Prevalence of Carcinoma in Appendectomy Specimens for Patients Presenting With Acute Appendicitis: A Single-Center Study

Omotara Lesi 1, Sarah-Jane Walton 1, Nikhil Nanjappa Ballanamada Appaiah 1, Noreen Rasheed 2, Jayasiri Dahanayaka 3, Philip Ideawor 4, Abdalla Saad Abdalla Al-Zawi 3, 5

1. General and Colorectal Surgery, Basildon and Thurrock University Hospital, Mid and South Essex NHS Foundation Trust, Basildon, GBR
2. Radiology, Basildon and Thurrock University Hospital, Mid and South Essex NHS Foundation Trust, Basildon, GBR
3. General and Breast Surgery, Basildon and Thurrock University Hospital, Mid and South Essex NHS Foundation Trust, Basildon, GBR
4. Pathology, Basildon and Thurrock University Hospital, Mid and South Essex NHS Foundation Trust, Basildon, GBR
5. General and Breast Surgery, Anglia Ruskin University, Chelmsford, GBR

Corresponding author: Omotara Lesi, omotaralesi@gmail.com

Abstract

Introduction
Acute appendicitis is the most common general surgical emergency globally. Its etiology includes the presence of luminal obstruction by faecoliths, lymphoid hyperplasia, impacted stool, and rarely by appendiceal or caecal cancer. Malignancy related to acute appendicitis is usually seen in the older age group.

Aim
To identify the subset rate of patients operated for acute appendicitis who have appendiceal carcinoma and analyze the outcome of their post-operative management.

Material and methods
A retrospective study of a cohort of 529 patients aged > 40 diagnosed with acute appendicitis with subsequent appendectomy in the period between 1 January 2014 and 31 December 2019 at Basildon and Thurrock University Hospital, Essex, United Kingdom was conducted. We analyzed the clinical data of the cohort including demographic information, diagnosis, pre-operative imaging, histological diagnosis as well as post-operative management where indicated.

Results
The median age of patients was 54.5 years (range 40–92). The male to female ratio in the appendicectomy cohort was 1:1.1. About 45% were aged 40–49 years, 24.8% were aged 50–59 and 30.2% were ≥60 years. Post-operative histology revealed acute appendicitis in 82.4% of the group. In 11% of the patients, the histology revealed the presence of other benign pathology as mucocele of the appendix, acute diverticulitis, follicular hyperplasia, and fibrous obliteration. The diagnosis of appendicular malignancy was seen in 1.9%.

Conclusion
Incidental appendiceal cancers in the resected specimens after acute appendicitis are rare but may be associated with a poor prognosis. It is recommended to consider such diagnosis in particular when dealing with acute appendicitis in older patients with longer symptom history, and in presence of peri-appendicular mass.

How to cite this article
Lesi O, Walton S, Ballanamada Appaiah N, et al. (November 15, 2021) Prevalence of Carcinoma in Appendectomy Specimens for Patients Presenting With Acute Appendicitis: A Single-Center Study. Cureus 13(11): e19611. DOI 10.7759/cureus.19611

Introduction
Acute appendicitis is one of the most common causes of acute abdomen in adults with an estimated lifetime risk of 7–8% [1]. Also, it is recognized as the most frequent general surgical emergency in the world with around 50,000 appendectomies performed yearly in the UK [2]. The highest incidence occurs in the second and third decades of life, with the pathology less common in both extremes of life [3]. The etiology includes the presence of luminal obstruction by faecaliths, lymphoid hyperplasia, impacted stool, parasitic infestation, and rarely by an appendiceal or caecal cancer [3, 4]. The obstruction of the lumen can lead to increased intramural pressure thereby affecting venous and lymphatic outflow. This will subsequently lead to impaired vascular and lymphatic flow with attendant ischemia. The inflammatory process can result in perforation, abscess formation as well as generalized peritonitis [5]. Luminal obstruction by neoplasms is usually seen in the elderly, this relationship was first reported by Dr. Shears in 1906 [6].
The aim of this study was to determine the incidence of appendicular cancer in patients over 40 years who had undergone appendicectomy as well as assess their further management outcome.

**Materials And Methods**

This retrospective study analyzed data of patients ≥ 40 years who underwent appendicectomy in the period between 1 January 2014 and 31 December 2019 at Basildon and Thurrock University Hospital, Essex, United Kingdom. Patients were collated from the hospital’s clinical portal record. Data collected included demographic data (gender, age, etc), pre-operative imaging, initial diagnosis, intra-operative findings and histological diagnosis, post-operative management.

The inclusion criteria included patients with a diagnosis of acute appendicitis and no other acute abdominal pathology identified as well as patients with proven appendiceal cancers after surgery. Those excluded were patients with acute abdomen of unknown cause.

**Results**

A total of 529 appendicectomies were performed during the study period. The M:F ratio in the cohort was 1:1.1. The median age of patients was 54.5 years (range 40-92 years). Around 45%, or 238 patients were aged 40-49 years, 131 patients (24.8%) were aged 50-59 and 160 patients (30.2%) were 60 years and above (Table 1).

| Age Range (Years) | N (%)   |
|-------------------|---------|
| 40-49             | 238 (45%) |
| 50-59             | 131 (24.8%) |
| 60-69             | 90 (17%) |
| 70-79             | 56 (10.6%) |
| 80-89             | 13 (2.5%) |
| ≥ 90              | 1 (0.2%) |

**TABLE 1: Age distribution of all patients who underwent appendicectomy**

Pre-operative investigations were done in the majority of patients: 487 patients (92%) had pre-operative CT scans, 20 patients (3.8%) had abdominal ultrasound scans, two patients had magnetic resonance imaging (MRI) while 20 patients did not have any pre-operative investigations.

Histology diagnosis revealed the presence of acute appendicitis in 82.4% of patients. There was negative appendicectomy in 4.7% of the patients while there was an incidental finding of appendicular tumors in 10 patients (1.9%). In 11% of the patients, there was the presence of mucocele of the appendix, acute diverticulitis, follicular hyperplasia, and fibrous obliteration (Table 2).

| Appendicular pathology        | N(%)   |
|-------------------------------|--------|
| Acute Appendicitis            | 436(82.4%) |
| Other benign changes          | 58(11%) |
| Normal                        | 25(4.7%) |
| Malignant tumours             | 10(1.9%) |
| Neuro-endocrine tumours       | 6(1%)  |
| Adenocarcinoma                | 4(0.8%) |

**TABLE 2: The histopathology of the resected appendices in 529 patients**

The incidental appendicular malignancies included: neuroendocrine tumors, adenocarcinoma of the...
appendix, and mucinous adenocarcinoma of the appendix (Table 3).

| No. | Age | Sex | Pre-op CT | Operative procedure | Operative findings | Appendicular histology | T stage | Adjuvant treatment |
|-----|-----|-----|----------|--------------------|-------------------|-----------------------|--------|-------------------|
| 01  | 45  | F   | AA       | EMA                | AA                | Adenocarcinoma of appendix | T4     | Referred to tertiary centre |
| 02  | 46  | F   | AA       | EMA                | AA                | AA, WD NET           | T1     | SFU               |
| 03  | 53  | F   | AA       | EMA                | Necrotic AA       | AA with NET          | T1     | SFU               |
| 04  | 54  | F   | AA       | EMA                | AA, abscess       | NET                  | T1     | SFU               |
| 05  | 64  | F   | AA       | EMA                | AA, abscess       | mucinous adenocarcinoma | T3     | Right hemicolecotomy |
| 06  | 65  | M   | AA       | EMA                | AA, abscess       | WD, NET              | T1     | SFU               |
| 07  | 67  | M   | AA       | EMA                | AA                | PD mucinous adenocarcinoma | T4     | Right hemicolecotomy -declined |
| 08  | 68  | M   | AA       | EMA                | AA                | NET                  | T4     | Palliative       |
| 09  | 68  | F   | AA       | EMA                | AA, abscess       | PD mucinous secreting adenocarcinoma | T4 | Cytoreductive surgery and intra-peritoneal chemo |
| 10  | 74  | F   | Perforated AA | EMA         | AA, abscess       | NET                  | T4     | Right hemicolecotomy |

**TABLE 3**: Malignant appendiceal tumors detected in 10 patients with pre-operative diagnosis of acute appendicitis

AA: acute appendicitis; EMA: emergency appendicectomy; NET: neuroendocrine tumour (carcinoid); WD: well differentiated; PD: poorly differentiated; SFU: surgical follow-up

Post-operative bowel investigations were done in only 79 patients (14.9%) with abnormal findings seen in 29 patients (5.5%). Out of the 79 patients, only 19 patients (5.6%) had their post-operative investigations within three months of appendicectomy while the remaining 60 patients had theirs between six months to six years of the study period for varying reasons like change in bowel habits or through bowel cancer screening program.

Also, 26 patients (4.9%) had benign polyps detected during colonoscopies, another patient had high-grade dysplastic polyp while yet another person was diagnosed with caecal cancer. The patient with caecal cancer had an appendicectomy for CT-confirmed and histological diagnosis of acute appendicitis a year prior to cancer diagnosis. The following year after surgery, he was investigated for anemia and colonoscopy confirmed the presence of caecal cancer in the appendiceal orifice. He later had a right hemicolecotomy and histology showed advanced colon cancer (pT4aN0M0). A second patient had a histology diagnosis of T3 appendiceal tumor after appendicectomy. Radical surgery was advised; however, the patient declined surgery and any luminal investigations within three months and CT staging was done five months later for abdominal symptoms which revealed a separate transverse colon tumor with metastases. The patient was sent for palliative care.

**Discussion**

The first reported case of an appendiceal tumor was in 1882 [7], other studies have appeared in the literature since 1903 when Elting reported a review and case series [8]. Appendiceal tumors are rare, about 0.9%–1.4% of the tumors are seen during histology diagnosis of resected appendiceal specimens. The age-adjusted incidence is 0.12 cases per one million people per year [9], it is reported in both genders, however, some authors claim that the majority of patients were female [10, 11]. The most common primary appendiceal tumor is carcinoid tumor and it makes up 32-85% while adenocarcinomas (mucinous, signet ring, or non-mucinous) make up 4-20% of the tumors [12]. In our study, out of the 529 patients aged over 40 years who underwent appendicectomies, 10 patients had malignant appendiceal tumors with 60% of the tumors showing carcinoids while 40% were revealed to be adenocarcinomas in the histopathology. Appendiceal tumors are mostly located at the tip of the appendix with a maximal size of <1 cm in 60–80% of cases with a five-year survival of 83% for all stages [13].
In the majority of cases of appendiceal malignancy, patients present with symptoms of acute appendicitis or a palpable mass [14]. This was similar in our study with all the patients presenting with features of acute appendicitis [14]. Acute appendicitis is usually caused by fecaliths, lymphoid hyperplasia, impacted stool, parasitic infestation, and rarely by a neoplasm (see Figure 1). Patients could also present features of a perforated appendix if the neoplasm obstructs the lumen of the appendix [12]. Rarer features include the presence of pelvic mass, hydrenephrosis, Crohn’s disease, haematuria, anemia, vesico-appendiceal fistula, and caecal intussusception [5, 15, 16]. The presence of symptoms of carcinoid syndrome occurring in patients with carcinoid tumors is rare, and in usual circumstances, they indicate the presence of liver metastases. In patients with carcinoid tumors, levels of urinary 5-hydroxy-indoleacetic acid (5-HIAA), urinary and serum serotonin levels can be used to monitor the progression of the disease [9].

**FIGURE 1: Causes of acute appendicitis**

Illustration by Dr Abdalla Saad Abdalla Al-Zawi.

In this study, the diagnosis of appendiceal tumors was not made pre-operatively; this is also seen in the published studies [17]. The radiological findings of appendiceal carcinoids are limited due to the small size of the tumors and their location in the distal aspect of the appendix (Figures 2-3). Ultrasound scan findings include the presence of a hyperechoic round mass at the tip of the appendix where CT findings suggestive of carcinoid tumor include the presence of a focal, soft tissue mass with enhancement. On MRIs, they appear as T1 isointense and T2 isointense-hyperintense masses with contrast enhancement [18]. Adenocarcinoma on the other hand appears in the CT scan as a subtle infiltrating mass, as well as prominent inflammatory changes around the appendix as well as enlargement of the appendix CTS scan [19].
There is evidence of acute appendicitis with thickening of the appendix measuring 10 mm in diameter, and marked inflammatory stranding in the periappendiceal and pericaecal fat (A-B, yellow arrows). There is a periappendiceal fluid collection measuring 20 x 25 mm (A-B, yellow arrows). The appendix is seen extending into the right hemi-pelvis. Several enlarged mesenteric nodes were noted to be medial to the appendix (C), red arrows. The post-operative histology showed appendiceal cancer.

Appearances were suggestive of acute appendicitis. The post-operative histology showed appendiceal cancer.

The International Classification of Diseases for Oncology (ICD-O), 2nd edition groups appendiceal tumors into five categories: colonic-type (non-mucinous) adenocarcinoma, mucinous adenocarcinoma, signet-ring...
cell carcinoma, goblet cell carcinoid/adenocarcinoid, and malignant carcinoid [20]. The non-mucinous adenocarcinoma occurs less frequently than the mucinous type (Figure 4) in which mucin is involved in more than 50% of the lesion [12, 21]. Our study shows that majority of the patients with adenocarcinoma had a mucinous type. Adenocarcinomas usually arise from an adenomatous polyp or serrated adenoma. The mucinous type usually causes myxoma peritonei and about half of patients with mucinous tumors will usually have transcoelomic spread and associated pseudomyxoma peritonei [22]. McCusker et al., in 2002, reported that showed a five-year survival rate of 44% for mucinous subtype, 52% for colonic subtype, and 20% for signet ring cell subtype [20].

FIGURE 4: Appendix showing extensive infiltration of the wall by a mucinous adenocarcinoma (red box)

Carcinoid tumors of the appendix could be classical carcinoid or goblet cell carcinoid tumors. Classical carcinoid tumors arise from neuroendocrine tissue in the primitive gastrointestinal tract [9], while goblet cell carcinoid arises from pluripotent intestinal epithelial crypt-base cells, it is characterized by dual neuroendocrine and mucinous differentiation [23]. Goblet cell carcinoid has pathologic features which are seen in both appendiceal carcinoid and colonic signet ring cell adenocarcinoma and it is noted that 20% of the tumors, also have a propensity for metastases to ovaries and peritoneum [24]. Our study did not distinguish between goblet cell carcinoid and classical carcinoid appendiceal tumors. The management of appendiceal tumors post appendectomies depends on the histological type, size, and location of the tumor. In patients with goblet cell carcinoids, a right hemicolectomy is usually performed after the initial appendicectomy, this is because the rate of metastases is high [23]. The completion surgery should be done within three months of the appendicectomy operation. Appendicectomy alone could be done in those with localized T1 tumors (<1cm). Patients with larger tumors, lesions locally advanced as in invasion of the caecum, serosa, or mesoappendix advised having right hemicolecotomy. It is also recommended that women with this tumor should have bilateral salpingo-oophorectomy regardless of age. Those with peritoneal carcinomatosis may have multiple peritoneectomies as well as intraperitoneal chemotherapy while patients with liver metastases [25].

All the patients in this study diagnosed with T1 carcinoid tumors had only appendicectomies except one of them who had a right hemicolecotomy for a 10mm tumor invading the muscle and with Ki67 less than 10%. Adjuvant chemotherapy is recommended in those with lymph node involvement while those with intra-abdominal metastases require aggressive debulking surgery followed by adjuvant chemo-radiotherapy [26]. Hata et al. published a review in 2002, the paper reiterated that well-differentiated adenocarcinoma invading the submucosa or adenocarcinoma of any differentiation limited to the mucosa can be safely treated with appendicectomy [27]. On the other hand, adenocarcinoma with lymphatic/vascular invasion, poorly differentiated tumors, those with a massive invasion of the submucosa as well as advanced appendicular cancer are treated with secondary right hemicolecotomy with lymph node excision. All the patients in this study with advanced disease were offered adjuvant treatment such as right hemicolecotomy, cytoreductive surgery, or chemotherapy. Appendicular carcinoid exhibit a variable spectrum of biological behavior, the patient gender, and tumor pathomorphological are associated with OS (overall survival) in advanced cases of appendiceal carcinoma [10]. The published reports have shown that elevated pre-
management tumor marker levels as CEA, CA 19-9 and CA125, to be associated with higher rates of disease recurrence and reduced survival after complete cytoreductive surgery. Other factors associated with poor prognosis include poor tumor differentiation and extension beyond the appendiceal mucosa [28]. The Ki-67 proliferative index which has been placed in prognosis prediction in some areas as breast cancer [29], claimed to be of no prognostic significance for some appendicular tumors as goblet cell carcinoid tumors [30].

Conclusions
Fortunately, incidental appendiceal cancers in the resected specimens after acute appendicitis are rare, however may be associated with poor prognosis. It is recommended to consider such diagnosis in particular when dealing with acute appendicitis in older patients with longer symptom history, and in presence of periappendicular mass. There were some limitations to the study; small sample size and a short follow-up period. The patients reviewed were over 40 years and though the incidence is higher in older age groups, some younger patients with malignancy would have been not included in the study.

Additional Information
Disclosures
Human subjects: Consent was obtained or waived by all participants in this study. Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References
1. Stewart B, Khanduri P, McCord C, Obene-Yepaoh M, Uruna S, Vega Rivera F, Mock C: Global disease burden of conditions requiring emergency surgery. Br J Surg, 2014, 101:e9-22. 10.1002/bjs.9329
2. Baird DL, Simillis C, Kontovounios C, Rashheed S, Tekkis PP: Acute appendicitis. BMJ, 2017, 357:j1703. 10.1136/bmj.j1703
3. Bhangoo A, Sareide K, Di Saverio S, Assarsson JH, Drake FT: Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. Lancet, 2015, 386:1278-87. 10.1016/S0140-6736(15)00275-5
4. Tayfur M, Balci MG: Pathological changes in appendectomy specimens including the role of parasites: A retrospective study of 2400 cases of acute appendicitis. Niger J Clin Pract. 2019, 22:270-5. 10.4103/njcp.njcp_271_18
5. Shroff N, Bhargava P: Metastatic colonic adenocarcinoma presenting as acute appendicitis. Radiol Case Rep. 2021, 16:2129-32. 10.1016/j.radcr.2021.04.077
6. Lai HW, Loong CC, Tai LC, Wu CW, Lui WY: Incidence and odds ratio of appendicitis as first manifestation of colon cancer: a retrospective analysis of 1875 patients. J Gastroenterol Hepatol. 2006, 21:1695-6. 10.1111/j.1440-1746.2006.04426.x
7. Hennessy MM, Ivanovski IF: Appendiceal adenocarcinoma-Two unique cases of adenocarcinoma ex-goblet cell carcinoid. Clin Case Rep. 2019, 7:806-8. 10.1002/ccr3.2078
8. Elting AW: IX. Primary Carcinoma of the Vermiform Appendix, with a Report of Three Cases. Ann Surg. 1903, 7:549-74.
9. O’Donnell ME, Badger SA, Beattie GC, Carson J, Garstin WI: Malignant neoplasms of the appendix. Int J Colorectal Dis. 2007, 22:1259-48. 10.1007/s00384-007-0504-0
10. Khan F, Vogel RI, Diep GK, Tuttle TM, Lou E: Prognostic factors for survival in advanced appendiceal cancers. Cancer Biomark. 2016, 17:457-62. 10.3233/CBM-160662
11. Lu Y, Li F, Ma R, Fang L, Qi C: Clinicopathological features of low-grade appendiceal mucinous neoplasms confined to the appendix. Front Oncol. 2021, 11:696846. 10.3389/fonc.2021.696846
12. Shaib WL, Ans R, Shamseddine A, et al.: Appendiceal mucinous neoplasms: diagnosis and management. Oncologist. 2017, 22:1107-16. 10.1634/theoncologist.2017-0081
13. Benedix F, Reimer A, Gastinger I, Mroczkowski P, Lippert H, Kube R: Primary appendiceal carcinoma--epidemiology, surgery and survival: results of a German multi-center study. Eur J Surg Oncol. 2010, 36:763-71. 10.1016/j.ejso.2010.05.025
14. Cortina R, McCormick J, Kohn P, Perry RR: Management and prognosis of adenocarcinoma of the appendix. Dis Colon Rectum. 1995, 38:848-52. 10.1007/BF02049842
15. da Silva JJ, Caetano C, da Rocha AM, Lamas NJ, Lago P, Pedrotto IM: A rare case subepithelial tumor in a Crohn’s Disease patient. Autops Case Rep. 2020, 11:e2020211. 10.4522/acr.2020.211
16. Rosat A, Pérez E, Sánchez JM, González OB, Barrera M: Vesico-appendiceal fistula secondary to adenocarcinoma of the appendix: a case report and literature review. Pan Afr Med J. 2020, 37:97. 10.11604/pamj.2020.37.97.10653
17. Nitecki SS, Wolff BG, Schlinkert R, Sarr MG: The natural history of surgically treated primary adenocarcinoma of the appendix. Ann Surg. 1994, 219:51-7. 10.1097/00000658-199401000-00009
18. Pickhardt PJ, Levy AD, Rohmann CA Jr, Kende AI: Primary neoplasms of the appendix: radiologic spectrum of disease with pathologic correlation. Radiographics. 2005, 25:645-62. 10.1148/rg.2530251534
19. Deshmukh S, Verde F, Johnson PT, Fishman EK, Macura KJ: Anatomical variants and pathologies of the vermiform. Emerg Radiol. 2014, 21:545-52. 10.1007/s10140-014-1206-4
20. McCusker ME, Coté 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, 94:5307-12. 10.1002/cncr.10589
21. Saad Abdalla Al-Zawi A: Adenocarcinoma of appendix mimicking acute appendicitis: A case report and literature review. Eur J Pharm Med Res. 2018, 5:104-107.
22. Iwuagwu OC, Jameel JK, Drew PJ, Hartley JE, Monson JR: Dig Surg. 2005. 10.1159/000087134
23. Roy P, Chetty R: Goblet cell carcinoid tumors of the appendix: An overview. World J Gastrointest Oncol. 2010, 2:251-8. 10.4251/wjgo.v2.i6.251
24. Chen KT: Appendiceal adenocarcinoid with ovarian metastasis. Gynecol Oncol. 1990, 38:286-8. 10.1016/0090-8258(90)90057-r
25. Plöckinger U, Couvelard A, Falconi M, et al.: Consensus guidelines for the management of patients with digestive neuroendocrine tumours: well-differentiated tumour/carcinoma of the appendix and goblet cell carcinoma. Neuroendocrinology. 2008, 87:20-30. 10.1159/000109876
26. Kalpande S, Pandya J, Sharma T: Adenocarcinoma mimicking appendicular lump: a diagnostic dilemma-a case report. World J Surg Oncol. 2016, 14:283. 10.1186/s12957-016-1056-9
27. Hata K, Tanaka N, Nomura Y, Wada I, Nagawa H: Early appendiceal adenocarcinoma. A review of the literature with special reference to optimal surgical procedures. J Gastroenterol. 2002, 37:210-4. 10.1007/s0053502000023
28. Tafllampas P, Dayal S, Chandrakumaran K, Mohamed F, Cecil TD, Moran BJ: Pre-operative tumour marker status predicts recurrence and survival after complete cytoreduction and hyperthermic intraperitoneal chemotherapy for appendiceal Pseudomyxoma Peritonei: Analysis of 519 patients. Eur J Surg Oncol. 2014, 40:515-20. 10.1016/j.ejso.2013.12.021
29. A Saad Abdalla Al-Zawi: The Oncotype DX recurrence score impact on the management of ER+VE, HER2-VE, node negative breast cancer. Medical Research Journal. 2021, 6:4. 10.5603/MRJ.e2021.0041
30. Liu E, Telem DA, Warner RR, Dikman A, Divino CM: The role of Ki-67 in predicting biological behavior of goblet cell carcinoid tumor in appendix. Am J Surg. 2011, 202:400-3. 10.1016/j.amjsurg.2010.08.036