Adenocarcinoma as a Cause of Acute Appendicitis

Paul H. Sugarbaker*
Department of Gastrointestinal Malignancies, MedStar Washington Hospital Center, USA

Abstract
Adenocarcinoma as a cause of acute appendicitis is unusual, occurring in approximately 1.0% of all cases of appendicitis. Nevertheless, management of appendiceal adenocarcinoma as a routine appendicitis may have an adverse outcome for the patient. Iatrogenically, a contained malignant process may be converted into a disseminated disease that will have a lethal outcome. Staging of appendiceal adenocarcinoma and the shortcomings of the TNM are reviewed. The new standard of management for a contained or disseminated appendiceal neoplasm presenting as acute appendicitis is presented. The integrity of the thin wall of the appendix, both before and after the resection of an appendiceal neoplasm is crucial in optimal treatment planning. The histologic grade of invasive versus non-invasive disease and the extent of disease outside the appendix are important prognostic indicators. Cytoreductive surgery (CRS) and hyperthermic perioperative chemotherapy (HIPEC) are now standard of care if peritoneal dissemination is documented. Judgments regarding the need for right colon resection as compared to appendectomy only in patients with different grade histology are described. Adenocarcinoma as a cause of appendicitis is rare but since appendicitis is such a common disease process, the general surgeon and surgical oncologist must be prepared to definitively treat an appendiceal neoplasm. There are new paradigms for patient management that are now a standard of care.

INTRODUCTION
Appendiceal adenocarcinoma as a cause of appendicitis is a rare event. Consequently, when the surgeon sees a patient with appendicitis the index of suspicion for an appendiceal malignancy is low. Surgical management of appendicitis caused by appendiceal adenocarcinoma with the same technology as the management of an infectious appendicitis can result in a needless poor outcome, even a needless lethal outcome. Misdiagnosis and mismanagement can result in death because of iatrogenic peritoneal metastases or local-regional disease recurrence. This manuscript reviews the prevalence of appendiceal adenocarcinoma associated with appendicitis, explains that a wide spectrum of histologic subtypes may be present, and then summarizes a management plan that will optimize the outcome.

DIAGNOSIS
To establish a perspective regarding appendiceal adenocarcinoma, the incidence in relation to colon cancer may be considered. Appendiceal cancer is estimated at 1% of the incidence of colorectal adenocarcinoma. Therefore, if there are approximately 150,000 colorectal cancers in the United States each year, one suspects 1,500 patients to present with an appendiceal adenocarcinoma [1].

At Vilnius University Hospital, Vilnius, Lithuania, between January 2003 and August 2013 there were 3,100 patients diagnosed with appendicitis [2]. Of these, 25 patients had appendiceal adenocarcinoma as a cause of the appendicitis. From these data, the incidence of cancer with appendicitis is estimated at 0.8%. This incidence of appendiceal malignancy of just less than 1% of appendicitis diagnoses causes this combined condition to create a high risk for misdiagnosis in that there is a low index of suspicion. It is not only of increased risk for the patient who may be sub-optimally treated but also of increased risk for the surgeon who may be held responsible for a misdiagnosis and adverse outcome as a result of inappropriate treatment [3].

The combined condition of an appendiceal adenocarcinoma together with appendicitis, it is a common initial diagnosis of an appendiceal neoplasm. Esquivel and colleagues reviewed the initial symptoms and signs of 217 patients with Pseudomyxoma Peritonei. All of these patients had an appendiceal neoplasm [4]. Of these patients, 36 men had appendicitis as the condition that led to the diagnosis of pseudomyxoma peritonei. This is an incidence of 34%. In 22 women, a diagnosis of appendicitis led to the diagnosis of appendiceal neoplasm in five patients for an incidence of 22%. Elias and colleagues found 29% of their patients with an appendiceal mucinous neoplasm presenting with localized abdominal pain or appendicitis [5]. Although
appendiceal adenocarcinoma is rare, there can be no doubt that appendiceal adenocarcinoma may be associated with localized abdominal pain and appendiceal inflammation caused the cancer to be discovered.

**Prognostic implications of adenocarcinoma as a cause of acute appendicitis**

If appendicitis is associated with an appendiceal adenocarcinoma, Gonzalez and coworkers presented data to suggest that the malignancy was likely to be a high-grade neoplasm [6]. They reported on 25 patients with lymph node positive appendiceal epithelial neoplasms. Sixty percent of this group presented with an appendicitis as the predominant clinical feature. In contrast, Esquivel and colleagues reported an incidence of 25% in patients with low histologic grade appendiceal malignancy [3]. Gonzalez et al. reported that appendicitis occurred more frequently if the cancerous process was in the mid-portion or towards the base of the appendix (Figure 1). High-grade neoplasms in this part of the appendix were likely to cause occlusion of the appendiceal lumen and perforation with fecal contamination of the peripappendiceal tissues. If the malignancy was of low-grade, the appendix would become diluted from the accumulation of adenomatous epithelial cells producing large quantities of mucus. This malignant mucocele would expand over months and years and eventually cause a “blowout” of the distal appendix with the release of mucoid fluid with low histologic grade epithelial cells into the free peritoneal cavity [7]. This would eventually result in the pseudomyxoma peritonei syndrome (Figure 1). The diagrams in Figure 1 illustrate the two histologic types of epithelial adenocarcinoma. Not only is the probable position within the appendix influenced by the adenocarcinoma histology, but also the likelihood that appendicitis will occur as a result of disease progression.

**TNM staging of epithelial appendiceal malignancy**

The TNM staging of appendiceal epithelial neoplasms is similar to the TNM staging of other gastrointestinal cancers [8]. However, there are important exceptions that should be noted because of the high likelihood of peritoneal metastases with this malignancy. The T-stage may vary from epithelial dysplasia (Tis) to full thickness invasion of the bowel wall including mucinous adenocarcinoma within the right lower quadrant (T4a) or appendiceal cancer invading into other organs or structures (T4b). N1 indicates 1-3 lymph nodes positive for cancer and N2 indicates 4 or more positive lymph nodes. M0 indicates no evidence for cancer cells or tumor deposits outside the appendix. M1a indicates tumor nodules or malignant cells outside the appendix and beyond the right lower quadrant. Stage 4a indicates grade 1 tumor cells outside of the appendix. Stage 4b indicates grade 2 or 3 peritoneal metastases outside of the appendix or peritoneal metastases combined with N1 or N2 lymph node deposits of cancer.

As indicated by the M-stage of the TNM system, a low histologic grade of peritoneal metastases is expected to show an improved survival over histological high-grade peritoneal metastases (stage 4a versus stage 4b). As recently reviewed by Carr and colleagues, a low-grade appendiceal mucinous neoplasm (LAMN) is usually associated with low histologic grade of peritoneal metastases. These low-grade mucinous tumor accumulations within the abdomen and pelvis are referred to as disseminated peritoneal adenomucinosis (DPAM). A high-grade appendiceal mucinous neoplasm (HAMN) usually results in a high histologic grade of peritoneal metastases known as peritoneal mucinous carcinoma (PMCA) [9]. However, Ronnett and colleagues demonstrated that caution must be used when assessing the histologic grade of the primary tumor as compared to the peritoneal metastases [10]. In approximately 6% of patients, the histology of the primary appendiceal neoplasm and the peritoneal dissemination do not agree. Also, in some instances small areas of high-grade disease will exist within an otherwise bland histopathologic pattern of peritoneal metastases. These discordant features may be present in approximately 10% of patients with peritoneal metastases from appendiceal adenocarcinoma. The prognosis of a particular patient will depend upon a thorough examination of multiple specimens gathered from the curative surgical surgery used to definitively treat the primary appendiceal adenocarcinoma and the peritoneal metastases. A less accurate assessment of prognosis will occur if any of the clinical material is limited to the primary appendiceal neoplasm. The peritoneal metastases may be less histologically aggressive (PMCA to DPAM) or more histologically aggressive (DPAM to PMCA) than the primary appendiceal tumor.

A second caveat in using the TNM system for appendiceal malignancy occurs because the estimation of the extent of peritoneal metastases is not quantitated. A large difference in survival occurs with a small or moderate extent of peritoneal metastases as compared to the abdomen and pelvis being filled by disease. In order to better define the extent of peritoneal metastases, the peritoneal cancer index (PCI) has been used to estimate extent of disease with considerable prognostic value [11]. The diagram in (Figure 2) shows the methodology for estimating the extent of peritoneal metastases. This quantitative assessment varies between 0 and 39. There are abdominopelvic regions 0-12 and the extent of disease as none, small, moderate, or large volume as estimated by the lesion size (0-3). If there is a layering or confluence of disease the lesion size is 3.

Figures (3A,3B) shows the impact on survival that the PCI produces for A) adenomucinosis patients or B) peritoneal mucinous carcinoma patients. Although some high-grade adenocarcinomas of the appendix may disseminate to systemic sites early in the natural history of the disease (M1b), this is very unusual. The prognosis is largely dependent upon the histologic type of the appendix malignancy and the extent of peritoneal dissemination [12].

Although the surgeon cannot influence the histologic type of the disease he or she can, as a result of surgical technique, affect the extent of cancer dissemination. Misdraji and coworkers reported on 49 patients with LAMN confined to the appendix with a median follow-up of 6 years [13]. None of these patients experienced recurrence. They conclude that a malignant mucocele, no matter how large, with LAMN histology and an absence of perforation is a clinically benign process. In contrast, the long-term outlook for patients with low-grade tumors and peritoneal spread was guarded with over half dying of disease after 10 years. It cannot be overemphasized that every effort must be made in removing...
Figure 1 Diagram to illustrate the position within the appendix of high-grade (intestinal type) epithelial neoplasms. In a high grade appendiceal cancer, cancer cells may gain access to the free peritoneal space at the primary cancer site (A) or by perforation at some site along the appendix (B). The arrows indicate possible sites for cancer cells to gain access to the free peritoneal space.

Diagram to illustrate the position within the appendix of a low-grade mucinous epithelial neoplasm. The arrows indicate that cancer cells may gain access to the free peritoneal space through a perforation at the tip of the appendix. (From reference 6 with permission)

Figure 2 The peritoneal cancer index (PCI) uses 13 abdominal and pelvic regions and extent of peritoneal metastases in each region to quantitate the disease process. The score varies from 0 to 39. The lesion size (LS) is used to quantitate the size of peritoneal nodules. LS-0 indicates no tumor seen, LS-1 indicates tumor implants up to 0.5 cm, LS-2 indicates tumor implants between 0.5 and 5 cm, and LS-3 indicates tumor implants larger than 5 cm or a layering of cancer. The distribution of tumor is determined within 13 abdominopelvic regions. (From reference 11 with permission).

a mucocele of the appendix to avoid rupture of the specimen as the appendectomy is being performed. Breach of the wall of the appendix means that peritoneal metastases is likely to result in the future.

Even more dangerous is the traumatic removal of an appendix with HAMN. A piecemeal removal of the appendix by laparoscopy after a difficult dissection is likely to cause an intraperitoneal dissemination and/or laparoscopy port site recurrence. This iatrogenic cancer dissemination may result in an early death from rapid progression of an aggressive PMCA. Wide atraumatic resection of the appendiceal malignancy along with adjacent peritoneal surfaces that may be infiltrated, negative margin of resection on the caecum and removal of the entire mesoappendix to assess regional (appendiceal) lymph node involvement is the goal of resection of a suspect appendiceal neoplasm. Certainly, if cancer is suspected in a patient with a diagnosis of appendicitis special precautions are required while performing the appendectomy procedure.

Radiologic differential diagnosis of infectious appendicitis versus adenocarcinoma causing appendicitis

In a patient with symptoms and signs of appendicitis a CT is usually performed to help confirm the physical and laboratory findings [14,15]. Table (1) compares and contrasts the description of radiologic findings that may be seen with an infectious appendicitis as compared to an appendiceal adenocarcinoma. One must remember that in these patients the two pathologies,
infection and cancer, exist simultaneously. Distinguishing the very unusual additional diagnosis of appendiceal adenocarcinoma in patients who will also have infectious appendicitis would be of great value and substantially change the surgical approach to appendectomy. That is, the surgeon should proceed with the simple removal of the appendix itself as compared to the wide resection of an appendiceal neoplasm as described below. Simple appendectomy can be performed by laparoscopy while the radical appendix resection is best performed by laparotomy. If appendicitis with adenocarcinoma exists, the appendix must be removed intact with minimal trauma to the resected specimen. Also, if malignancy is suspected, some additional diagnostic studies are indicated intraoperatively. Cytology specimens from the peritoneal space within the hepatorenal pouch and also the pelvis should be obtained. In addition, a conscious effort to see and then record the presence of peritoneal metastases from the undersurface of the right hemidiaphragm, the greater omentum, the ovaries, and pelvic peritoneum is necessary.

In a patient with an appendiceal adenocarcinoma, an
appendiceal mass or cystic structure in the anatomic site of the appendix referred to as a mucocele, will often be present. There may be calciﬁcations in the peripendical regions. Also, enhancing nodules may be seen in the wall of a mass or mucocele. Associated ﬁndings such as ovarian metastases, right subdiaphragmatic scalloping, pelvic ﬂuid, or mucus accumulation may occur. The omentum may be inﬁltrated by mucinous tumor. Finally, one should look for lymphadenopathy in the ileocolic lymph node group [13].

New standard of care for appendiceal adenocarcinoma

Because appendiceal perforation in association with peritoneal metastases occurs rather early in the natural history of this disease and because the mucinous peritoneal metastases show a relative sparing of bowel surfaces, a new treatment strategy for appendiceal neoplasms has become the standard of care [14]. For both DPAM and PMCA histologies, a combined treatment of cytoreductive surgery and hyperthermic perioperative chemotherapy (HIPEC) is selectively used. The cytoreductive surgery combines the parietal peritonectomy procedures with visceral resections with a goal of complete visible removal of tumor from the abdomen and pelvis. After the cytoreduction the peritoneal space is ﬂooded with a chemotherapy solution for 30-90 minutes depending upon the chemotherapy agent chosen for treatment. The chemotherapy solution is heated to 42-43°C using a hyperthermia pump to recirculate the chemotherapy solution [15].

If the inﬂamed appendix is determined to be accompanied by an adenocarcinoma or if the index of suspicion is high, a new approach to the appendectomy procedure has been suggested. This new procedure has been called radical appendectomy [16]. The procedure starts with a thorough assessment of the abdomen and pelvis in a search for peritoneal metastases or positive cytology caused by the appendiceal adenocarcinoma. Biopsies form the peritoneum of the right retrohepatic space, undersurface of the right hemidiaphragm, pelvis, and greater omentum are performed. Also, cytology specimens are taken from the right paracolic sulcus and pelvis. The surgical procedure does not start with a dissection of the appendix but with a peritomectomy of the right paracolic sulcus several centimeters or even several inches from the inﬂamed appendix. The dissection proceeds beneath the caecum by ligating and dividing the appendiceal artery. This artery is removed as part of the radical appendectomy specimens along with 3 or 4 appendiceal lymph nodes. Medially, the terminal ileum is traced back to the ileocecal valve and the small apron of fat on the antimesenteric border of the terminal ileum (sometimes referred to as the fold of Treves) is included as part of the specimen. Other omental appendages at the base of the caecum can be included but the anterior caecal artery must be preserved. A decision is made to transect the appendix at its base or use a stapler to perform a caecotomy. The goal is a negative margin of resection at the base of the appendix.

There is yet another departure from standard recommendations for oncologic surgery in the management of an appendiceal adenocarcinoma, either with or without appendicitis as a presentation. In the past, an appendiceal malignancy greater than 2 cm in diameter was recommended for a routine right colon resection with ileocolic lymph node removal. However, Gonzalez-Moreno and Sugarbaker presented clinical data on 501 patients with a median follow-up of 4 years. The survival of patients who were lymph node positive compared to those who were determined lymph node negative or had lymph nodes not examined, showed no impact on survival (p=0.155). The median survival for the lymph-node positive group was 7 years (95% conﬁdence interval, 3.86-10.14 years); 5-year survival was 50.73%, and 10-year survival was 40.58%. For the group without pathologic assessment of their regional lymph nodes, the median survival was 13 years (95% conﬁdence interval, 9.0-17.0 years); 5-year survival was 71.97%, and 10-year survival was 55.57%. Median survival had not yet been reached for the group with documented negative regional lymph nodes; their 5-year survival was 78.17%, and their 10-year survival was 55.72% [5]. The surgical procedure (appendectomy alone versus right hemicolectomy) had an inﬂuence on patient survival by univariate analysis (p<0.001). A survival advantage was shown for patients treated by appendectomy alone (median survival 18 years; 95% conﬁdence interval, 14-22 years) compared with those who underwent right colectomy (median survival 10 years; 95% conﬁdence interval, 8-12 years). However, when survival data were adjusted to control for other variables in the Cox proportional hazard regression model, the surgical procedure had no statistically signiﬁcant impact on survival (p=0.258) [17]. Also, Foster and colleagues noted that lymph node involvement is rare in appendiceal malignancies and that a selective use of right hemicolectomy should be recommended for appendiceal neoplasms. In 48 patients who had appendectomy alone and 72 patients who had a right hemicolectomy, there was no difference in recurrence rates (p=0.12) or in death resulting from disease (p=0.27) [18]. In patients with intestinal-type appendiceal adenocarcinoma, a higher incidence of lymph node positivity suggests routine right hemicolectomy. But the incidence of lymph node positivity in mucinous tumors (4.2%) indicates right hemicolectomy should be performed selectively and not as a routine procedure.

Information regarding the selection of patients with appendiceal adenocarcinoma for appendectomy versus right colon resection plus ileocolic lymphadenectomy has been published. Because the incidence of lymph node involvement of patients with intestinal type appendiceal adenocarcinoma is 66.7%, all of these patients are recommended for ileocolonectomy with lymph node dissection [17]. In contrast, appendiceal mucinous adenocarcinoma of LAMN histology that has DPAM peritoneal metastases has an incidence of lymph node metastases of 0-5%. In this group of patients, lymph nodes along the appendicular artery should be sampled. However, right colon resection with lymphadenectomy should not be performed to remove occult positive lymph nodes.

The group of patients with HAMN as a primary appendiceal mucinous adenocarcinoma and PMCA peritoneal metastases should have a selective approach to right colectomy [19]. Recent data shows that the incidence of regional lymph node metastases is dependent on the grade of differentiation of the peritoneal metastases. For well differentiated or moderately differentiated PMCA, lymph node positivity was 6.0%. Routine right colectomy with ileocolonectomy is not indicated. However, if the PMCA histology is poorly differentiated the incidence of lymph node

metastases along the appendiceal artery or within the ileocolic group is 29%. This group includes the patients with signet ring histology. Right colon resection with ileocolic lymph node dissection should be routinely included in this group of PMCA patients (Figure 4).

In summary, neoplastic appendicitis does occur although it is unusual. Iatrogenic dissemination of the neoplasm with appendectomy must be prevented for optimal management. Radiologic findings by CT prior to appendectomy may help in the differential diagnosis. The surgical approach to infectious as compared to neoplastic appendectomy differs greatly. In patients with peritoneal metastases from an appendix neoplasm, the new standard of care is cytoreductive surgery and hyperthermic perioperative chemotherapy. Right hemicolectomy should not be used routinely but selectively on patients with mucinous malignancy. The results of treatment of peritoneal metastases from an appendiceal neoplasm are surprisingly good.

REFERENCES