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Retrospective case-control study to predict a potential underlying appendiceal tumor in an acute appendicitis context based on a CT-scoring system.

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Retrospective case-control study to predict a potential underlying appendiceal tumor in an acute appendicitis context based on a CT-scoring system.

Abbreviation list

NET: neuroendocrine tumor

PLR: positive likelihood ratio

NLR: negative likelihood ratio

SE: sensitivity

SP: specificity

LAMN: low appendiceal mucinous tumor

IRB: institutional review board

ROC: receiver operating characteristic

IQR: interquartile range

OR: odds-ratio

Highlights

- In an appendicitis context, a patient with an appendicolith is 3-fold less likely to have an appendiceal neoplasm than a patient without this incidental finding.
- Mural calcifications are the strongest positive predictive factor of an underlying tumor with an OR=47.
- Using a cutoff ≥ 1 , our diagnostic score has a positive likelihood ratio = 13.5 for an underlying tumor.

Key words: multidetector computed tomography; appendicitis; appendiceal neoplasms.

Abstract

OBJECTIVES: To assess CT signs to discriminate an appendiceal tumor versus a non-tumoral appendix in an acute appendicitis context.

METHODS: A 10-year bicentric retrospective case-control study was performed in adults. Patients with a histopathological appendiceal tumor and appendicitis were paired for age and sex with patients with non-tumorous appendicitis (1/3 ratio, respectively). Two senior radiologists blindly analyzed numerous CT findings with final consensus to perform univariate and multivariate statistical analyses. A diagnostic CT scan score was calculated with a bootstrap internal validation. Reproducibility was assessed based on the kappa statistic.

RESULTS: A total of 208 patients (51 +/- 21 years; 114 males) were included (52 patients in the tumor group and 156 in the non-tumor group). In the multivariate analysis, an appendicolith and fat stranding were protective factors with OR = 0.2 (p = 0.01) and OR = 0.3 (p = 0.02), respectively, while mural calcifications (OR = 47, p = 0.0001), an appendix mass (OR = 7.1, p = 0.008), a focal asymmetric wall abnormality (OR = 4.9, p = 0, 001), or a ≥ 15 mm diameter (OR = 3.5, p = 0.009) were positive predictive factors of an underlying tumor. Using a ≥ 1 cut-off, our diagnostic score had an AUC = 0.87 (95% CI, 0.82-0.93) and a positive likelihood ratio = 13.5 (95% CI, 6.7-27.1).

CONCLUSION: We developed a reliable scoring system based on CT findings, which is highly predictive of an underlying appendiceal neoplasm in an appendicitis context using a ≥ 1 cut-off.

Main body

I. Introduction

The appendiceal tumor incidence on appendectomy specimens from patients presenting with acute appendicitis ranges from 0.9% to 1.7% (1,2). Acute appendicitis is the initial clinical presentation of primary neoplasms of the appendix in about 40-50% of cases, generally due to occlusion of the appendiceal lumen by the tumor (1,3). Appendiceal tumors can be benign or malignant (4) and classified in two main groups: epithelial and neuroendocrine tumors (NET). A recent review of the literature (5) revealed that the neoplasm rate may range from 10% to 29% in patients presenting with complicated appendicitis (phlegmon or abscess). The ideal treatment approach in that context is still controversial. There are, for instance, proposals for indirect non-surgical treatment (percutaneous drainage and antibiotics). When conservative treatments have a positive initial outcome, there is often a dilemma as to whether or not to perform an interval appendectomy or maintain a nonoperative approach. Yet not subjecting the appendix to histological analysis is the main disadvantage of the latter. Mällinen *et al.* (6) argued in favor of routine interval appendectomy in this setting given the high rate of underlying neoplasm (20%) they found in their randomized trial comparing interval appendectomy and MRI follow up. Nonoperative management is also a therapeutic alternative to surgery when the patient presents with uncomplicated appendicitis (7). It is thus of paramount importance to forewarn the surgeon when there is suspicion of an underlying tumor so as to accurately target the treatment (8). A major virtue of preoperative detection of an appendiceal tumor is that—instead of having to manage the situation under emergency conditions—it provides an opportunity to schedule surgery during working hours when a trained oncological surgeon may be available. Forewarning the surgeon is especially crucial in such cases to avoid peroperative perforation of the appendix, which could affect the prognosis by increasing the risk of recurrence. The quality of the primary excision (including mesoappendix resection) and the absence of mucin in the abdominal cavity at the end of the surgery are the main prognostic factors (4, 9–11).

Preoperative diagnosis of an appendicular tumor in an appendicitis context is quite challenging for both the surgeon and radiologist (12,13). **In the literature, there is**

no case – control study assessing predictive values of CT features for diagnosing potential underlying appendiceal tumor.

Our study was thus focused on assessing exhaustive CT signs to be able to discriminate an appendiceal tumor versus a non-tumoral appendix in an acute appendicitis context. We aimed to build a predictive diagnostic scoring system to be able to forewarn surgeons on the likelihood of an underlying tumor.

II. Materials and methods

A. Patient selection

This retrospective bicentric study was approved, and informed consent was waived, by our institutional review board (IRB) (N°2018_IRB-MTP_04-07).

We ran a retrospective case-control study based on data from two French tertiary referral hospitals (Lapeyronie University Hospital in Montpellier and Saint Joseph's Hospital in Paris). From amongst all appendectomies performed on adults over a decade (January 2007 to December 2017) based on findings from the pathology department and medical information department databases at each center, we selected consecutive adult patients (> 18 years old) presenting with an appendiceal neoplasm ('tumor' group). Among a total of 4,244 appendectomies (2,170 in Montpellier and 2,074 in Paris), 187 patients (4.4%) had an appendiceal neoplasm (98 patients in Montpellier and 89 patients in Paris). The inclusion criteria for patients in the 'tumor' group were: patients admitted for a) a right lower abdominal pain, who had undergone b) a preoperative CT with intravenous contrast material and who were diagnosed as having c) an appendicitis with an appendiceal neoplasm (including non-neoplastic appendiceal mucinous lesions) at histopathology examination. Patients less than 18 years old, or who had not undergone CT examination or who presented with an incidentally diagnosed appendicular tumor without abdominal pain, were not eligible. Among the 187 patients with an appendiceal tumor, 111 (59%) were excluded because they had not undergone preoperative CT and 24 (13%) were excluded because they did not have pain (Fig. 1). Finally, 52 patients (28%) were included in the tumor group (25 patients in Montpellier and 27 in Paris).

The control group subjects ('non-tumor' group, n=4057) were selected from the same period, as recommended (14), as follows: patient admitted for a) a right lower

abdominal pain investigated by b) preoperative CT with intravenous contrast material and with a diagnosis of c) appendicitis without neoplasm at pathology examination. One of the authors (BM, junior radiologist with 5 years' experience) reviewed the electronic medical charts of the selected patients and matched three control subjects for each case patient as follows: subjects in the non-tumor group were sorted according to age, gender and then the date of the CT examination, starting with the most recent CT. For each patient in the tumor group, the author (BM) manually selected the first three patients of the same gender and age (same age at the date of the CT), in the sorted non-tumor group database, who had undergone CT within the same year or no more than a year's delay to that of the tumor patient. This procedure was repeated to obtain 156 control subjects.

All patients (tumor and non-tumor group, n=208) were then anonymized and randomly assigned on a joint file to enable a blinded review.

All clinical (age, gender), surgical (type of surgery, complication) and pathological (tumor type, type of appendicitis) data of the included patients were recorded by the same author (BM). A complicated appendicitis was defined if the following words were used in the description of appendicitis in the histological and/or the surgical reports: "perforation", "perforated", "gangrenous", "abscess" or "phlegmon".

B. Imaging techniques

CT scans were performed at the two centers using a 64-detector row machine (Lightspeed VCT 64; General Electric Medical Systems, Milwaukee, Wis) with 1.375 pitch, 0.7 ms tube rotation time, 120 kVp and dose-modulation software to determine the milliamperere-second value on the basis of body weight (noise index, 20; 130–700 mA).

Images were acquired from the dome of the liver through the pubis with infra-millimetric slices (0.675 mm) to enable multiplanar reconstruction. CT images were also reconstructed at 3-mm section thickness in the axial, coronal and sagittal planes.

All CT scans were performed with intravenous iodinated contrast agent, i.e. lobitridol (Xenetix 300, Guerbet, Aulnay-sous Bois, France), lomeprol (Iomeron 300, Bracco Imaging, France), or Iopromide (Ultravist 300, Bayer Healthcare, Lerverkusen, Germany) administered with a power injector at 2-3 mL/s during the portal venous phase (70-80 s delay). Unenhanced CTs were also available for 60 patients (29%). Few CT scans were acquired with colorectal enema (n=11 (5%)). No oral contrast was given.

C. Imaging review

CTs were reviewed independently by two blinded readers who are senior radiologists specialized in emergency radiology (CO, MD with 7 years of experience and PT, MD with 30 years of experience) on a dedicated picture archiving and communication system unit (Centricity PACS, General Electric Healthcare). Multiplanar reconstructions were available in the axial, coronal and sagittal planes. We provided guidelines for the readers reviewing the CT scans to help them understand all of the radiologic signs based on scans from five patients who were not included in the final study. The readers were blinded to the surgical and pathological outcomes but they were aware that all CT examinations involved patients with appendicitis.

Interpretation discrepancies were resolved by consensus by a senior emergency radiology specialist (IM, MD with 12 years of experience) for the purpose of the statistical analyses.

The two readers assessed the CT images for the following signs: (a) appendix maximal transversal diameter; (b) periappendiceal fat stranding; (c) appendicolith; (d) appendix mural curvilinear calcification (15); (e) appendix content (air, liquid or mixed); (f) ileocaecal lymph nodes with a short axis diameter > 8 mm; (g) focal asymmetrical wall abnormality involving either a focal wall irregularity or a focal hyper-enhancement (Fig. 2); (h) appendix mass characterized by an enlargement of the appendix with complete loss of its normal tubular shape (16) (Fig. 2); (i) appendix diverticulum viewed as a rounded, para-appendicular outpouching; (j) local complications such as perforation (free intraperitoneal gas or loss of appendix wall enhancement) or abscess (Fig. 2); (k) wall thickening of the cecum and/or the ileum with a wall thickness > 3 mm; (l) CT signs of peritonitis reflected by a thickened and enhanced peritoneal layer; (m) intraperitoneal free fluid; or (n) malignant peritoneal involvement reflected by enhanced nodes suggesting peritoneal carcinomatosis.

The readers were finally asked to answer the question: Do you think there could be an underlying tumor? They were asked to grade their answer from 1 to 5 (1: no, there's no tumor, 2: it is unlikely, 3: I don't know, 4: it is likely, and 5: yes, there's an underlying tumor).

D. Statistical analysis

Interobserver agreement for qualitative CT findings was determined with the κ statistic and classified as follows: $\kappa=0-0.2$, slight agreement; $\kappa=0.21-0.4$, fair agreement; $\kappa=0.41-0.6$, moderate agreement; $\kappa=0.61-0.8$, substantial agreement; and

$\kappa=0.81-1$, almost perfect agreement (17). Disagreements for categorical variables between the two readers were resolved by consensus. Consensual data were then used for the final statistical analysis.

Reproducibility between continuous variables was assessed using the intra-class correlation coefficient. Average of the measurements between the two readers was used for final statistical analysis.

We compared CT signs between patients with an appendiceal tumor (tumor group) and those without tumor (non-tumor group). Pearson Chi square or Fisher tests were used for comparison of categorical variables, and Student t test or Wilcoxon rank-sum test for comparison of continuous variables, as appropriate. The diagnostic performances (sensitivity, specificity, likelihood ratio) of each CT finding were also calculated. Cutoffs for significant continuous variables were identified by plotting receiver operating characteristic (ROC) curves and computing the Youden index to ensure relevance for input in a multivariate model.

All CT findings with a univariate p value ≤ 0.2 were input in a multivariate logistic regression model to gauge their independent association with an appendiceal tumor. A stepwise procedure was used to select the final model. We established a diagnostic score using the Beta/Sullivan technique to assign a rounded up numerical value to each of the significant CT findings included in the final prediction model, in relation to their β parameter (logistic regression estimates) (18,19). Then, for each patient, we were able to calculate a score corresponding to the sum of the number assigned to each variable present in the model. A ROC curve was plotted to estimate the best cut-off of this model for differentiating tumor group from non-tumor group, and its diagnostic performances. We used the bootstrap method to internally validate the score by sampling with replacement for 1,000 iterations. We compared the obtained diagnostic score AUC with that of each of the readers' subjective scores using the DeLong test.

Statistical significance for all tests was set at $p < 0.05$. SAS version 9.4.4 software (SAS Institute, Cary, NC, USA) and R version 3.4.4 software (R Foundation for Statistical Computing, Vienna, Austria, 2018) were used to perform the statistical analyses.

III. Results

A. Population

A total of 208 patients (94 females (45%), 114 males (55%)) were included in the study. The mean age of the population was 51 years (SD=21 y) with a median of 52 years (range = 18-94) and an interquartile range (IQR) = [34-66].

The tumor group (n=52) included 10 adenocarcinomas (19%), 26 mucinous lesions (50%) (16 LAMN, 4 serrated polyps and 6 non-neoplastic appendiceal mucinous lesions), 13 neuroendocrine tumors (25%), 2 goblet cell tumors (4%) and 1 lymphoma (2%).

Size of the tumor was not reported on all the pathology reports (35 missing data). Among the available data (N=17, 33%), mean size of adenocarcinomas was 18 mm (N=4), of mucinous lesion (LAMN) was 62 mm (N=3), of neuroendocrine tumors was 10.6 mm (N=9) and of goblet cell tumor was 15 mm (N=1).

The surgical findings are reported in Table 1. Among the 13 patients (25%) in the tumor group that had an additional surgery, 8 (61%) had undergone a right hemicolectomy.

B. Univariate comparison of CT findings between the tumor and non-tumor groups

Comparison and diagnostic performances of the CT signs between the tumor and non-tumor groups are reported in Tables 2 and 3.

Mural calcification and appendiceal mass were the two leading CT signs that predicted an underlying appendiceal tumor, with PLR=13.5 (95% CI, 3-60) and PLR=18 (95% CI, 5.86-61), respectively. We noted mural calcifications in 7/38 (18%) of our epithelial tumors, accounting for 78% (7/9) of all of the appendiceal tumors with calcifications. The other two patients with mural calcifications had neuroendocrine tumors.

Some CT signs such as malignant peritoneal involvement was not significant (p=1). Only one subject from the non-tumor group presented with this sign unrelated to acute appendicitis but to a known left colon cancer. In our cohort, no patients from the tumor group showed malignant peritoneal involvement.

Focal asymmetric wall abnormality of the appendix and/or a mass were detected respectively in 9/10 (90%) and 7/10 (70%) of adenocarcinoma cases, 11/26 (42%) and 6/26 (23%) of the mucinous lesions while both signs were found in 5/13 (38%) of the NET cases.

The mean appendix diameter of the 208 patients was 14.3 mm (± 7.8). In the tumor group (n=52), the median appendix diameter was 15 mm (range = 7 - 63) with an interquartile range (IQR) = [11-27], whereas in the non-tumor group (n=156), the median appendix diameter was 12 mm (range = 6 - 24) with an IQR = [10-14] ($p < 0.0001$). Using the ROC curve, the best cutoff for discriminating a tumorous vs. a non-tumorous appendix was set at 15 mm.

A. Multivariate analysis and diagnostic score

All the multivariate analysis results are reported in Table 4.

Fat stranding and the presence of an appendicolith emerged as protective factors of appendiceal neoplasm, with OR=0.28 ($p=0.0228$) and OR=0.22 ($p=0.144$), respectively. Four other CT signs remained positive predictive factors of an underlying tumor, including two major signs, i.e. mural calcification (OR=47.05; $p=0,0001$) and appendiceal mass (OR=7.1; $p=0.0082$).

The mathematical cutoff leading to the best diagnostic performance was found to be at 0.5. Consequently, a score of ≥ 1 would suggest the possible presence of an underlying appendiceal tumor (Fig. 3). The ROC curve plotted on the basis of our scoring system showed an AUC of 0.88 (95% CI, 0.83-0.93) (Fig. 4).

Using a cutoff ≥ 1 , our score had 69% sensitivity (95% CI, 57-82), 95% specificity (95% CI, 91-98), 13.5 PLR (95% CI, 6.7-27.1) and 0.3 NLR (95% CI, 0.2-1) in our cohort (Fig.5). The internal bootstrap validation of our score gave an AUC of 0.87 (95% CI, 0.82-0.93).

B. Subjective diagnostic performances of the blinded readers

The analysis of the two blinded readers' answers to the question "Do you think there could be an underlying tumor?" showed that the AUC for Readers 1 and 2 were 0.759 (95% CI, 0.689-0.829) and 0.762 (95% CI, 0.679-0.844), respectively.

Subjective diagnostic performances of the two readers were less accurate than the diagnostic performances of our diagnostic score (AUC = 0.88) with $p=0.001$ for reader 1 and $p=0.002$ for reader 2.

C. Inter-observers' agreement

All the reproducibility results were reported in Table 2.

The concordance between the two blinded readers was excellent for most of the defined CT signs, especially for the six signs included in our diagnostic score, with kappa statistic ranging from 0.75 to 1 (substantial to almost perfect agreement).

IV. Discussion

Our results suggested that CT is a reliable technique for predicting underlying tumors of the appendix in an inflammatory appendiceal setting. We developed an accurate CT diagnostic score that outperformed readers' subjective assessments using six reliable CT findings (mural calcification, mass, focal asymmetric wall abnormality, appendix diameter ≥ 15 mm, fat stranding and appendicolith), while achieving a high diagnostic performance (AUC=0.88) and high positive likelihood ratio (PLR=13.5), implying that it could have a substantial impact with regard to clinical decisions. When the score is greater or equal to 1, the radiologist should warn the surgeon for performing an appropriate resection including especially the whole mesoappendix, and at times a cecotomy or even a hemicolectomy. The option between an open surgery vs. a laparoscopy should be discussed in that context.

This was the first study to our knowledge to assess diagnostic values of CT findings for an appendix tumor in an acute appendicular setting while including a control group. Pickhardt *et al.* (3), in a series of 22 appendiceal tumors revealed by appendicitis and screened by preoperative CT, did not include a control group (i.e. inflamed appendix without tumor), which is essential for calculating predictive values. Moreover, their results were not based on predictive statistics but rather on subjective assessments and the CT readers were aware that each patient had a proven appendiceal tumor, thus biasing the CT analysis. Given the low prevalence of appendiceal tumors in an appendicitis context (less than 2% 1,2), the fact that a high number of patients with a neoplastic appendix were included was a major feature of our study. Indeed, there were half as many patients (17 and 22 patients, respectively) in the retrospective cohorts of appendix tumors (3,13) that were explored by CT in an appendicitis setting, and all other studies just dealt with appendectomy cohorts

regardless of the clinical symptoms. We opted to include non-neoplastic appendiceal mucinous lesions (i.e. mucocèles) in the tumor group because they must be resected to ensure the absence of underlying serrated polyps or dysplasia (20-21). Mucocèles result from chronic luminal obstruction and, like other appendicular tumors, require cautious and careful surgical care to avoid per-operative perforation.

Appendiceal neoplasms are a challenge for radiologists as they mimic acute appendicitis, so it is crucial to provide radiologists with simple tools that could reveal the potential presence of a tumor. Non-operative treatment is now the standard care in many acute infectious abdominal pathologies (cholecystitis, perforated diverticulitis, tubo-ovarian abscess, etc.) that were previously treated surgically. This decreased frequency of surgery raises concern since fewer incidental and early-stage cancers will be diagnosed. Although many appendiceal tumors can have an indolent course, there is still a risk of peritoneal dissemination and cancer-related mortality (22). The tumor location, depth, dimensions and possible invasion of the mesoappendiceal region are key factors for calculating the disease recurrence or progression rate (23). In our study, 25% of patients in the tumor group required further surgery, including 61% of whom required a right colectomy. It is therefore crucial to forewarn surgeons to enable them to perform a complete mesoappendiceal resection with simultaneous full examination of the small bowel and peritoneal cavity, thus avoiding the need for subsequent exploratory surgery to detect peritoneal tumor extension (24).

Predicting the occurrence of an adverse event or outcome is a major issue in clinical medicine. Clinical prediction models and associated points-based risk-scoring systems are popular statistical methods for describing the relationship between a multivariable set of patient risk factors and the risk of occurrence of an adverse event, which can facilitate medical decision making. We developed a diagnostic score based on CT findings as CT is the first-line imaging technology used most widely to investigate suspicion of appendicitis in adults. We performed a paired-study on age and gender in order to assess the independent relationship between the CT aspect of appendicitis and the risk of an underlying neoplasm regardless the patient age. Interestingly, we did not corroborate the association between complicated appendicitis and an underlying neoplasm as the complication rate was similar in the two groups (17.3% in the tumor group and 25.6% in the non-tumor group). The positive likelihood ratio of a tumor in a complicated appendicitis setting was very low (0.87) in our study, which is much too low

to alone indicate the need for specific care. Age is clearly a confounding factor with regard to the risk of an underlying tumor in a complicated appendicitis context, as pointed out by Mällinen *et al.* (6) and Loftus *et al.* (13). The worrisome prevalence of an underlying tumor found in previous study conducted to assess the risk of a hidden malignant tumor in a complicated appendicitis setting was probably due to the higher rate of complicated appendicitis in older patients, which prompted the authors to include a high number of advanced age patients (5). They thus found a very high tumor rate, but regardless the age, a complicated appendicitis has an equal chance of being tumorous or not. Hence it is crucial to look for other CT findings predictive of a neoplasm.

Among the significant CT findings with regard to our diagnostic score, we corroborated the relevance of the 15 mm diameter cut-off for suspicion of an underlying appendiceal tumor, as previously reported by Pickhardt *et al.* (3). One point was assigned to this CT finding with our diagnostic score, that is sufficient to consider an underlying appendix neoplasm but if this sign is associated with an appendicolith then the total score is no longer suspicious for an underlying neoplasm. The PLR of an underlying tumor when there is an appendicolith was shown to be at 0.33 in our study, indicating that a patient with an appendicolith was approximately 3-fold less likely to have an appendiceal neoplasm than a patient without an appendicolith. An appendicolith causes appendiceal obstruction, leading to mucus stasis, appendix distension and infection whereas when no appendicolith is present a tumor is more likely to be the cause of the lumen obstruction leading to appendicitis. Furthermore, Marotta *et al.* (20) in their retrospective study including only mucoceles but not in an inflammatory context, showed that distal dilatation of the appendix with a normal segment of the appendix between the base of the appendix and the beginning of the mucocele, without appendicolith, was more related to an underlying neoplasia (87% at histopathology) than to non-neoplastic mucocele.

Unsurprisingly, mural calcifications were closely associated with an appendix neoplasm (OR=47.6). Mural calcifications arise from fibrous reorganization or tumoral necrosis. Mural calcifications are not specific to any kinds of appendicular tumor, although they seem to be more frequent in epithelial tumors (7/9 in our series), especially in well-differentiating mucinous neoplasms (LAMN). Sagebiel *et al.* (15) showed that 31.9% of their patients with epithelial tumors had wall calcifications, with

the majority being peripheral eggshell calcifications, i.e. a pattern that differs from coarse calcifications that can potentially be mistaken for a luminal stercolith.

Furthermore, we found that an appendicular mass was associated with an underlying tumor with an OR=7.1, which was consistent with the findings of previous study (13), as well as with a focal asymmetric wall abnormality (OR = 4.86). In our study, 70% of adenocarcinomas displayed as a mass and 90% of them had a focal asymmetric wall abnormality, suggesting that these patterns are more likely to be associated with malignant epithelial tumors. Moreover, adenocarcinomas in other intestinal locations display similar features and the CT diagnosis is based on the presence of irregular asymmetric bowel wall thickening or masses with exoluminal growth.

Our study had several **limitations**. The first one was related to its retrospective design, which can bias diagnostic performance assessment as retrospective reads have been shown to be more accurate than prospective reads (25). We performed a retrospective study because of the low appendiceal neoplasm prevalence, which precludes prospective inclusion. The tumor prevalence (4.4%) in our whole eligible population was slightly higher than in other series (1-2,26), probably due to the exclusion of pediatric patients, consequently boosting the appendiceal tumor rate. This latter may also have been biased by the inclusion of patients explored by CT, potentially more severe than those explored by ultrasound. **In our practice, ultrasound remains the primary imaging tool in cases of suspected appendicitis for young non-obese patients with low biologic inflammatory signs and for pregnant women. For the other cases or when there are atypical findings or signs of complicated appendicitis using ultrasound, we usually perform directly an abdominal and pelvic CT.** The retrospective design allowed us to increase the number of patients in the tumor group and thus the statistical power, but at the cost of a large number of missing data especially regarding the CT images availability (more than 50% of the eligible patients had not undergone a preoperative CT and were thus excluded). Nevertheless, patients in our tumor group had a median age of 52 years (IQR=34-66), which was in line with that reported in a similar published study where a median age of 53 years (IQR=35-61) was reported (13).

Second, some groups of appendicular tumors were underrepresented. For example, we included only one lymphoma and two goblet cell tumors. However, the

proportion of each tumor type was similar to the proportions reported in previous studies (3,27), with a majority of epithelial and neuroendocrine tumors, along with a few other types.

Third, the tumor prevalence was artificially raised to 25% in our study cohort as we matched three control subjects to one tumorous appendix. We therefore decided to report likelihood ratios and not predictive values as diagnostic performance measures are independent of the disease prevalence.

Finally, our diagnostic performance estimates may have been biased since we used the same data to come up with the thresholds. The AUC was also estimated from the same data used to develop the model, and was likely an optimistic estimate. These findings thus need to be validated in future studies on other external samples.

V. Conclusion

We developed a reliable scoring system based on CT findings, which was highly predictive of an underlying appendiceal neoplasm in an appendicitis context. The surgeon should be warned as to the positive likelihood of an underlying appendiceal tumor when the CT score is equal to or greater than 1, thus providing an opportunity for appropriate care.

References

1. Connor SJ, Hanna GB, Frizelle FA. Appendiceal tumors: retrospective clinicopathologic analysis of appendiceal tumors from 7,970 appendectomies. *Dis Colon Rectum*. 1998;41(1):75–80.
2. Marudanayagam R, Williams GT, Rees BI. Review of the pathological results of 2660 appendicectomy specimens. *J Gastroenterol*. 2006; 41(8):745–749.
3. Pickhardt PJ, Levy AD, Rohrmann CA, Kende AI. Primary Neoplasms of the Appendix Manifesting as Acute Appendicitis: CT Findings with Pathologic Comparison. *Radiology*. 2002;224(3):775-81.
4. Carr NJ, Bibeau F, Bradley RF, Dartigues P, Feakins RM, Geisinger KR, et al. The histopathological classification, diagnosis and differential diagnosis of mucinous appendiceal neoplasms, appendiceal adenocarcinomas and pseudomyxoma peritonei. *Histopathology*. 2017;71(6):847-58.

5. Teixeira FJR Jr, Couto Netto SDD, Akaishi EH et al. 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.
6. Mällinen J, Rautio T, Grönroos J et al. Risk of Appendiceal Neoplasm in Periappendicular Abscess in Patients Treated With Interval Appendectomy vs Follow-up With Magnetic Resonance Imaging: 1-Year Outcomes of the Peri-Appendicitis Acuta Randomized Clinical Trial. *JAMA Surg.* 2019;154(3):200-207.
7. Salminen P, Tuominen R, Paajanen H, et al. Five-Year Follow-up of Antibiotic Therapy for Uncomplicated Acute Appendicitis in the APPAC Randomized Clinical Trial. *JAMA.* 2018;320(12):1259-1265.
8. McCutcheon BA, Chang DC, Marcus LP, et al. Long-Term Outcomes of Patients with Non-Surgically Managed Uncomplicated Appendicitis. *J Am Coll Surg.* 2014;218(5):905-13.
9. Clift AK, Kornasiewicz O, Drymoussis P, et al. Goblet cell carcinomas of the appendix: rare but aggressive neoplasms with challenging management. *Endocr Connect.* 2018;7(2):268-77.
10. Shaib WL, Assi R, Shamseddine A, et al. Appendiceal Mucinous Neoplasms: Diagnosis and Management. *The Oncologist.* 2017;22(9):1107-16.
11. Bartlett DJ, Thacker PG, Grotz TE, et al. Mucinous appendiceal neoplasms: classification, imaging, and HIPEC. *Abdom Radiol (NY).* 2019;44(5):1686-1702.
12. Bhangu A, Søreide K, Di Saverio S, Assarsson JH, Drake FT. Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. *The Lancet.* 2015;386(10000):1278-87.
13. Loftus TJ, Raymond SL, Sarosi GA, et al. Predicting appendiceal tumors among patients with appendicitis: *J Trauma Acute Care Surg.* 2017;82(4):771-5.
14. Schulz KF, Grimes DA. Case-control studies: research in reverse. *Lancet.* 2002;359(9304):431-4.
15. Sagebiel TL, Mohamed A, Matamoros A, 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.

16. Lee KS, Tang LH, Shia J, et al. Goblet cell carcinoid neoplasm of the appendix: clinical and CT features. *Eur J Radiol.* 2013;82(1):85-9.
17. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics.* 1977;33(1):159–74.
18. Sullivan LM, Massaro JM, D’Agostino RB. Presentation of multivariate data for clinical use: The Framingham Study risk score functions. *Stat Med.* 2004;23(10):1631-60.
19. Mehta HB, Mehta V, Girman CJ, Adhikari D, Johnson ML. Regression coefficient–based scoring system should be used to assign weights to the risk index. *J Clin Epidemiol.* 2016;79:22-8.
20. Marotta B, Chaudhry S, McNaught A, Quereshy F, Vajpeyi R, Chetty R, Ghai S. Predicting Underlying Neoplasms in Appendiceal Mucoceles at CT: Focal Versus Diffuse Luminal Dilatation. *AJR* 2019 Aug;213(2):343-348.
21. Wang H. et al. Appendiceal Mucocele: A Diagnostic Dilemma in Differentiating Malignant From Benign Lesions With CT. *AJR* 2013; 201 : 590-595.
22. Overman MJ, Fournier K, Hu CY, et al. Improving the AJCC/TNM staging for adenocarcinomas of the appendix: the prognostic impact of histological grade. *Ann Surg.* 2013;257(6):1072-8.
23. Alexandraki KI, Kaltsas GA, Grozinsky-Glasberg S, Chatzellis E, Grossman AB. Appendiceal neuroendocrine neoplasms: diagnosis and management. *Endocr Relat Cancer.* 2016;23(1):R27-41.
24. Pape UF, Perren A, Niederle B, et al. ENETS Consensus Guidelines for the management of patients with neuroendocrine neoplasms from the jejunum-ileum and the appendix including goblet cell carcinomas. *Neuroendocrinology.* 2012;95(2):135-56.
25. Sheedy SP, Earnest F 4th, Fletcher JG, Fidler JL, Hoskin TL. CT of small-bowel ischemia associated with obstruction in emergency department patients: diagnostic performance evaluation. *Radiology.* 2006;241(3):729-736.
26. Lietzén E. Appendiceal neoplasm risk associated with complicated acute appendicitis—a population based study. *Int J Colorectal Dis.* 2019;34(1):39-46.
27. Dupre MP, Jadavji I, Matshes E, Urbanski SJ. Diverticular disease of the vermiform appendix: a diagnostic clue to underlying appendiceal neoplasm. *Hum Pathol.* 2008;39(12):1823-6.

Legends:

Table 1: Surgical findings according to the tumorous status of the appendix.

Table 2: CT characteristics in the whole population (208 patients) and univariate comparison between the tumor and non-tumor groups with interobserver agreement.

Table 3: Diagnostic performance of each CT sign for an appendiceal tumor.

Table 4: Significant CT findings in the multivariate analysis for predicting the presence of an underlying appendiceal neoplasm in an acute appendicitis context with their appropriate points in the final score based on the β parameter in the statistical analysis.

Figure 1: Flow chart of patients included in the tumor group (n=52 patients)

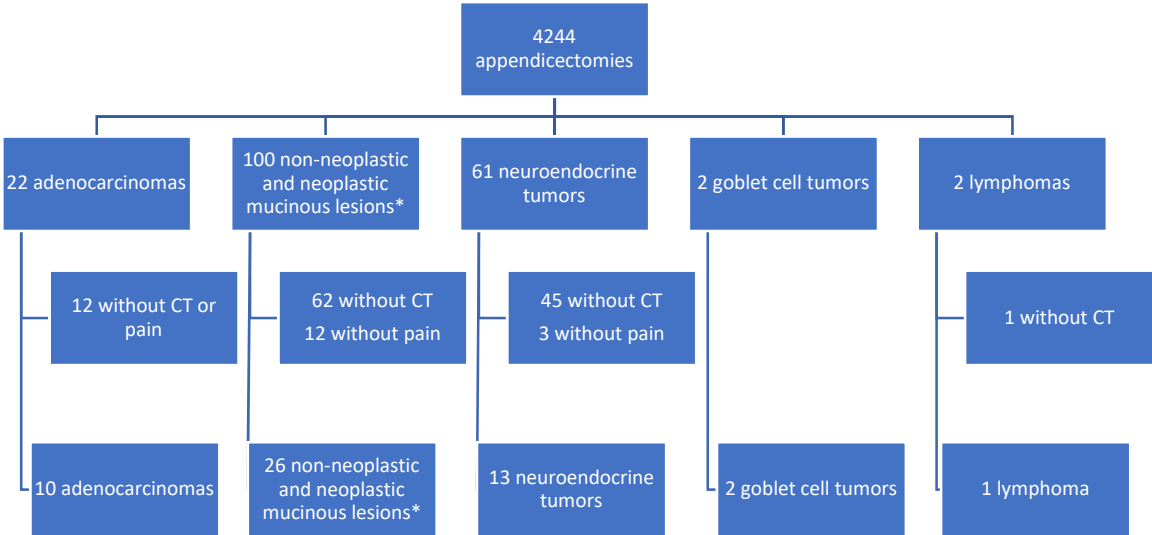
Figure 2: Illustration of some specific CT findings that were assessed. All CT images obtained in a portal-venous phase. A (coronal) = Appendicular mass (arrow), final diagnosis was a lymphoma; B (axial) = Focal asymmetric wall abnormality of the appendix (arrow); final diagnosis was goblet cell tumor. C (coronal) = Complicated appendicitis with perforation with free gas (arrow) and a stercolith (arrow-head) at the appendix basis, final diagnosis was a non-tumorous appendix; D (sagittal) = Complicated appendicitis with abscess, note the stercolith (arrow-head) and the appendix basis (arrow), final diagnosis was a non-tumorous appendix.

Figure 3: Success of the CT diagnostic score in a 45-year-old patient. Axial plane and portal phase. Note the dilated appendix greater than 15 mm (arrow) counting for 1 point, and an intra luminal mass within the dilated appendix (arrowhead) counting for 2 points. Then, the total CT score is equal to 3 and an underlying neoplasm should be considered. Final histology diagnosed both a serrated polyp that probably have led to the intra luminal mucoid secretion, and an associated carcinoid tumor corresponding to the intra luminal mass.

Figure 4: ROC curve of the CT diagnostic score (AUC = 0.88).

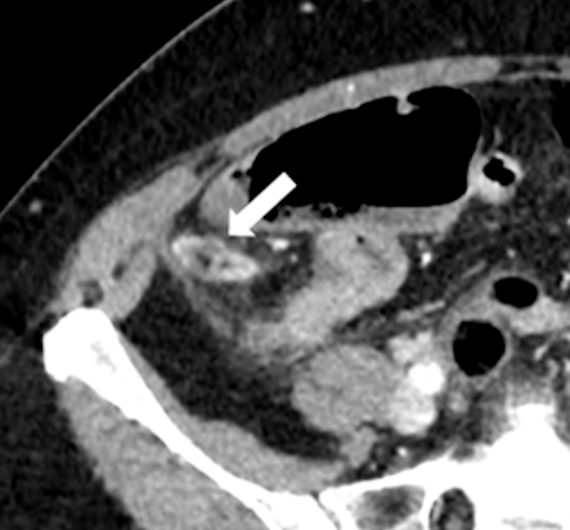
Figure 5: A perforated appendicitis in a 56-year-old patient with a CT diagnostic score < 1, thus ruling out an underlying neoplasm. Axial oblique plane and portal phase. The appendix (arrow) has a diameter greater than 15 mm (arrowhead) counting for 1 point and a peripheral fat stranding counting for -1 point, thus the total score is equal to zero. Final histology corroborated the absence of an appendiceal tumor.

Fig 1: Flow chart of patients included in the tumor group (n=52 patients)

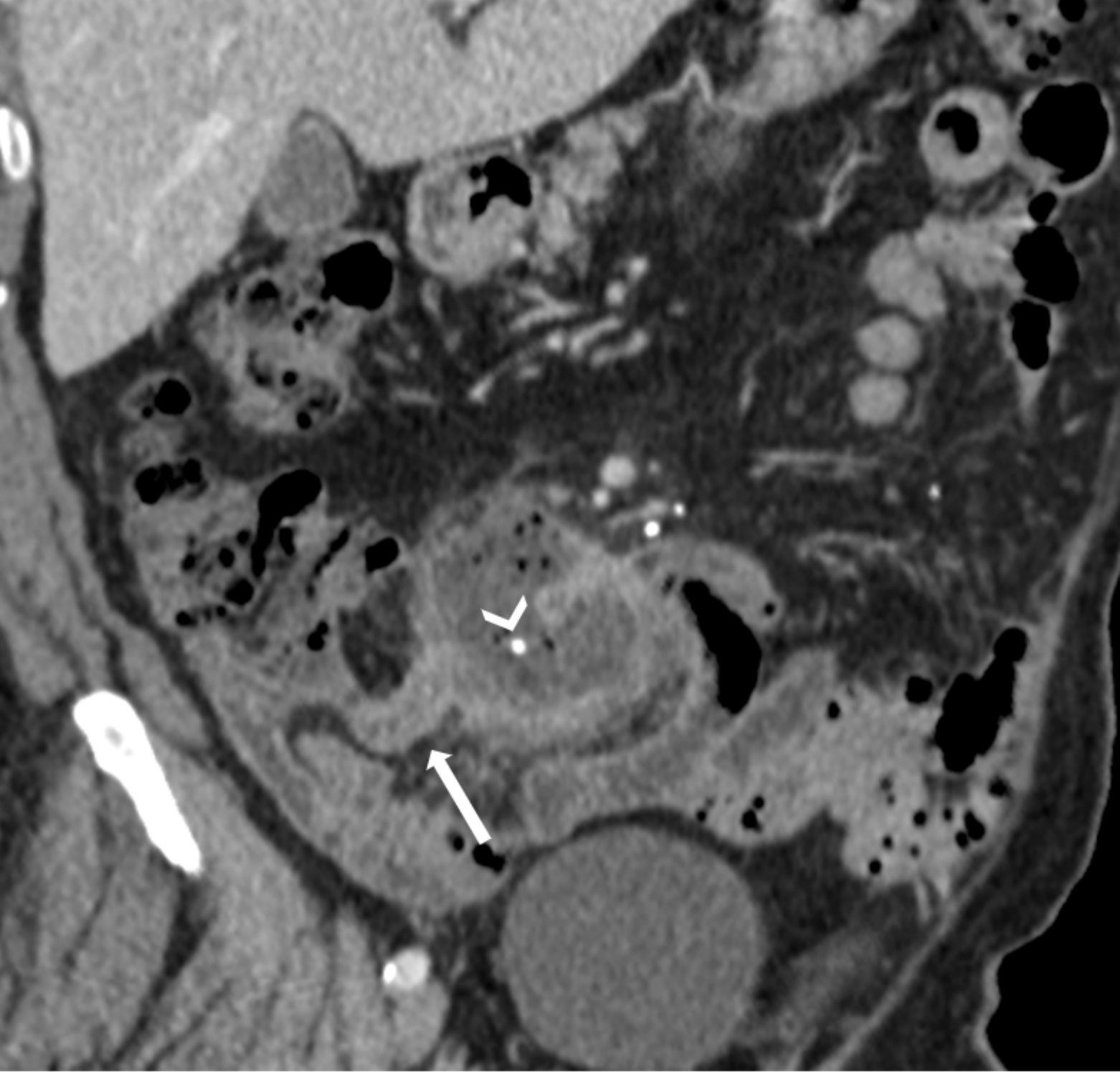


* Non-neoplastic mucinous lesions correspond to mucocele; neoplastic mucinous lesions correspond to serrated polyps or noninvasive mucinous appendiceal neoplasms (LAMN).

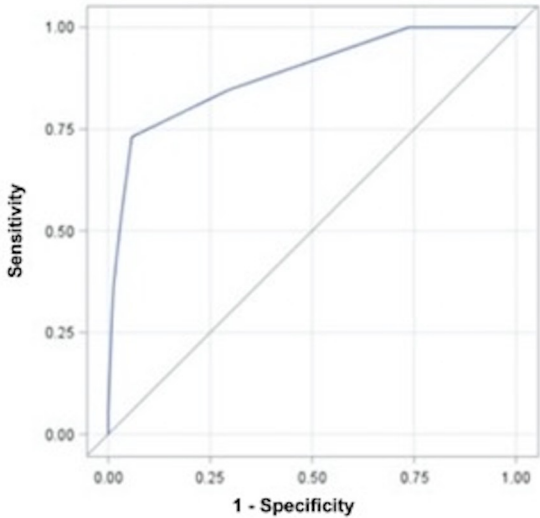












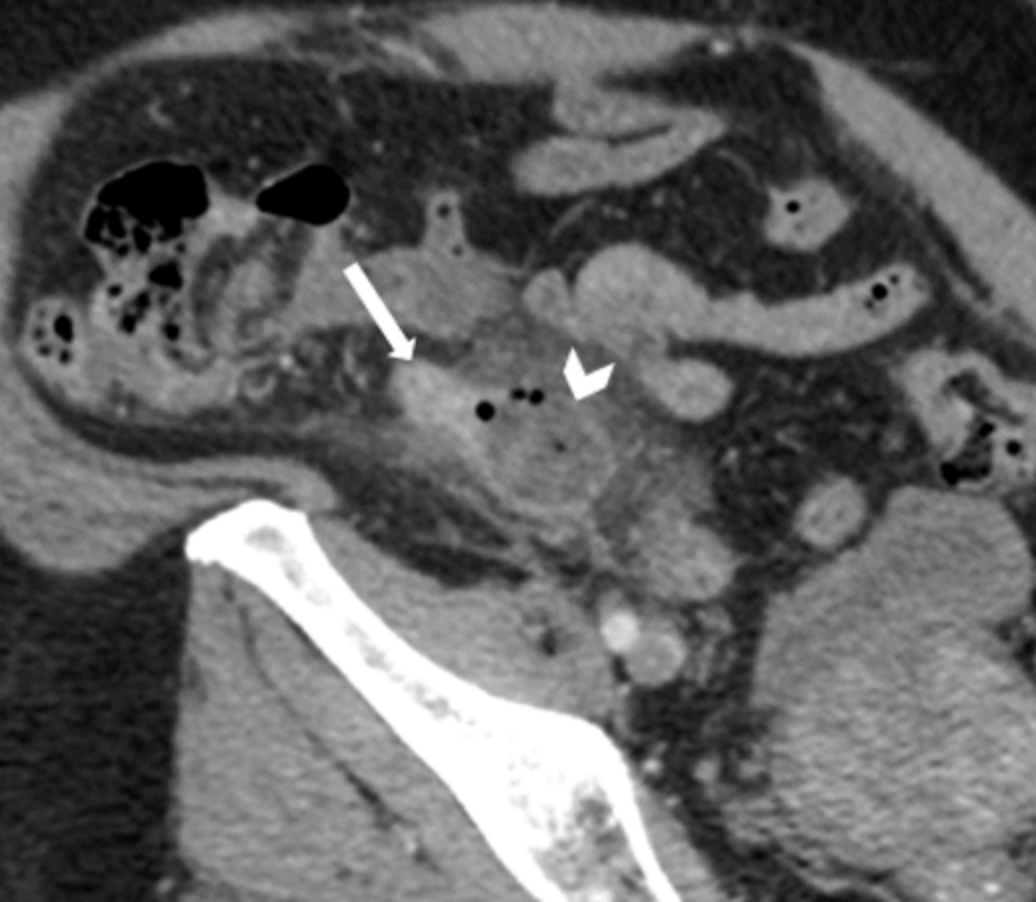


Table 1:

	Tumor group N = 52 (%)	Non tumor group N = 156 (%)
Type of surgery		
Laparotomy	6 (11.5)	19 (12.2)
Laparoscopy	46 (88.5)	137 (87.8)
Additional surgery	13 (25)	1 (0.6)
Per-operative and histological complications*	9 (17.3)	40 (25.6)

* A complicated appendicitis includes perforation of the appendix, empyema or abscess formation.

Table 2:

CT features	Total pop N = 208 (%)	Tumor group N = 52 (%)	No tumor group N = 156 (%)	p value	Kappa (CI 95%)
Fat stranding	176 (85)	39 (75)	137 (88)	0.0265*	0.86 (0.77-0.95)
Appendicolith	70 (34)	7 (13)	63 (40)	0.0004*	0.93 (0.88-0.99)
Mural calcification	11 (5)	9 (17)	2 (1)	<0.0001**	1 (1-1)
Appendix content					
Liquid	147 (71)	44 (85)	103 (66)	0.0108*	0.87 (0.80-0.95)
Mixed	61 (29)	8 (15)	53 (34)		
Adenopathy	22 (11)	7 (13)	15 (10)	0.4348*	0.93 (0.86-0.99)
Mass	22 (11)	19 (36)	3 (2)	<0.0001*	0.76 (0.59-0.92)
Focal asymmetric wall abnormality	51 (24)	29 (56)	22 (14)	<0.0001*	0.75 (0.64-0.86)
Diverticular appendix	20 (10)	13 (25)	7 (5)	<0.0001*	0.78 (0.63-0.94)
Local complication [§]	49 (24)	11 (21)	38 (24)	0.6372*	0.88 (0.80-0.96)
Liquid effusion	78 (37)	21 (40)	57 (37)	0.6198*	0.80 (0.72-0.88)
Peritonitis	94 (45)	19 (36)	75 (48)	0.1477*	0.86 (0.79-0.93)
Cecal wall thickening	29 (14)	7 (13)	22 (14)	0.908*	0.86 (0.77-0.96)
Ileal wall thickening	40 (19)	11 (21)	29 (19)	0.6845*	0.79 (0.68-0.89)
Malignant peritoneal involvement	1 (0,5)	-	1 (0,6)	1**	0.66 (0.05-1)

*: Chi² test, **Fisher test

§: Local complications are defined either by the presence of a perforation (free intraperitoneal gas or loss of appendix wall enhancement) or an abscess.

Table 3: Diagnostic performance of each CT sign for an appendiceal tumor.

CT Features	Sensitivity (CI 95%)	Specificity (CI 95%)	PLR (CI 95%)	NLR (CI 95%)	OR (CI 95%)
Fat stranding	75% (61-85)	12% (7.5-18)	0.85 (0.72-1.01)	2.05 (1.09-3.86)	0.42 (0.19-0.92)
Appendicolith	13% (6-26)	60% (50-67)	0.33 (0.16-0.68)	1.45 (1.23-1.72)	0.23 (0.10-0.54)
Mural calcification	17% (8-30)	98% (95-99)	13.5 (3-60)	0.83 (0.74-0.95)	16.12 (3.36-77.39)
Appendix content*	15% (7-28)	66% (58-73)	0.45 (0.23-0.89)	1.28 (1.09-1.51)	0.35 (0.16-0.81)
Adenopathy	13% (6-25)	90% (85-94)	1.4 (0.6-3.24)	0.96 (0.85-1.08)	1.46 (0.56-3.81)
Mass	36% (23-51)	98% (94-99)	18 (5.86-61)	0.64 (0.53-0.8)	29.36 (8.21-105.02)
Focal asymmetric wall abnormality	56% (42-69)	86% (80-92)	3.96 (1.46-5.41)	0.52 (0.35-0.66)	7.68 (3.78-15.61)
Diverticular appendix	25% (14-39)	95% (91-98)	5.57 (2.35-13.2)	0.78 (0.67-0.92)	7.09 (2.65-18.98)
Local complication [§]	21% (11-35)	76% (68-82)	0.87 (0.48-1.57)	1.04 (0.88-1.23)	0.83 (0.39-1.78)
Liquid effusion	40% (27-55)	63% (55-71)	1.11 (0.75-1.63)	0.94 (0.73-1.21)	1.12 (0.62-2.24)
Peritonitis	36% (23-51)	52% (44-60)	0.76 (0.51-1.13)	1.22 (0.95-1.58)	0.62 (0.33-1.19)
Cecal wall thickening	13% (5-26)	86% (79-91)	0.95 (0.43-2.1)	1.01 (0.89-1.14)	0.95 (0.38-2.37)
Ileal wall thickening	21% (11-35)	81% (74-87)	1.14 (0.61-2.11)	0.97 (0.83-1.14)	1.18 (0.54-2.56)
Malignant peritoneal involvement	0.6% (0-6)	99% (93-100)	-	1.01 (0.99-1.02)	<0.001 (<0.001->999.99)
Liver metastasis	5% (1.2-16)	99% (96-100)	9 (0.96-84)	0.95 (0.89-1.02)	9.49 (0.96-93.32)
Ovarian metastasis	0.6% (0-6)	100% (96-100)	-	0.99 (0.99-1.02)	<0.001 (<0.001->999.99)
Appendix diameter ≥ 15 mm	59% (46-73)	81% (75-87)	3.1 (2.1-4.7)	0.5 (0.35-0.69)	6.46 (3.26-12.83)

* = mixed content

PLR = positive likelihood ratio, NLR = negative likelihood ratio, OR = Odds-Ratio

§: Local complications are defined either by the presence of a perforation (free intraperitoneal gas or loss of appendix wall enhancement) or an abscess.

Table 4:

CT Features	OR	CI 95%	p - value	Beta parameter (*)	CT score point
Fat stranding	0.28	0.10-0.84	0.0228	-1.2547	-1
Appendicolith	0.22	0.06-0.74	0.0144	-1.5283	-1
Mural calcification	47.05	6.64-333.5	0.0001	3.8513	3
Mass	7.1	1.66-30.29	0.0082	1.9592	2
Focal asymmetric wall abnormality	4.86	1.84-12.83	0.0014	1.5807	1
Appendix diameter \geq 15 mm	3.5	1.36-9.0	0.0096	1.2513	1

(*) β parameter = multivariate logistic regression estimates (raw β)

OR = Odds-Ratio