

## Evaluating the Surgical Management of Appendiceal Neoplasms Diagnosed following Appendicectomy

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### Abstract

Appendix neoplasms are rare tumours and are often incidentally diagnosed. Management of tumours post operatively are dependent on tumour type, size and histological features.

### *Aims*

To evaluate the incidence of appendix neoplasms managed in a large Irish hospital and to determine compliance with international guidelines such as European Neuroendocrine Tumour Society (ENETS) and American Society of Colon and Rectal Surgeons (ASCRS) for appendiceal neuroendocrine tumours (NET) and low grade appendiceal mucinous neoplasms (LAMN) respectively.

### *Methods*

A prospectively maintained gastrointestinal oncology database was studied over a six year period (July 2016-July 2022). Data gathered include patient demographics, clinical presentation, management and follow up. Histopathological staging was according to the American Joint Committee on Cancer (AJCC) 8<sup>th</sup> edition.

### *Results*

The incidence of appendix neoplasm amongst patients who underwent appendicectomy over the study period was 1.3% (16/1,259). These comprised of 8 NET, 5 LAMN, 2 invasive adenocarcinoma and 1 adenocarcinoid. The majority were managed with appendicectomy (14/16, 87.5%). Following discussion at tumour board meeting, one patient underwent right hemicolectomy. Four patients were enrolled on a surveillance programme. A further four with LAMN underwent only appendicectomy and one had appendicectomy and partial caecectomy. Surveillance was not deemed necessary in any of the LAMN cases.

### *Conclusion*

Findings on incidence of appendix neoplasm in our centre is comparable to that reported in larger series (2.0%). Clinician adherence to the recommended consensus guidelines and literature for appendiceal NET and LAMN cases we had over the study period were satisfactory.

## Introduction

Appendiceal neoplasms are rare tumours, with an incidental histological diagnosis occurring in less than 2.0% of appendicectomies performed<sup>1</sup>. Approximately 30.0 - 50.0% of appendiceal tumours are diagnosed following as an episode of acute appendicitis, which necessitates emergency appendicectomy for definitive treatment<sup>2</sup>. In recent years, there is an increased prevalence of appendiceal tumours diagnosed<sup>3</sup>, which this is likely due to the increased number of appendicectomies performed<sup>3</sup>, and recent data illustrates that there are 124.4 appendicectomies performed annually per 100,000 people in the Republic of Ireland<sup>4,5</sup>. On the contrary, patient can also be symptomatic with severe abdominal pain with associated haematochezia necessitating a right hemicolectomy with confirmed histopathological findings of low-grade appendiceal neoplasms (LAMN)<sup>6</sup>. Therefore, given the increased prevalence of such tumours, it is important that the surgeons' appreciation for the histopathological and clinical characteristics of the disease spectrum aligns with contemporary surgical practice<sup>7</sup>.

There are five main histopathologic subtypes of appendiceal neoplasms<sup>8</sup>. These include mucinous adenocarcinomas (46.0%), adenocarcinomas (30.0%), goblet cell carcinoids (12.0%), pseudomyxoma peritonei (PMP) (7.7%), and signet ring cell carcinomas (5.2%)<sup>8</sup>. On occasion, neuroendocrine tumours (NETs) of the appendix may be also be diagnosed and these tend to be indolent cancers which are increasingly prevalent in recent decades<sup>9</sup>. NETs may be functional tumours, and are most commonly located in the small bowel, followed closely by rectum and appendix<sup>10,11,12</sup>. Notwithstanding biological differences in these tumours, surgical resection with appendicectomy is the definitive strategy in treating appendiceal cancers, particularly in cases of LAMN<sup>13</sup>. Importantly, high-grade appendiceal neoplasms typically require surgical management with right hemicolectomy<sup>13</sup>. Surveillance of appendiceal cancers may be indicated in certain incidences, which include tumours >1cm with any poor prognostic features (i.e. high Ki-67 expression, tumours involving the base of the appendix, meso-appendiceal invasion of >3mm, grade 2 NET, or tumour vascular invasion)<sup>13</sup>. Overall, it is imperative that such cancers are managed in the setting of by the tumour board to ensure optimisation of patient outcomes for those diagnosed with appendiceal cancers<sup>14</sup>. Thus, appraisal of the management of such practices is of the utmost importance, particularly when large volume datasets suggest managing these cancers in accordance with multidisciplinary meeting (MDM) decisions improves long-term oncological outcomes<sup>15</sup>. Accordingly, the aim of the current study was to audit our institution's experience with the management of appendiceal neoplasms over a 6 year eligibility period.

## Methods

### *2.1 Patient Selection*

Institutional review board permission was not required, as this is an audit of the management of appendiceal cancers. A single centre, retrospective audit of all patients who underwent appendicectomy during a 6 year eligibility period (July 2016 to July 2022) were included. All patients had to have their surgery at the Department of General Surgery in Galway University Hospital in the Republic of Ireland. Both open and laparoscopic appendicectomy were considered for inclusion with confirmation sought through local hospital operating theatre register. Patients with confirmed histopathological diagnosis of acute appendicitis were excluded while confirmed appendiceal neoplasms following appendicectomy were included. Patient demographics, clinical presentation, management and follow up plan were obtained from Evolve© (Kainos Group PLC, Belfast, Northern Ireland) electronic patient medical record system.

### *2.2 Histopathologic and Immunohistochemical Appraisal*

Assessment of each resected surgical specimen report was performed using the institution's specimen record system, i-Lab© (ISOFT HEALTH (Ireland) Ltd., Liffey Park Technology Campus, Ireland). Tumour specimens were analysed in accordance with the American Joint Committee on Cancer (AJCC) 8<sup>th</sup> edition for diagnostic and staging of these appendiceal neoplasms as per the tumour, nodes and metastasis (TNM) staging<sup>16</sup>. Histological presence of mucin confined in the appendix is diagnostic for LAMN<sup>17</sup>. In this centre, staining with Chromogranin A, Synaptophysin, and CD56 were used to identify NET<sup>18</sup>, while mitotic count and Ki-67 proliferation indices were utilised to grade tumours<sup>19</sup>. Histopathological tumour grading of appendiceal NET was established using the World Health Organisation (WHO) Grading of Neuroendocrine Neoplasms<sup>3</sup>.

### *2.3 Multidisciplinary Approach to Treatment*

Clinical abdominal examinations were performed by Consultant general surgeon. If performed, pre-operative computed tomography (CT) imaging was then evaluated by Consultant radiologist with expertise in gastrointestinal pathology. Resected specimens were then analysed by a Consultant Histopathologist with a special interest in gastrointestinal malignancy. Reports were then utilised to aid discussion in gastrointestinal MDM held weekly in our institution. This facilitates tailored treatment strategies and management plans for each patient in appreciation of best practice guidelines based on clinical, radiological, histopathological data as well taking each patient's wishes into consideration.

### *2.4 Patient Follow Up*

Record of patients' follow up plan was recorded in a prospectively maintained database. The institutional electronic patient medical records were then assessed for the MDT consensus or clinic letters for follow up plan post-appendicectomy on each patient. This included colonoscopy, ultrasound sonography, octreotide scan, positron emission tomography (PET) scan, magnetic resonance imaging (MRI) scan and CT surveillance based on tumour stage and size.

## 2.5 Statistical Analysis

Basic descriptive analyses were performed. Data were analysed using Statistical Package for Social Sciences (SPSS) version 26 (International Business Machines Corporation, Armonk, New York).

## Results

### 3.1 Patient Demographics

During the 6 year eligibility period, a total of 1,259 patients were diagnosed with acute appendicitis and underwent appendicectomy in our institution. Of these 1,039 had confirmed appendicitis on their histopathology specimen (82.5%). Out of the 1,259 cases, 16 patients had appendiceal neoplasms and met inclusion criteria for the current study (1.3%). In total, 7 patients were male and 9 patients were female (44.0% and 56.0% respectively). The mean age at the time of appendiceal cancer diagnosis was (range: 10-74 years, median age: 28).

### 3.2 Appendiceal Neoplasms

Out of the 16 included cases of appendiceal cancers, 8 were NET (50.0%), 5 were LAMN (31.0%), 2 were invasive adenocarcinoma (12.5%) and 1 case was an adenocarcinoid tumour (12.5%). In this study, 10 had symptomatic presentations (63%), while 6 had asymptomatic presentations (37%)

### 3.3 Appendiceal Neuroendocrine Tumours

The majority of patients with appendiceal NET were females (63.0%, 5/8 cases) and (37%, 3/8 cases) were males. The mean age at the time of appendiceal NET diagnosis was 22.4 (range 10-41 years, median age: 22). Of the 8 NET cases, 6 were grade 1 tumours (75.0%) and 2 were grade 2 tumours (25.0%). The majority of tumours were <1.0 cm (50.0%, 4/8 cases), with 25.0% of tumours being 1.0-2.0 cm and >2.0cm in size respectively (both 2/8 cases). Most cases of appendiceal NET underwent appendicectomy (87.5%, 7/8 cases) and one patient underwent right hemicolectomy (12.5%). In contrast to ENETS guidelines which recommended no specific follow up plan for tumour size <1cm, 1 patient received post operative CT scan. As indicated in ENETS guidelines, another patient with tumour size of 1-2cm received a follow up Octreotide scan and colonoscopy and 2 patients with tumour size of ≥2cm received a follow up Octreotide scan, CT scan and MRI scan, whilst another patient underwent post-operative CT scan, PET scan, MRI scan and colonoscopy.

### 3.4 LAMN

Of the 5 cases of LAMN, 80.0% were stage pTis (4/5 cases) and there was just one case with pT4 disease (1/5 case). There were more male patients with LAMN (60.0%, 3/5 cases) compared to females (40.0%, 2/5 cases). The mean age at diagnosis for LAMN was 60.4 years (range 44-74 years, median age 64).

All 4 of the pTis LAMN cases underwent laparoscopic appendicectomy. Of these, 2 with were followed up with surveillance CTs and colonoscopy (50.0%, 2/4), another had an interval

colonoscopy only (25.0%, 1/4) and one patient was discharged following postoperative review in the colorectal clinic (25.0%, 1/4). The one patient with pT4 disease underwent laparoscopic caecectomy and underwent post-operative surveillance with both CT and colonoscopy. Overall follow up plan for these tumours were in keeping with ASCRS guidelines for tailored postoperative management depending on tumour features and patients characteristics.

### 3.5 Outcomes

All 16 patients included in this analysis were free of disease recurrence at median follow up of 38.0 months (range: 6-41 months).

## Discussion

This study represents the first review of contemporary management of appendiceal cancers in a large Irish teaching hospital. The most important finding in this review of 1,259 patients who were managed for acute appendicitis, is the data illustrating the excellent oncological and survival outcomes observed by these patients at intermediate term follow up. Accordingly, despite just 1.3% of patients yielding cancerous histology, recent efforts<sup>20</sup> to increase clinician awareness of how to appropriately manage appendiceal tumours prove to have been fruitful in surgical practice in our unit.

Though NET accounted for histology in just 0.2-0.7% of all appendicectomies performed during this eligibility period, these cancers represent for 50.0% of all appendiceal neoplasms<sup>15,16</sup>. Preoperative diagnosis is very challenging for the surgeon, with a proportion of patients typically being asymptomatic when harbouring these tumours<sup>21</sup>. For example, a population-based study performed by Alkhayyat et al. illustrated that female patients were more likely to be diagnosed with appendiceal NETs than their male counterparts, with Caucasians being most likely to be diagnosed with NET (12). Furthermore, Moris et al. previously highlighted that the incidence rate of NET is highest in those aged 15-29 years old<sup>11</sup>, largely in keeping with the demographics of the current study: Overall, 63.0% of all patients were female, 100.0% were Caucasian, and 50.0% were 18 years or younger at the time of diagnosis. Thus, this illustrates that our study supports the perceptions cast of classical appendiceal NET and raises awareness of this potential diagnosis for prospective patients.

Furthermore, surgical adherence to international guidelines was investigated. Within the ENETS Consensus Guidelines, experts recommend that no definite follow up plan is required for resected tumours <1cm, however regular follow up investigations for tumours between 1-2cm with significant risk factors for lymph node metastases (i.e.: basal appendiceal tumour, mesoappendiceal invasion of >3mm, grade 2 disease or the presence of lymphovascular invasion) is recommended (3). The current analysis illustrates that despite patients not being placed formally on a surveillance program, 3 patients (including 1 patient with tumour size between 1-2cm and 2 with >2cm tumours) underwent post-operative followed up, all of whom were negative for disease recurrence. Therefore, this practice may be challenged and considered controversial, due to the rarity of such

tumours developing distant metastases, combined with the potential unnecessary overexposure of these patients to repeat high dose radiation cumulatively due to repeat CT as part of surveillance<sup>22,23</sup>, particularly in an economically challenged healthcare service, as seen in the Republic of Ireland. Furthermore, the influence of surveillance and its accuracy in identification of tumour recurrence remains controversial with the perceived benefit remaining somewhat unclear at present<sup>4</sup>.

Importantly, both NCCN and NANET guidelines provide congruency in recommending that tumours >2cm require active surveillance (24): For NCCN, routine thorough history and physical exam, tumour marker levels measurement (i.e.: 5-Hydroxyindoleacetic acid (5-HIAA) and chromogranin) and CT and/or MRI imaging as clinically indicated. Similar is recommended by NANET, where these investigations are due every 3-6 months in the first 12 months post operatively, before being conducted every 6-12 months for at a minimum of 7 years subsequently (24). There is however some discordance between this guidelines where ENETS highlights the sensitivities of tumour markers and imaging in detecting tumour recurrence<sup>4</sup>, which is not highlighted in NCCN<sup>25</sup>. In their recent study, Bahmad et al. demonstrated that 15.0% of patients with NET present with metastatic disease, thus the role of tumour markers combined with imaging and endoscopy is imperative to accurately stage these tumours, while ensuring the detection of synchronous lesions if present<sup>1</sup>.

When evaluating the incidence of disease recurrence and mortality following appendiceal neoplasms, previous studies have demonstrated that the risk of recurrence may be delayed until 25 years after initial diagnosis, illustrating the indolent nature of these tumours<sup>26</sup>. In the current analysis, the overall survival was 100.0% at 38.0 months follow up, consistent with the 10 year survival rate of 100.0% as previously observed by Murray et al.<sup>23</sup> In a previous multicentre observational study from Germany, patients with NET experienced an 83.1% overall survival at 5-years compared to 49.2% in other non-carcinoid appendiceal neoplasms<sup>14</sup>. Thus, it may be potentiated that these tumours indolent biology, accurate diagnosis and definitive surgical management seem to enhance the prognoses which may be expected for those diagnosed with appendiceal NET<sup>11</sup>. Notwithstanding NET diagnoses propagating reassuring prognoses, there remains widespread inconsistencies in institutional adherence to recommended surveillance regimens<sup>27</sup>. From their analysis of United States registry data, Heller et al. highlighted that 32.4% of patients with appendiceal NET of <2cm tumours underwent right hemicolectomy while 31.3% of patients with >2cm tumours were treated with definitive appendicectomy management of NET (27). Though surgical approach was not associated with poorer overall survival for these patients, the rationale for non-adherence should be further elucidated, as assessed in the current analysis.

There is considerable variability in the presentation of patients with LAMN. While a study by Yu et al. observed that the majority of patients with LAMN typically have symptomatic presentations (82.3%) (28), while another study by Rymer et al. has yielded results directly contradictory to these findings, through suggesting that as high as 50% of patients are asymptomatic at presentation<sup>29</sup>. In the current study, most patients presented with symptoms suggestive of acute appendicitis, while two were asymptomatic and were diagnosed incidentally on imaging. Importantly, LAMN is typically



detectable on imaging<sup>30</sup>, yet just 2 patients in the current study had LAMN identified on CT scan pre-operatively. Therefore, the authors advocate for surgeons to consider the *a priori* diagnosis of LAMN in the setting of a bulky macroscopic appendiceal mass that previously appeared normal on preoperative imaging.

According to the American Society of Colon and Rectal Surgeons (ASCRS) guidelines, patients with localised low-grade tumours rarely require close postoperative surveillance, due to these tumours rarely disseminating and progressing to PMP. If indicated, an MRI scan with aforementioned tumour markers measured every 6 months for 24 months seems a valid strategy, due to most recurrences occurring within this time frame<sup>31</sup>. Other more advanced cases, such as those with tumour perforation, indeterminate surgical margins, and lymphatic and/or peritoneal involvement, typically will require CT or MRI every 4 to 6 months for the first 2 and annually after for  $\geq 5$  years<sup>31,32</sup>. A previous review of the Peritoneal Surface Oncology Group International (PSOGI)/European Reference Network (ERN EURACAN) clinical guidelines for the management of appendiceal neoplasms and PMP, authors recommended that follow up plans for PMP should involve physical examination and routine CT of the thorax, abdomen and pelvis (TAP) every 6 months for the first 24 months<sup>33</sup>. Thereafter this disease is then followed up by repeat physical examination, tumour marker measurement every 6 months, and CT TAP each year, in particular for 24 months post cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC)<sup>33</sup>. In the current analysis, this was not audited due to the prevalence of no advanced cases. A local protocol was developed and implemented based on the finding of a retrospective study performed in India where authors reiterated that unless intraoperative mucin spillage is evident (or other clinical suspicion), no post-operative surveillance is necessitated for these tumours<sup>34</sup>. Several previous studies have reassured the authors of the current study that there is a low recurrence rate associated with totally resected appendiceal tumours, however clinician adherence to recommendations seems variable with post-operatively in patients discussed in the multidisciplinary team setting, with overcautious decisions triggering surveillance<sup>20, 35, 36</sup>. This hypothesis seems a likely explanation for the surveillance observed in the current study.

In conclusion, these data has reconfirmed the rarity of appendiceal neoplasms with just 1.3% of appendicectomies performed yielding malignant histology in our centre. Clinician adherence to the recommended consensus guidelines for the management of appendiceal NET and LAMN cases during the study period were satisfactory. The majority of these patients may be satisfactorily managed in a tertiary regional referral centre, in accordance with guidelines. Hence, we may conclude that clinician adherence towards recommended follow up plan and surveillance post appendicectomy in our institution was satisfactory over the study period.

**Declarations of Conflicts of Interest:**

None declared.

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