Original Study

Multidisciplinary Perspective on the Management of Appendiceal Adenocarcinoma: Case Review of 10 Patients From a University Hospital and Current Considerations

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Abstract

We assessed a series of 10 cases of histologically proven appendiceal adenocarcinoma and concluded that it ought to be managed in the same way as a cecal adenocarcinoma.

Background: Adenocarcinoma of the vermiform appendix is rare. It constitutes less than 0.5% of all gastrointestinal malignancies. Pathologically, appendiceal neoplasms are categorized into various subtypes depending on cell lineage. **Patients and Methods:** We considered a case series of appendiceal invasive adenocarcinomas from 2004 to 2013 managed in a teaching hospital. We discuss our management dilemmas, given the lack of randomized controlled trial data that exist. A detailed look at the histopathology, case series, and literature is presented. **Results:** Ideal standards ought to be constructed for the management of this rare pathology, with a particular focus on exploring the indications and potential benefits, as well as difficulties, of ileocolic lymphadenectomy. **Conclusion:** Appendiceal adenocarcinoma ought to be managed in the same way as a cecal adenocarcinoma.

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Introduction

The appendix shares all the same layers as the large bowel. The mucosa is made up of several different cell types, including enterocytes (columnar epithelial cells—these comprise the majority), goblet cells (the second most frequent—these secrete mucus), and neuroendocrine cells (these secrete hormones). Each of these cell lineages can become neoplastic.[1]

Epithelial neoplasms of the appendix can be broadly classified as benign, of uncertain malignant potential, and malignant (Table 1). Nonadenomatous polyps include hyperplastic polys and nondysplastic sessile-serrated lesions. They are often incidental findings associated with acute appendicitis. These lesions can be associated with adenocarcinoma elsewhere in the large bowel and hence are an indication for colonoscopy.[2]

Invasive adenocarcinoma of the appendix resembles its colonic counterparts and is graded according to the same criteria. Many patients with appendiceal adenocarcinoma present with acute appendicitis due to the luminal obstruction. Interestingly, appendiceal adenocarcinomas are usually of goblet cell origin, despite the higher number of enterocytes, and hence are classified as mucinous carcinomas. These are high-grade mucinous adenocarcinomas, not to be confused with low-grade mucinous neoplasms. This latter entity instead comprises well-differentiated neoplasms that have cytological appearances resembling adenomas but with the propensity to spread as pseudomyxoma without distant metastases.[3] Nonmucinous adenocarcinomas of the appendix (enterocyte origin) resemble the usual type of colonic adenocarcinoma and do not produce pseudomyxoma peritonei.

Management of appendiceal adenocarcinoma is controversial. Traditionally, surgeons have advocated right hemicolectomy for a complete ileocolic lymphadenectomy. If there are negative prognostic features, such as perforation, lymph node involvement, or

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Table 1 Classification of Epithelial Neoplasms of the Appendix

Classification	Neoplasm Type	Comments
Benign	Nonadenomatous polyps and adenomas (tubular, tubulovillous, villous, sessile-serrated).	Noninvasive lesions confined to the appendix. Can be associated with synchronous colonic neoplasms.
Uncertain malignant potential/low-grade malignancy	Low-grade mucinous neoplasms/well-differentiated, low-grade mucinous adenocarcinoma.	Can spread as pseudomyxoma peritonei.
Malignant	Adenocarcinoma (high-grade mucinous and nonmucinous, including signet ring cell subtypes).	Very similar to their colonic counterparts.

extramural vascular invasion (EMVI), adjuvant therapy may be indicated.

We present our experience of 10 patients diagnosed with appendiceal carcinoma over a 10-year period, and we review the literature.

Methods and Results

The hospital pathology database was searched for primary diagnosis of appendiceal carcinoma from 2004 to 2013. A total of 12 patients were identified. Notes were examined specifically looking at presenting symptoms, initial management (operation or imaging), histological diagnosis of appendiceal cancer, adjuvant therapy (further surgery or chemotherapy), and outcome from the time of diagnosis. Two patients were excluded because of the lack of operative intervention, resulting in 10 patients (Table 2).

Discussion

Appendiceal adenocarcinoma is rare, and when diagnosed, like all cancers, it ought to be discussed in a regional multidisciplinary team meeting, with both patient factors and tumor factors considered in management decision making.

Our small series shows features consistent with the literature. Mucinous adenocarcinoma was the most common cancer, despite not being the most populous mucosal appendiceal cell line. Patients generally had stage II or higher disease. Interestingly, many right hemicolectomy specimens showed no nodal involvement (N0 = 5/9). Most of our patients went on to have right hemicolectomy and experienced an average disease-free survival of 3 to 4 years.

Anatomically, the appendicular artery is an end artery and a branch (usually) of the posterior cecal artery, which itself comes off the ileocolic artery. The lymphatics travel along the arterial supply. Lymphatic spread of colorectal cancer follows these, with occasional skip metastases.[4] We were interested in whether an ileocolic lymphadenectomy is indicated in fit patients without metastases to improve overall survival.

Obvious advantages of ileocolic lymphadenectomy include staging the tumor and potentially removing all viable cancer cells as a mesocolic excision. The disadvantages include further surgery, generally in a hostile environment, as these tumors may present with perforation, as well as associated morbidity or the need for a right hemicolectomy, which may result in anastomotic dehiscence or damage to adjacent structures.

The difficulty arises in cases in which the patient will likely go on to receive adjuvant therapy anyway, according to well-recognized poor prognostic indicators such as perforated appendiceal tumors (pT4b, TNM, 5th edition), or those with features of EMVI (subserosal and mesoappendicular). Would it ever be acceptable to avoid the morbidity of reoperation and proceed straight to chemotherapy without right hemicolectomy? Some think that proof of AJCC stage III disease is mandatory before chemotherapy[5] and that accurate pretreatment risk stratification ought to be done despite the risk of repeat (and often more challenging) surgery.

This can be addressed in the question of whether it is the lymphadenectomy itself improves survival (by removal of lymph node metastases). Or is it the more accurate prognostication (and stage shift) afforded by lymphadenectomy that results in administration of chemotherapy that improves overall survival?

Lymphadenectomy has been advocated by many as offering 3 things in colorectal cancer (and by extension appendiceal adenocarcinoma): prognosis and indication for adjuvant therapy; potential for cure; and marker of quality of surgery.[6]

Lymphadenectomy as Prognosis and Indication for Adjuvant Therapy

There is no doubt that appropriate anatomic and adequately sized lymphadenectomy is an excellent prognostic marker of colorectal cancer. This has been shown in numerous studies, and certainly the greater the lymph node collection, and the more closely lymph nodes are examined, the more metastases are found,[6,7] thus more correctly defining disease stage and leading to the administration of adjuvant chemotherapy. Conversely, in cases of truly node-negative disease, with a large sample of examined nodes, such patients are likely to have a more favorable tumor biologically and are likely to do well—but not due to intervention (aside from appropriate colectomy) but rather due to tumor characteristics.

Many studies have demonstrated an improvement of survival correlated with a higher number of nodes in lymphadenectomy.[8,9] Chen and Bilchik[9] concluded that adequate lymphadenectomy, as measured by analysis of at least 15 lymph nodes, correlated with improved survival, independent of stage, patient demographics, and tumor characteristics. The added advantage offered may, however, be explained by the administration of chemotherapy as a result of upstaging. Current UK recommendations are for a minimum of 12 lymph nodes for pathologic assessment.[10] Whether rigid targets are helpful is a matter of continued debate, although a higher number of collected lymph nodes seems to correlate with better outcome.[8,9]

The stage migration effect of more accurate lymph node assessment is known as the Will Rogers phenomenon. This is an apparent and direct result of the increase in number of lymph nodes assessed. Population statistics show that moving poorer candidates from a better-prognosis group to a worse-prognosis group actually improves the survival for both the truly lower-risk group and the group they are going into. For example, patients with Dukes C disease