Occult appendix pathology in patients undergoing colorectal cancer resection: is there a role for incidental appendectomy?

Francesco Fabio (francesco.difabio@hhft.nhs.uk)
Colorectal Surgery, Basingsgtoke North Hampshire Hospital

Prabhu Ravi
Colorectal Surgery, Basingsgtoke North Hampshire Hospital

Niccolo Allievi
Colorectal Surgery, Basingsgtoke North Hampshire Hospital

Kashuf A Khan
Colorectal Surgery, Basingsgtoke North Hampshire Hospital

Abu Abduelraheim
Colorectal Surgery, Basingsgtoke North Hampshire Hospital

Brendan Moran
Colorectal Surgery, Basingsgtoke North Hampshire Hospital

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Abstract

Purpose
The risk to benefit balance of incidental appendectomy in patients undergoing left colorectal cancer resection is unclear. The aim is to assess the proportion of histologically abnormal appendices in patients undergoing colorectal cancer resection in a unit where standard of care is appendectomy, with consent, when left-sided resection is performed.

Methods
Retrospective study on prospectively collected database, conducted in a single tertiary-care centre. Overall, 717 consecutive patients undergoing colorectal cancer resection between January 2015 and June 2021 were analysed. The primary outcome was the proportion of histologically abnormal appendix specimens at incidental appendectomy. Secondary outcome was complications from incidental appendectomy.

Results
Overall, 576/717(80%) patients had appendectomy at colorectal cancer surgery. In total, 234/576(41%) had a right-/extended-right hemicolectomy or sub-total colectomy which incorporates appendectomy, and 342/576(59%) had left-sided resection (left-hemicolectomy, anterior resection or abdomino-perineal excision) with incidental appendectomy.

At definitive histology, 534/576(92.7%) had a normal appendix. The remaining 42/576(7.3%) showed abnormal findings, including: 14/576(2.4%) inflammatory appendix pathology, 2/576(0.3%) endometriosis, 8/576(1.4%) hyperplastic polyp, and 18/576(3.1%) appendix tumours, which encompassed 6 low-grade appendiceal mucinous neoplasms (LAMN), 3 carcinoids and 9 serrated polyps.

In the 342 patients who had incidental appendectomy, 10(2.9%) had a neoplasm (2 LAMN, 3 carcinoids and 5 serrated polyps). There were no complications attributable to appendectomy.

Conclusion
Patients undergoing left sided colorectal cancer surgery with an appendix in situ may benefit from a co-incidental appendectomy to treat the small proportion of synchronous neoplasms and eradicate the risk of metachronous appendicitis or a subsequent appendix tumour.

Introduction
The risk to benefit balance of removing a macroscopically normal appendix during colorectal cancer surgery is debateable. Benefits may accrue by removal of incidental pathology and avoidance of future
appendicitis or malignancy, balanced against complications attributable to an appendectomy.

Luminal pathology detected in a normal looking appendix include inflammatory changes, benign polyps and neoplasms. Appendix neoplasms are rare, and the age-adjusted incidence is 0.12 cases per one million people per year [1, 2]. Approximately 50% of appendix neoplasms present as acute appendicitis [3], and the remainder found incidentally at radiological imaging, during laparotomy or laparoscopy for other abdominal pathology or detected pathologically in incidental appendectomy specimens [4].

In reports on large numbers of appendectomy specimens, the proportion of appendiceal neoplasms has been estimated to range from 0.8 to 1.4% [1]. However, appendiceal neoplasms are more frequent in patients who present with an appendix mass. Reports of interval appendicectomy after initial conservative treatment suggest that 6–12% have an underlying appendix neoplasm [5, 6].

The aim of this study is to assess the proportion of histologically abnormal appendices in patients undergoing colorectal cancer resection in a unit where standard of care is incidental appendectomy, with consent, when left colon or rectal cancer resection is performed.

**Materials & Methods**

This is a retrospective single-centre study on a prospectively collected data base of 717 consecutive patients undergoing colorectal cancer resection between January 2015 and June 2021. The data is based on service delivery and assessment, and thus does not require formal review by the Institutional Review Board.

It is standard of care in our unit to perform incidental appendectomy, with fully informed consent, when left colon or rectal cancer resection is performed based on previous publications in this field [7–10].

Incidental appendectomy is defined as the removal of a macroscopically normal looking vermiform appendix whilst performing another abdominal operation.

Consecutive patients comprised two groups, those undergoing colorectal cancer resection with right hemicoleectomy, extended-right hemicoleectomy or sub-total colectomy which incorporates appendectomy, and patients undergoing left-sided resection (left-hemicoleectomy, anterior resection or abdomino-perineal excision) with incidental appendectomy. Patients with known primary and metastatic appendix neoplasia were excluded.

The primary tumours of the appendix include epithelial and non-epithelial tumours. An epithelial tumour can be benign (the muscularis mucosae is intact), such as tubular, tubulo-villous, villous adenoma or serrated polyp, or malignant, including low grade appendiceal mucinous neoplasm (LAMN), high-grade appendiceal mucinous neoplasm (HAMN), mucinous adenocarcinoma, signet-ring cell adenocarcinoma, and non-mucinous intestinal-type adenocarcinoma. The non-epithelial tumours include carcinoid tumours and mesenchymal tumours [11, 12].
Demographics, American Society of Anaesthesiologists (ASA) Physical Status Classification System and the open/laparoscopic approach were reviewed.

Histopathology reports were retrieved from hospital records. The proportion who had previous appendicectomy and those who had the appendix left in situ at left colon or rectal resection were recorded.

All patients were discussed at the colorectal cancer multidisciplinary team meeting (MDT). When a neoplasm of the appendix was reported by the pathologist, a formal referral was made to the dedicated peritoneal malignancy MDT in case of an epithelial appendiceal neoplasm, or to the carcinoid MDT in case of a neuro-endocrine tumour, to establish a definitive management or surveillance plan.

The study period of 5.5 years was considered an appropriate interval within which to achieve a meaningful number of cases to assess study outcomes.

The primary outcome is the proportion of histologically abnormal appendix specimens at incidental appendectomy. Secondary outcome was specific complications from incidental appendectomy.

Data were collected in an Excel spreadsheet. The analyses were performed using the statistical software STATA (College Station, Texas). Median values and interquartile range (IQR) were considered for continuous variables as their value distribution was skewed. Pearson's chi-square test was applied for analysis of categorical variables. The level of statistical significance was set at p < 0.05.

Results

The median age of the 717 patients included was 70 years (IQR: 62–77 years) and 422/717(59%) were male.

Overall, 36(5%), 502(70%), 177(24.7%), and 2(0.3%) patients were ASA 1, 2, 3, and 4, respectively. The laparoscopic approach was used in 438/717(61%) operations.

A total of 91(13%) patients had previous appendicectomy. In the right-sided resection group, 37/271(14%) had previous appendicectomy vs. 54/446(12%) in the left-sided resection group. In 50/446(11%) patients undergoing left sided or rectal resection the appendix was not removed due to technical difficulties or where consent had not been documented.

The appendix was available for histopathological analysis in 576/717(80%) patients undergoing colorectal cancer surgery. Of these, 234/576(41%) had a right hemicolecetomy, extended-right hemicolecetomy or sub-total colectomy which incorporates appendectomy. The remaining 342/576(59%) had left-sided resection (left-hemicolecetomy, anterior resection or abdomino-perineal excision) with incidental appendectomy.
At definitive histology, 534/576(92.7%) had a normal appendix. The remaining 42/576(7.3%) showed abnormal findings, including: 14/576(2.4%) inflammatory appendix pathology, 2/576(0.3%) endometriosis, 8/576(1.4%) hyperplastic polyp, and 18/576(3.1%) appendix tumours, which encompassed 6 LAMN, 3 carcinoids and 9 serrated polyps.

In the 342 patients who had incidental appendectomy, 10(2.9%) had a neoplasm (2 LAMN, 3 carcinoids and 5 serrated polyps).

The definitive histology of the appendix specimen in patients having right-sided resection or sub-total colectomy vs. patients having left-sided resection and incidental appendectomy showed no substantial differences (Table 1).

Table 1. Characteristics of the 717 patients.

<table>
<thead>
<tr>
<th></th>
<th>Right-hemicolectomy or sub-total colectomy (n=271)</th>
<th>Left-sided resection with incidental appendectomy (n=446)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No appendix available for histopathological analysis</td>
<td>37/271 (14%)</td>
<td>104/446 (23%)</td>
</tr>
<tr>
<td>-Previous appendectomy</td>
<td>37/271 (14%)</td>
<td>54/446 (12%)</td>
</tr>
<tr>
<td>-Appendix not removed</td>
<td>-</td>
<td>50/446 (11%)</td>
</tr>
<tr>
<td>Appendix available for histopathological analysis</td>
<td>234</td>
<td>342</td>
</tr>
<tr>
<td>Normal appendix</td>
<td>216 (92.3%)</td>
<td>318 (93.0%)</td>
</tr>
<tr>
<td>Inflamatory pathology</td>
<td>6 (2.5%)</td>
<td>8 (2.3%)</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>0</td>
<td>2 (0.6%)</td>
</tr>
<tr>
<td>Hyperplastic polyp</td>
<td>4 (1.7%)</td>
<td>4 (1.2%)</td>
</tr>
<tr>
<td>Appendix neoplasms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serrated polyp</td>
<td>8 (3.4%)</td>
<td>10 (2.9%)</td>
</tr>
<tr>
<td>LAMIN</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

Excluding patients who had previous appendectomy, the proportion of appendixes left in place during left-sided resection was double when the laparoscopic approach was adopted, 39/247(16%) vs. 11/145(8%) in open procedures (p = 0.019).

There were no complications attributable to appendectomy.

Discussion
The decision on whether to remove a normal looking appendix during colorectal cancer resection should be based on the likelihood of finding incidental appendix pathology and prevention of future appendix pathology balanced against the safety of the procedure. The current data demonstrates that 42/576 (7.3%) of incidental appendectomy specimens had abnormal findings at definitive histology with 18/42 (43%) having a tumour, including 6 LAMN, 3 carcinoids and 9 serrated polyps.

The prevalence of appendix tumours in appendicectomy specimens has been reported in recent large series to be between 0.8%-1.4% [1]. These data are mainly based on patients who have appendectomy for appendicitis, with little data on appendix pathology at incidental appendectomy for macroscopically normal-looking appendices. In this series,1.6% of patients overall had an appendix malignant tumour, with 1.5% when considering only incidental appendectomy during left-sided colorectal resection. Similarly, 1.6% of patients had a premalignant appendix tumour (i.e.: serrated polyp), with 1.5% when considering only incidental appendectomy during left-sided colorectal resection.

The rates of appendiceal pathology reported here may seem higher than observed in generic colorectal resection practice. This is undoubtedly due to a department interest in appendix tumours with dedicated pathologists prepared to analyse the appendix, even if part of a right hemicolectomy specimen.

Historically, the most common primary appendiceal tumour diagnosed after appendectomy for appendicitis was carcinoid in up to 85%, with epithelial appendix neoplasms in about 20% [1]. In this report the most common tumour type was a LAMN. It is now well established that ruptured appendiceal epithelial neoplasms are the predominant cause of pseudomyxoma peritonei (PMP) [12, 13] and removal of a non-ruptured appendiceal tumour can abolish the risk of subsequent PMP development.

In a patient where a carcinoid tumour is accidentally found in the specimen, appendicectomy alone is adequate treatment for tumours < 1cm in diameter where complete resection has been achieved. For tumours measuring between 1 and 2cm in diameter, right hemicolecotomy is selectively advocated, particularly with high-risk features such as mesoappendix invasion > 3mm, presence of angioinvasion, and Grade 2 histology. For tumours > 2cm in diameter, due to a greater risk of nodal involvement, right hemicolecotomy is recommended [14].

Seventeen appendix specimens (2.9%) were found to contain polyps, including serrated polyps (1.5%) and hyperplastic polyps (1.4%).

Serrated polyps are histologically similar to the sessile serrated lesions of the colon and rectum [12]. However, it has been shown that the molecular pathological changes are different from those found in colorectal lesions. In particular, KRAS mutations are more common and BRAF mutations less common in appendiceal serrated polyps, reflecting the fact that the serrated pathway in the appendix is probably different from that in the colon and rectum [15]. Although appendix serrated polyps are rare lesions, published series report an association of appendiceal serrated polyps with appendicitis and malignant progression [16–18]. Serrated polyps are pre-cancerous lesions and differentiating them from hyperplastic polyps is clinically important. Rubio et al [17] previously warned about aggressiveness of
serrated polyps and Chezar at al [16] more recently published data suggesting that at least a subset of LAMNs may arise from a precursor serrated polyp.

Hyperplastic polyps tend to be overall rarer in the appendix compared with the incidence in the colon and rectum [12] and are commonly benign lesions.

Over 2% of patients in this series showed evidence of inflammatory changes in the appendix. It is unclear if this finding reflects a potential higher future risk of developing appendicitis, if the appendix was left in situ. Appendicitis is a common problem and approximately 40,000 people are admitted to hospital in England annually with appendicitis and it has been estimated that the lifetime risk of appendicitis is approximately 1 in 13 [19]. We propose that preventing future appendicitis in patients having major resectional cancer surgery is beneficial to avoid potential diagnostic dilemmas and significant technical difficulties should a subsequent appendicectomy be required.

In patients with endometriosis, the appendix seems to be involved in 2.6% [20]. However, as our data confirm, endometriosis is quite rare in incidental appendicectomy specimens [21].

We did not encounter any complications attributable to appendectomy. There are some reasonable concerns about the risk of adding morbidity when an appendectomy is performed. This may be more of an issue at a laparoscopic procedure for left-sided colon or rectal cancer where, performing an appendectomy may be more complex due to suboptimal positioning of the ports and fatigue of the operating team. Thus, the laparoscopic approach was associated with a higher number of non-removal of the appendix.

There is uncertainty regarding a possible increased risk of wound infection when an appendectomy is added during a “clean” procedure such as cholecystectomy or hysterectomy, and the literature is quite controversial [22–24]. However, preforming an appendectomy during a potentially contaminated operation, such as colorectal resection, is unlikely to be an additional risk of wound infection.

Recently there have been reports on the effect of appendectomy in determining changes in the colonic microbiome [25]. Research in this field is ongoing and still in its infancy. Further studies are needed to clarify the short- and long-term implications of microbiome changes related to appendectomy. It is unclear what effect incidental appendicectomy would have on the specific population in the present study undergoing surgery for a colorectal cancer with a median age of 70 years.

The main limitations of the study are related to the retrospective design and single-centre setting.

Patients undergoing left sided colorectal cancer surgery with an appendix in situ may benefit from coincidental appendectomy to treat the small proportion with synchronous neoplasms, polyps and inflammation and eradicate the risk of metachronous appendicitis, or a subsequent appendix tumour.

**Declarations**
Conflicts: The authors have no conflict of interest to disclose

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