

Appendiceal Tumors in Adults, Findings in 1870 Specimens

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Abstract

Purpose

The appendiceal disease is a frequent entity, with a non-negligible number of malignancies. There is an association of synchronous appendiceal tumors with other malignancies, therefore a routine appendectomy could be considered. The aim of our study is to analyze the number of cases of non-inflammatory appendiceal disease with unusual histopathological findings of appendix samples. Secondary aims are to analyze the recurrence and mortality of appendicular tumors.

Methods

A retrospective cohort study of all the appendectomy specimens in a period of time of 5 years was performed.

Results

A total of 1870 appendectomies were included. Non-inflammatory disease was found in 127 cases (5.5%) and malignant neoplasm in 33 patients (1.76%). Mucinous Cystadenoma was the most common benign tumor, representing 33.3 % of total cases. The most common appendiceal neoplasm was adenocarcinoma (11 patients) and neuroendocrine tumors (22 patients). Acute appendicitis was the most frequent surgical indications in those patients. In the adenocarcinoma group, older patients were more frequent ($p=0.003$), as was the presence of abscess ($p=0.016$). From the appendiceal neoplasm, 30% (10 patients) had a synchronous colorectal or gynecological cancer. Five-year survival for adenocarcinoma and neuroendocrine tumors was 53.6 % (95% CI 51-94) and 45.5 % (95% CI 26-72) ($p=0,373$).

Conclusions

Histopathological assessment of the appendix will allow early diagnosis of many unusual findings of the appendix. We recommend to considered routine appendectomy due to the high incidence of appendiceal tumors and a non-negligible number of synchronous colorectal and gynecological cancers.

Introduction

Acute appendicitis is the most common appendicular disease and one of the most common abdominal emergencies worldwide. Its classical treatment have been appendectomy, with the challenge of performing laparoscopic or open surgery, or even if the treatment could be feasible on an ambulatory setting [1]. In recent years new initiatives have emerged in their treatment, including non-surgical management for uncomplicated appendicitis [2–4].

Acute appendicitis is the most common presentation of appendiceal tumors in 30–79% of the cases [5–8]. Therefore, we should consider that by treating acute appendicitis only with antibiotics might not make us to detect appendiceal tumors [9].

The appendix vermiformis is considered the most common site for gastrointestinal carcinoid tumors, around 60% of all appendicular tumors [10] and it is an organ that could play a role in the development of colon cancer either as presumptive immune system function or to support beneficial bacterial gut flora [11].

Authors have suggested to perform appendectomy in patients with diagnostic of colorectal cancer during the surgical resection [12] due to synchronous appendiceal neoplasia in 1% to 4,1% of these patients [13]. In ovarian cancer appendectomy is routinely performed due to the high frequency of appendiceal metastasis [14; 15].

Therefore, it could be reasonable to consider the excision of the appendix not only in cases of acute inflammatory pathology.

Materials And Methods

The data of adults who underwent appendectomy in a single-center during 5 years was analyzed (2008–2013). Data was obtained retrospectively from the patient record documentation system of the department. Patients over 18 years who underwent appendectomy were included regardless of the preoperative diagnostic (acute appendicitis or appendectomy associated to other surgeries). Elective and emergency surgery cases were included.

The aim of this study is to analyze the unusual histopathological findings based on the histopathological analyses. Unusual findings were classified as mucinous cystadenoma, neuroendocrine tumor, mucosal hyperplasia, neuroma, adenocarcinoma, serrated adenoma, follicular hyperplasia, villous adenoma, tubular adenoma, signet ring cell carcinoma, neurofibroma and lipoma. Mucinous cystadenoma is not considered malignant neoplasia, for this reason was not included in the malignant tumors analysis.

Age, sex, presence of abscess, size of the abscess, presence of fever, number of days of pain before diagnostic, type of surgical procedure, pathology analysis, morbidity and follow up to June 2018 were acquired from database.

Morbidity was defined as the complication present in the first 30 days after the surgery according to the Clavien-Dindo classification.

Cancer staging and lymphatic involvement was analyzed in malignant tumors. The need and type of second oncological surgeries and postoperative treatment with chemotherapy was registered.

The biologic aggressiveness of the neuroendocrine tumors was measured following 2010 World Health Organization (WHO) classification: low grade (G1), intermediate grade (G2) and high grade (G3) [16]. The American Joint Commission on Cancer (AJCC) staging system for adenocarcinoma of the appendix was used.

Statistical analysis

Quantitative data are shown as the median or mean of values and their variability is expressed as the range or standard deviation (SD), as specified for each analysis. Qualitative data are shown as absolute values or percentages. For significance assessment of quantitative data, unpaired Student's T-test or two-tailed Mann-Whitney *U* test was applied, as specified for each analysis. For significance assessment of qualitative data, Fisher's exact test or Chi-squared test was applied. Survival was analyzed with the Kaplan-Meier estimate. Differences in the curves were analyzed by log rank testing. All analyses were carried out by SPSS Statistics version 21 and $P < 0,05$ was considered statistically significant.

Results

Demographics and clinical presentation

From January 2008 through December 2013 a total of 1870 patients who underwent appendectomy were included.

Unusual pathological findings were found in 127 cases (5,5%), 4 patients were excluded for not having all medical record during the hospitalization.

Among these 123 patients, the clinical and surgical information are shown in Table 1. There was a significant correlation among patients age with older patients in adenocarcinoma group ($p = 0,003$). An abscess was presented more frequently in adenocarcinoma than in carcinoids tumors ($p = 0,016$).

Table 1

Clinical and surgical information of the entire study population, neuroendocrine tumors and Adenocarcinoma study groups. Features were assessed at the end of the study and expressed as the mean of absolute values in percentages +/- standard deviation for each group. Fisher's exact test or two-tailed Mann-Whitney *U* test was applied for statistical analysis. A p value (*p*) < 0.05 was considered statistically significant.

VARIABLE	Unusual pathological findings (n = 123)	Neuroendocrine (n = 22)	Adenocarcinoma (n = 11)	<i>p</i>
Sex (female) n (%)	63 (51.2)	5 (22.7%)	2 (18.2%)	0.542
Age mean of years (SD)	63.86 (17.7)	48.18 (20)	69.64 (11.13)	0.003
Symptom duration days mean (SD)	3 (5.44)	3.33 (3.57)	5 (9)	0.158
Fever n (%)	24 (19.5%)	3 (13.6%)	4 (36.4%)	0.094
Abscess n (%) ¹	14 (11.4%)	1 (4.5%)	4 (36.4%)	0.015
Size abscess median in mm (SD)	2 (13.6)	2	2 (3.6)	0.729
ASA ² n (%)				0.736
ASA I	21 (17.1%)	5 (22.7%)	2 (18.2%)	
ASA II	63 (51.2%)	8 (36.6%)	5 (45.5%)	
ASA III	36 (29.3%)	7 (31.8%)	4 (36.4%)	
ASA IV	3 (2.4%)	2 (9.1)	0	
ASA V	0	0	0	
Surgical indication n (%)				0.068
Acute appendicitis	47 (38.2%)	8 (36%)	6 (54.4%)	
Colon and rectum neoplasia	26 (21.1%)	4 (18.2%)	1 (9%)	
Gynecologic neoplasia	14 (11.4%)	5 (22.5%)	0	
Incidental diagnostic ²	16 (13%)	4 (18%)	0	
Inflammatory bowel disease	3 (2.4%)	1 (4.5%)	1 (9%)	
Appendicular plastron	7 (5.7%)	0	2 (18%)	

¹Abscess= presence of an abscess; ²ASA= American Society of Anesthesiologists; ² Incidental diagnostic = incidental diagnostic during other surgeries; n = number; p = p value < 0.05.

VARIABLE	Unusual pathological findings (n = 123)	Neuroendocrine (n = 22)	Adenocarcinoma (n = 11)	<i>p</i>
Abdominal mass	6 (4.9%)	0	1 (9%)	
Other	9 (3.3%)	0	0	
Final surgical procedure n (%)				0.750
Appendectomy	85 (61.9%)	16 (62.7%)	3 (27%)	
Right colectomy	23 (18.7%)	5 (22.7%)	7 (63,6%)	
Left colectomy	1 (0.8%)	0	0	
Total colectomy	4 (3.3%)	1 (4.5%)	0	
Other	10 (8.1%)	0	1 (9%)	
¹ Abscess= presence of an abscess; ² ASA= American Society of Anesthesiologists; ² Incidental diagnostic = incidental diagnostic during other surgeries; n = number; p = p value < 0.05.				

Most of the patients presented with acute appendicitis and they were treated by simple appendectomy. Acute appendicitis was the most frequent surgical indication in patients with appendiceal tumors (42%).

An elective surgical treatment of colorectal and gynecological cancer was performed in 26 patients (21%) and 14 (11,4%) respectively. Out of these patients, in ten there was a synchronic appendiceal neoplasia (Table 1).

Preoperative diagnostic

Eighty-five patients had preoperative CT scan and twelve only an echography. None of the patients had an anatomopathological preoperative diagnosis of neuroendocrine tumor or carcinoma by biopsy, but six went to surgery with the diagnostic made by CT scan (data not shown).

Pathological and operative procedure analysis

The histopathologic characteristics of the 123 patients are summarized in Table 2. The largest single group of not malignant tumors were mucinous cystadenomas (33,3%), followed by mucosal hiperplasia (17,1%), neuroendocrine tumors (17,8%) and Neuroma (8,1%).

Table 2
Histopathologic characteristics. The histopathologic characteristics were quantified and expressed as absolute values and percentages.

Type	N	Percentage (%)
Mucinous Cystadenoma	41	33.3
Neuroendocrine tumor	22	17.8
Mucosal hyperplasia	21	17.1
Neuroma	10	8.1
Adenocarcinoma	9	7.3
Serrated adenoma	8	6.5
Follicular hyperplasia	3	2.4
Villous Adenoma	3	2.4
Tubular adenoma	2	1.6
Signet ring cell carcinoma	2	1.6
Neurofibroma	1	0.8
Lipoma	1	0.8
N = number.		

Thirty-Three patients had malignant appendiceal tumors, this represents 1,76% of all the specimen. Neuroendocrine tumors in 22 patients (17,9%) and 11 (8,9%) adenocarcinomas (two of them were ring cell carcinomas).

Most of the neuroendocrine tumors were G1 (86%), only three were G2 (1,4%). Ten neuroendocrine tumors were T1, only one was a T2.

Of all adenocarcinomas 6 were taken to a second surgery after de anatomopathological diagnostic, performing 5 right hemicolectomies and one ileocecectomy. Eight were T4 and only two had lymph node involvement. One was T1 and in two size was not specify.

After first surgery and staging, four patients with adenocarcinoma (36%) and two in the neuroendocrine (9%) group had already metastasis (one in neuroendocrine group received a second radical surgery, performing the exéresis of liver metastasis completely).

Outcome and follow-up

There was no difference on length of stay and morbidity between groups (Table 3). Two patients with an anastomotic leak went to surgery, all of them in the carcinoid group.

Table 3

Postoperative outcome and follow up. Information related to postoperative outcome and follow up of the two main groups was quantified and expressed as absolute values and/or percentages. For statistical analysis, Fisher's exact test or two-tailed Mann-Whitney *U* test was applied. A *p* value (*p*) < 0.05 was considered statistically significant.

VARIABLE	Neuroendocrine (n = 22)	Adenocarcinoma (n = 11)	<i>p</i>
Length of stay days n (range)	8.81 (1–50)	13 (2–34)	0.573
Morbidity n (%)	4 (18.2%)	2 (18.2%)	0.952
Clavien I	0	1 (9%)	
Clavien II	0	1 (9%)	
Clavien IIIa	2 (9%)	0	
Clavien IIIb	2 (9%)	0	
Clavien IV	0	0	
Clavien V	0	0	
Recurrence	1 (4.5 %)	2 (18.2%)	0.248
Overall survival mean (SD)	40.3 (30.p)	41 (32.6)	0.960
N = number; SD = Standard deviation			

With a mean follow-up of 40 months (SD of 30) recurrence of the gynecological or colon neoplasia was present in three patients (11,5%) and three had recurrence of the appendiceal tumor (9%). The neuroendocrine tumor had liver recurrence at 23 months from first surgery (appendectomy and right hepatectomy for liver metastasis was performed in the first surgery), at present the patient is alive.

Adenocarcinoma recurrence was in both cases a peritoneal recurrence. In one patient at 26 months and the other at two months from appendectomy. Both patients died due to disease progression.

Five patients had recurrence of gynecological cancer (41, 6%) and four had colorectal cancer recurrence (33%).

At the end of the study, fifteen patients died, three due to the progression of the gynecological neoplasia, eight due to the progression of the appendiceal neoplasia (6 carcinomas, 2 neuroendocrine) and four due to other causes not related to neoplasia.

Mortality rate at 5 years was 53.6 % (95% CI 51–94) in the carcinoid group and 45.5 % (95% CI 26–72) in the adenocarcinoma group.

There were no differences between carcinoma and neuroendocrine tumors in overall survival ($P = 0,373$) (Fig. 1).

Discussion

Our study analyses a high number of appendectomy specimens with a non-negligible number of non-inflammatory disease (5.5%) and malignant neoplasm (1.76%).

Primary neoplasia of the appendix are presented in 1% of all the specimen [5, 17], carcinoma and neuroendocrine tumors are the most common malignant neoplasias [18].

In Our study, the incidence of Malignancy was 1,76% out of all the appendectomy, this number is higher than previous studies. We removed from the analysis the mucinous cystadenoma but most articles include them as a appendiceal neoplasms [6; 18]. Our higher number of cases could be explained due to not treat pediatric patients in our hospital.

According to other studies, mean age of patients with appendiceal cancer was around fifty decade and with a higher proportion of women [18]. The average age was higher in Carcinoma group as other studies show [7].

The radiological diagnostic is difficult [19] and the intraoperative suspicion is important to not go unnoticed. In most of the cases it is an incidental diagnostic. Only six of our patients had a radiological diagnostic made by CT before surgery, the rest of patients had the definitive anatomopathologic analysis after the surgery. Due to the difficult diagnostic, an advanced stage with metastasis at the diagnostic was more frequent in adenocarcinoma tumors (36%) compared to the neuroendocrine ones (9%). Most of the neuroendocrine tumors were small G1 tumors compared to T4 stage in adenocarcinoma.

The presence of an abscess has been present in a high number of malignant appendiceal tumors [6]. Comparing the two main groups of neoplasia, there was a significant correlation among the presence of an abscess ($P = 0,015$) higher in carcinoma group. No other differences between the main groups were found.

In recent years there has been an increased interest in antibiotic therapy as primary treatment in selected patients and surgery has been questioned in acute appendicitis [3].

Whereas the nonsurgical treatment has been supported [20], the most common presentation of appendiceal tumors is in 30–79% of the cases as acute appendicitis [5–8] similar to our results (42%). This could make us question if we assume the risk of not finding a tumor if we choose the no surgical option in an acute appendicitis.

Corinne Vons et al described in a non-inferior randomized controlled trial, that the incidence of complicated appendicitis with peritonitis and postoperative peritonitis within 30 days after the start of treatment was significantly more frequent in the antibiotic group than in the appendectomy group.

This group found that the presence of a stercolith on preoperative CT scan was the only factor associated with a significantly increased risk of complicated appendicitis and was also associated with failure of antibiotic treatment for appendicitis. They suggest that emergency appendectomy remains the gold standard.

These last findings in Corinne Vons study are criticized by the APPAC trial and authors [21] concluding with level I evidence that 75–85% of uncomplicated appendicitis could be treated with ertapenem, a number similar to the one described at the Vons study.

Although several studies support the antibiotic treatment of acute appendicitis, there is a recurrence around 14% or even more 26,5% in a 1 year time [22–24].

Some systematic review and metanalysis conclude that although antibiotics may prevent some patients from appendectomies, surgery represents the definitive, one-time only treatment with a well-known risk profile [22; 25].

In our study 123 patients had unusual pathological findings (6,57 %). We recommend that a routinely histopathological examination must be carried out, even if the macroscopic appearance of the specimen is normal, like other authors suggest [26;28].

The objective of this article was not to discuss the appropriate surgical technique since this has been frequently treated in the literature previously [6].

From all the series of appendectomies, a high incidence of synchronous and metachronous colorectal cancer has been found [5] .

When we analyze the incidence of appendiceal tumors in patients with colorectal cancer the incidence is not negligible [13; 27; 28] finding from 0,3–4% depending on studies. If we calculate de incidence of malignant neoplasia in these studies that will be around 0,3 – 1,84%.

Exner et al describe a high number of abnormal findings (76,05%) if incidental appendectomy was performed during colorectal surgery and neoplasm occurs in 1,84% of cases [27] Out of all abnormal findings in this study, only eight (2,1%) had benign tumors and 2 (0,52%) had malignant tumors.

In our study the unusual findings (including appendiceal tumors) were presented in 26 patients (21,1%) with concomitant colorectal cancer and in 14 (11,38%) with gynecological neoplasia. This represents a 2,1% of all the specimens being not a negligible number. Ten patients had a synchronous neoplasia (25%).

Observing the incidence of synchronous or metachronous tumors with colorectal cancer or gynecological cancer; we agree with other authors to consider a routine appendectomy [12] since it does not increase de morbidity rate [29].

Being a retrospective analysis from a single institution and the low number of recurrences are limitations of our study.

Conclusion

Unusual findings in the appendix is a frequent entity with a non-negligible proportion of malignancy cases. We recommend to considered routine appendectomy in colorectal and gynecological cancer due to the high number of synchronous appendiceal neoplasm. Appendectomy is an easy and quick surgery with a low morbidity and an acceptable cost benefit.

Declarations

Ethical approval:

For this type of study formal consent is not required. This article does not contain any studies with human participants performed by any of the authors.

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Conflict of interest:

The authors declare that they have no conflict of interest.

Availability of data and material:

Not applicable

Code availability:

Not applicable

Consent to participate or publication:

Not applicable

Authors' contributions:

Lopez Gordo: protocol, data collection, data analysis, manuscript writing.

Frago: protocol, data analysis, manuscript writing, final revision

Galvez: data collection, manuscript writing, final revision

Kreisler: protocol, data collection, final revision

Biondo: protocol, final revision

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Figures

Survival probability

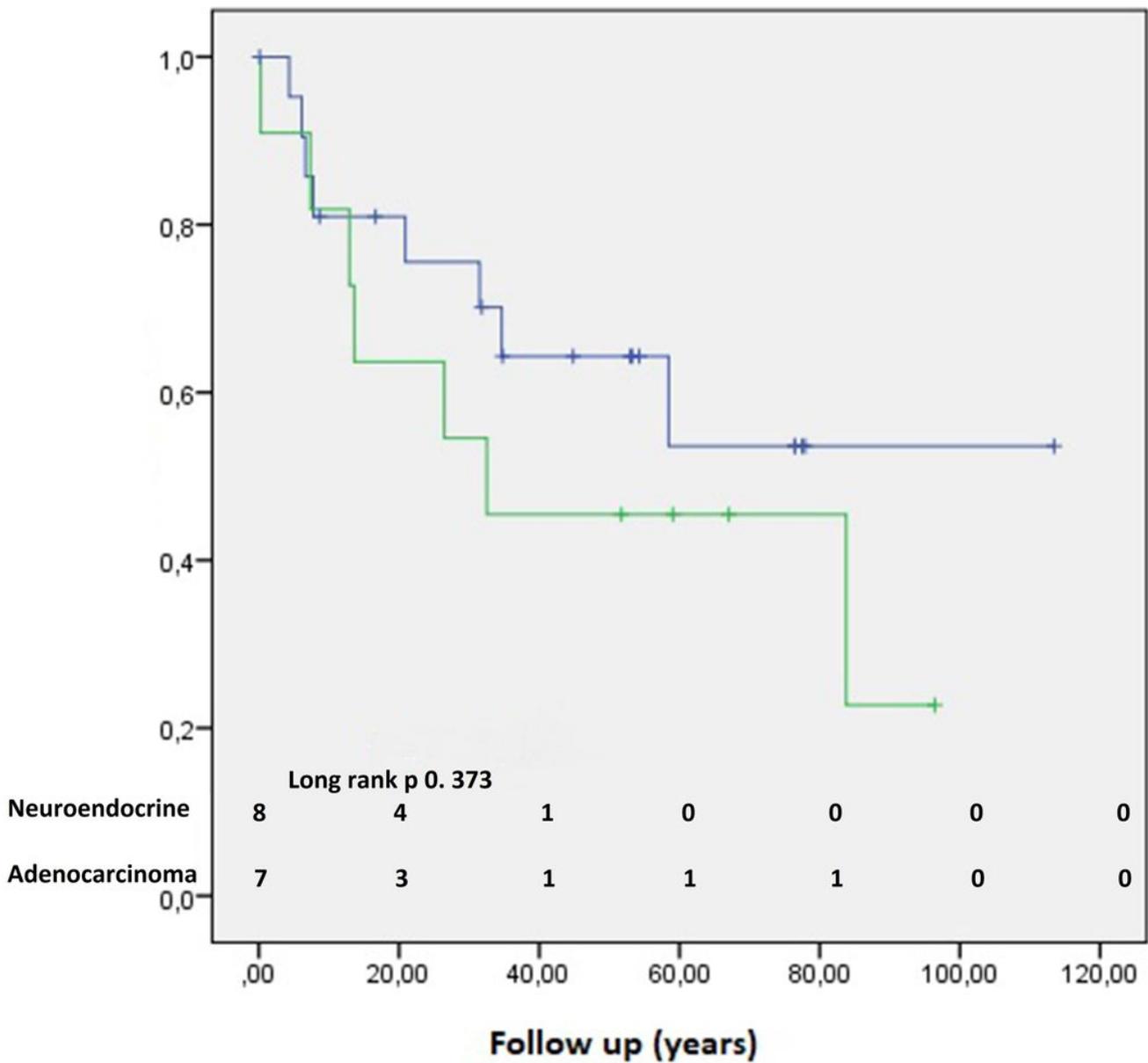


Figure 1

Kaplan-Meier curve of the overall survival (OS) for the Carcinoid (blue/upper line) and adenocarcinoma (green/lower line) group. A survival Kaplan-Meier curve on OS was calculated between main groups of malignant tumors.