)	61 (43%)	5 (9%)	
laparoscopic appendectomy	78 (28%)	17 (12%)	7 (13%)	
ileocecal resection	12 (4%)	19 (13%)	2 (4%)	
right hemicolectomy	8 (3%)	24 (17%)	17 (31%)	
HIPEC			6 (11%)	
other	2 (0.7%)	21 (15%)	14 (26%)	
<b>Acute appendicitis†</b>	n=276	n=142	n=54	<0.001
no	39 (14%)	127 (90%)	44 (81%)	
uncomplicated	142 (51%)	5 (3%)	1 (2%)	
complicated	93 (34%)	6 (4%)	3 (6%)	
unclear*	2 (0.7%)	4 (3%)	6 (11%)	
<b>Tumor histology</b>	n=276	n=142	n=54	<0.001
NET	167 (61%)	58 (41%)	7 (13%)	
MANEC, Goblet cell	36 (13%)	15 (11%)	1 (2%)	
adenocarcinoma	64 (23%)	42 (30%)	17 (31%)	
pseudomyxoma peritonei	9 (3%)	27 (19%)	29 (54%)	
<b>Metastasis†</b>	n=276	n=142	n=51	<0.001
no	225 (82%)	67 (47%)	9 (17%)	
local	10 (4%)	3 (2%)	5 (9%)	
disseminated	41 (15%)	72 (51%)	37 (69%)	
<b>Additional operation</b>	n=111 (40%)	n=41 (29%)	n=19 (35%)	<0.001
ileocecal resection	15		2	
right hemicolectomy	85	12	3	
HIPEC	6	20	6	
other	5	9	8	

Group 1: appendiceal tumor was found at surgery for suspected acute appendicitis,

Group 2: at surgery done for other indications, Group 3: at preoperative imaging

\*no histology or surgical report available, †based on histological and surgical classification

CT=computed tomography, MRI=magnetic resonance imaging, HIPEC= Hyperthermic Intra

Peritoneal Chemotherapy, NET=neuroendocrine tumor, MANEC= mixed adeno-neuroendocrine carcinoma

Table

Table 2. To estimate the risk of having appendiceal tumor among acute appendicitis patients, we compared patients with appendiceal tumor and acute appendicitis from FCR register data to patients with acute appendicitis diagnosis in NIHW register. Comparison was done between uncomplicated and complicated acute appendicitis, and uncomplicated acute appendicitis and complicated acute appendicitis presenting as periappendiceal abscess.

	Appendiceal tumor		Total <sup>^</sup>
	No <sup>o</sup>	Yes <sup>†</sup>	
<b>Uncomplicated appendicitis</b>	16927 (99.13%)	148 (0.87%)*	17075
<b>Complicated appendicitis</b>	3049 (96.76%)	102 (3.24%)*	3151
<b>Total</b>	<b>19976 (98.76%)</b>	<b>250 (1.24%)*</b>	<b>20226</b>
<b>Uncomplicated appendicitis</b>	16927 (99.13%)	148 (0.87%)*	17075
<b>Periappendiceal abscess</b>	1256 (95.01%)	66 (4.99%)*	1322
<b>Total</b>	<b>18183 (98.84%)</b>	<b>214 (11.63%)*</b>	<b>18397</b>

<sup>o</sup>NIHW register; <sup>†</sup>FCR register; <sup>^</sup>NIHW and FCR register patients; \*p<0.0001