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Short Communication

Neoplastic Appendicitis

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Keywords

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- Cytoreductive Surgery (CRS)
- Hyperthermic Perioperative Chemotherapy (HIPEC)
- Peritonectomy Procedures
- Mucocele
- Appendicitis

Abstract

Background: Appendiceal cancer as a cause of appendicitis is a rare event occurring in approximately 1.0% of all cases of appendicitis. Nevertheless, treatment of appendiceal cancer as appendicitis may have an adverse outcome for the patient, even iatrogenically converting a contained malignant process into a disseminated disease that will have a lethal outcome.

Methods: Staging of appendiceal cancer and the shortcomings of the TNM are reviewed. The new standard of management for a contained or disseminated appendiceal neoplasm is presented.

Results: The condition of the wall of the appendix, both before and after the resection of an appendiceal neoplasm is crucial in optimal treatment planning. The histologic grade of indolent versus aggressive disease and the extent of disease are important prognostic indicators. Cytoreductive surgery (CRS) and hyperthermic perioperative chemotherapy (HIPEC) are now standard of care if peritoneal dissemination has occurred. Judgments regarding the need for right colon resection in patients with low-grade histology have changed.

Conclusions: Cancer 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 optimally treat an appendiceal neoplasm. New paradigms for patient management have, in the recent past, become a standard of care.

INTRODUCTION

Appendicitis as a cause of appendiceal neoplasm is a rare event. Consequently, when the surgeon sees a patient with appendicitis the index of suspicion for an appendiceal malignancy is, not surprisingly, low. Nevertheless, management of appendicitis caused by cancer in the same manner as the management of an infectious appendicitis can result in a needless poor outcome. Misdiagnosis and mismanagement can result in death because of iatrogenic peritoneal metastases or local-regional disease recurrence. This manuscript seeks to review the prevalence of appendiceal adenocarcinoma associated with appendicitis, explain how a wide spectrum of histologic subtypes is important, and then summarize treatments that will optimize the outcome.

Diagnosis

To help create a perspective for thinking about appendiceal epithelial neoplasms, their incidence in relation to colon cancer may be considered. They are 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 epithelial neoplasm.

At Vilnius University Hospital, Vilnius, Lithuania, between January 2003 and August 2013 there were 3,100 patients diagnosed with appendicitis [1]. Of these, 25 patients had an associated appendiceal malignant neoplasm. From these data, the incidence of cancer with appendicitis is approximately 0.8%. This incidence of appendiceal malignancy of just less than 1% of appendicitis diagnoses causes this combined condition to be dangerous. It is not only dangerous for the patient who may be sub-optimally treated but also dangerous for the surgeon who may be held responsible for a misdiagnosis and adverse outcome as a result of inadequate treatment [2].

If the diagnosis of an appendiceal epithelial neoplasm is made, there is a high likelihood that appendicitis or localized abdominal pain led to this diagnosis. Esquivel and colleagues reviewed 217 patients with Pseudomyxoma peritonei. All of these patients had an appendiceal neoplasm [3]. 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 for an incidence of 22%. Elias and colleagues found 29% of their patients with appendiceal Mucinous neoplasm's presenting with localized abdominal pain or appendicitis [4]. There can be no doubt that appendiceal epithelial cancer is frequently associated with localized abdominal pain and a diagnosis of appendicitis caused the cancer to be discovered.

Prognostic implications of neoplastic appendicitis

If appendicitis is associated with an appendiceal epithelial neoplasm, Gonzalez and coworkers presented data to suggest that the malignancy was likely to be a high-grade neoplasm [5]. 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. As previously noted, Esquivel and colleagues reported an incidence of 25% in patients with low histologic grade appendiceal malignancy [3]. Gonzalez et al. reported that appendicitis was more common if the cancerous process was in the middle portion or towards the base of the appendix (Figure 1, top). High-grade neoplasm in this part of the appendix was likely to cause occlusion of the appendiceal lumen and perforation with fecal soilage of the periappendiceal tissues. If the neoplasm was of low-grade, the appendix would become dilated from the accumulation of adenomatous epithelial cells producing large quantities of mucus. This malignant Mucocele would expand over months and years and eventually cause an appendiceal "blowout" with the release of mucoid fluid with low histologic grade epithelial cells into the free peritoneal cavity [6]. This would eventually result in the Pseudomyxoma Peritonei Syndrome (Figure 1, bottom). Figures 1A and 1B are diagrams of the two histologic types of epithelial appendiceal neoplasm, their probable position within the appendix, and the likelihood that appendicitis will occur as a result of disease progression with appendiceal perforation.

TNM staging of epithelial appendiceal malignancy

The TNM staging of appendiceal epithelial neoplasms is, of course, similar to the TNM staging of other gastrointestinal cancers [7]. However, there are important exceptions that should be noted because of the high likelihood of peritoneal dissemination with this malignancy. The T-stage may vary from epithelial dysplasia (Tis) to full thickness invasion of the bowel wall including mucinous peritoneal tumor 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.

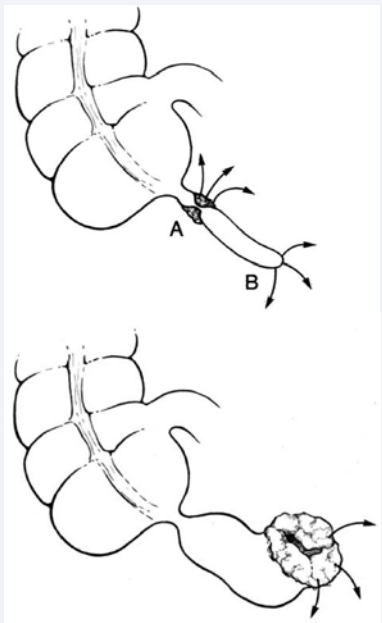

Figure 1 Diagram to illustrate the position within the appendix of high-grade (intestinal type, top) and low-grade epithelial neoplasms (bottom).

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) [8]. However, Ronnett and colleagues showed that caution must be used when assessing the prognosis from peritoneal metastases [9]. 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 histopathology pattern of peritoneal metastases. These discordant features may be present in approximately 10% of patients with peritoneal metastases from appendiceal mucinous neoplasms. The prognosis of a particular patient will depend most accurately upon a thorough examination of the specimens gathered from the cytoreductive surgery used to definitively treat the peritoneal metastases. A less accurate assessment of prognosis will be determined by 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 comes with the estimation of the extent of peritoneal metastases. A large difference in survival occurs with a small or moderate extent of peritoneal metastases as compared to the abdomen and pelvis being extensively involved. In order to better define the extent of peritoneal metastases, the peritoneal cancer index (PCI) has been used with considerable prognostic value (10). 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 and 3B shows the impact on survival that the peritoneal cancer index 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

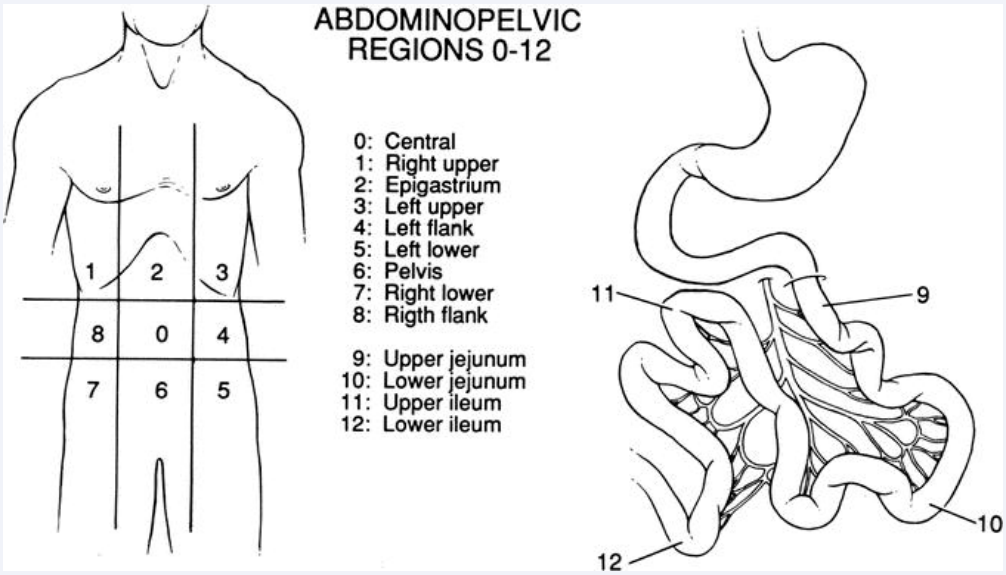

Figure 2 The peritoneal cancer index [PCI) uses the distribution in 13 abdominal and pelvic regions and extent of peritoneal metastases in each region to quantitative the disease process. The score varies from 0 to 39.

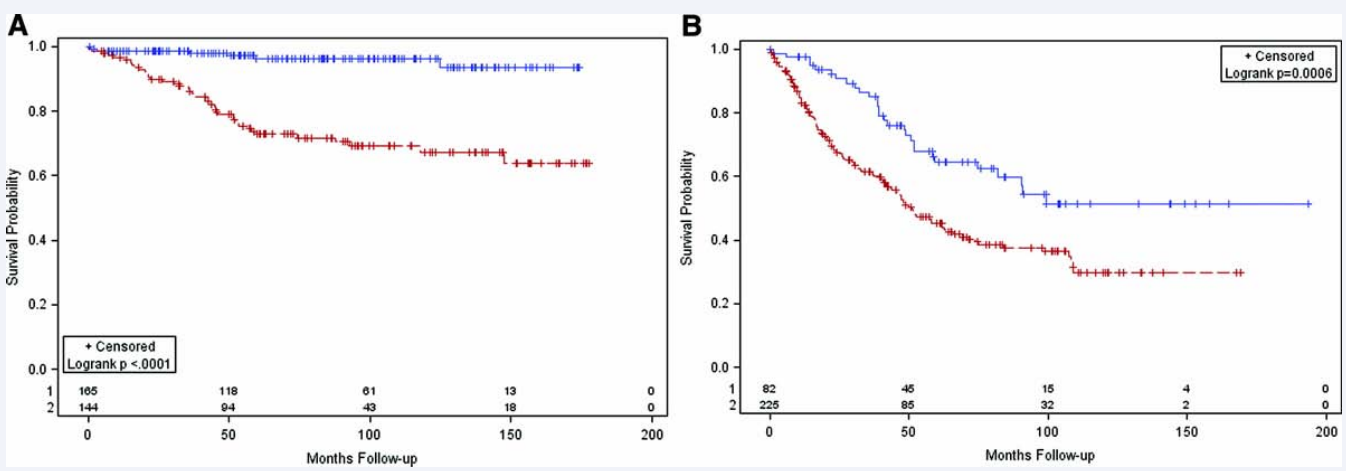

Figure 3 A. Adenomucinosis patients with PCI 1 to 20 [blue line, N=165) versus 21 to 39 (red line, N=144). B. Mucinous carcinoma patients with PCI 1-20 (blue line, N=82) versus 21 to 39 (red line, N=225).

unusual. The prognosis is largely dependent upon the histologic type of the appendix malignancy and the extent of peritoneal dissemination [11].

Although the surgeon cannot influence the histologic type of the disease, he/she can 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 [12]. None of these patients experienced recurrence. They conclude that a 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. Every effort must be made in removing a mucocele of the appendix to avoid rupture as the appendectomy is being performed. Breach of the wall of the appendix means that pseudomyxoma peritonei is likely to result in the distant 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 may result in 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 versus neoplastic appendicitis

In a patient with symptoms and signs of appendicitis a CT is usually performed to help confirm the physical and laboratory findings. Table (1) compares and contrasts the images that may be seen with an infectious appendicitis as compared to a neoplastic appendicitis. One must remember that in these patients the two pathologies, infection and neoplasia, exist simultaneously. Distinguishing the very unusual diagnosis of neoplastic appendicitis in patients who will also have infectious peritonitis 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 above. Simple appendectomy can be performed by laparoscopy while the radical appendix resection is best performed by laparotomy. 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 a neoplastic appendicitis an appendiceal mass or cystic structure in the anatomic site of the appendix referred to as a mucocele is often present. There may be calcifications in the periappendiceal 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 epithelial neoplasms

Because appendiceal peforation 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.

Table 1: Contrast of CT findings in a patient with infectious appendicitis versus neoplastic appendicitis.

Radiologic Finding	Infectious Appendicitis	Neoplastic Appendicitis
Appendiceal mass or mucocele	Absent	May be present
Appendiceal or periappendiceal calcifications	Absent	May be present
Enhancing nodules in wall of mass or mucocele	Absent	May be present
Ovarian metastases	Absent	May be present
Right subdiaphragmatic scalloping, pelvic fluid/ mucus accumulation	Absent	May be present
Omental infiltration	Absent	May be present
Right ileocolic lymphadenopathy	May be present	May be present

There is yet another departure from standard recommendations for oncologic surgery in the management of an appendiceal neoplasm, 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 Sugar baker 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) [15]. 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) [16]. 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.

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.

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