

# Management and Outcomes in Primary Tumors of the Appendix

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## ABSTRACT

*Primary tumors of the appendix are rare, comprising 1.1% of all appendectomy specimens. Nevertheless, it often presents in an emergent fashion, creating a need for a well-defined management algorithm that will ensure proper acute management. We performed a retrospective review of medical charts from 1982-2007 on all charts with a diagnosis of appendiceal neoplasm. A cohort of 41 patients was diagnosed with a primary appendiceal neoplasm from a total of 8560 appendectomies over the 25-year period. Several tumors were identified: adenocarcinomas (n = 16), carcinoid tumors (n = 15), mucinous cystadenocarcinoma (n = 7), and a combination of adenocarcinoma and goblet cell carcinoid of the appendix (n = 3). Twenty-one patients presented with an acute abdomen. Tumors were discovered intraoperatively in eighteen patients while performing other procedures. At diagnosis, metastatic disease was found in 41.5% of patients (n = 17); average survival ranged from 6 to 21 months based on tumor type. For patients with non-metastatic disease at diagnosis, all survived longer than 2 years and there were no cases of recurrence or post-operative metastasis. We devised an operative strategy dictated by initial presenting characteristics of the tumor. The presence of carcinoma should be suspected and searched for in patients over 40 presenting with acute appendicitis. Intraoperatively any suspicious mass should undergo frozen sectioning as the finding of a malignancy often necessitates a larger or repeat operation. The propensity of these neoplasms for presentation in the guise of acute appendicitis mandates that the surgeon be familiar with the appropriate management algorithm, both in and out of the operating room.*

**Keywords:** Appendix Cancer, Gastrointestinal Malignancy, Malignant Neoplasms of the Appendix

## 1. Introduction

Primary tumors of the appendix are rare. However, statistics show that one of the most common surgical emergencies in the United States today is still appendicitis [1]. Since the pathophysiology of appendicitis was first described in 1886 by Raymond Fitz, multiple etiologies of appendicitis have been discovered, ranging from obstruction via fecalith to obstruction with tumor [2]. Current management strategies described in the literature advocate aggressive right colonic resections for most tumor types. These recommendations are often based on data extrapolated from primary colonic tumors of similar histology. The objective of our study was to review our experience with primary tumors of the appendix, compare our management strategies with the other common management strategies described in the current literature, and use this information to better define an accepted management algorithm for primary appendiceal tumors.

## 2. Methods

All appendectomies performed at Providence Hospital and Medical Centers over a 25-year period from March 1982 to December 2007 were reviewed. Those patients with chart codes positive for appendiceal tumors were reviewed in detail. Only primary neoplasms of the appendix were analyzed. Patients with histology consistent with adenocarcinoma, carcinoid, mucinous cystadenocarcinoma, and mixed adenocarcinoid tumors were further evaluated. Patients with benign neoplasms and patients with metastatic disease to the appendix with a separate primary were not included in the study. Factors catalogued in the patients incorporated in the study included presenting symptoms, method of diagnosis, epidemiologic data, preoperative imaging, laboratory studies, intraoperative findings, operation performed, pathology results, use of postoperative chemotherapy, and eventual outcomes.

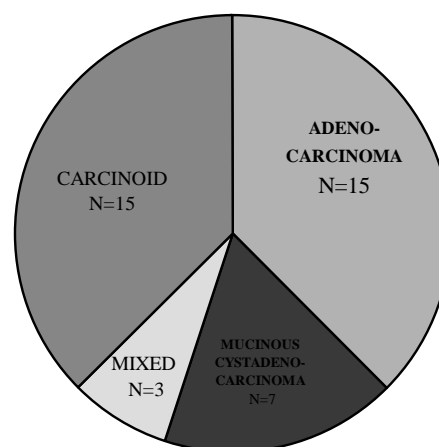
Epidemiologic factors analyzed included patient age at diagnosis, gender, and date of surgery. Patients were categorized as to whether or not they received preoperative imaging, the type of imaging performed, and whether the imaging was able to detect the presence of a neoplasm preoperatively, postoperatively on retrospective review, or not at all. Laboratory values evaluated including preoperative white blood cell count and hemoglobin. Intraoperative values recorded including the presence of gross metastatic disease, whether a neoplasm was suspected during the initial operation, whether a frozen section was performed. The operation performed as well as whether this was an initial operation or a completion operation. Patient survival in months, follow up for a minimum of 2 years, and complications were also noted. Complications which were looked for included wound infections, abscess formation, and development of pseudomyxoma peritonei. Outcomes were determined at surgery by pathologic examination and by clinical follow-up in all available patients. All patients were separated out by histologic classification and compared among those with similar neoplastic histology.

### 3. Results

Of the 8560 cases of appendicitis, primary neoplasms of the appendix were diagnosed in 41 patients, an incidence of 0.5%. The incidence of diagnosis of primary tumors of the appendix increased from 0.3% between 1982-2003 to 1.2% between 2003-2008. An investigation of this discrepancy revealed that prior to 2001, cases of grossly metastatic adenocarcinoma of the appendix with colonic spread were coded as adenocarcinoma of the colon rather than adenocarcinoma of the appendix. It is believed the true incidence of primary tumors of the appendix is closer to 1.2% within the institution. Two patients were lost to follow up and records were not available. Twenty-six patients were female (63%) and 15 were male (37%). The average age at diagnosis was 53 years. Clinical presentation was variable (**Table 1**). As might be expected, the majority of patients presented with signs and symptoms consistent with appendicitis. Forty-four percent presented with right lower quadrant abdominal pain and 7% presented with peritonitis while 22% of patients presented asymptotically. Twenty percent of patients presented with other symptoms secondary to metastatic disease such as carcinoid syndrome (N = 1), bowel obstruction (N = 3), dyspnea (N = 2), upper abdominal pain (N = 2), and vaginal bleeding (N = 1). The mortality rate in our series was 2%, with one death secondary to complications of distant metastatic disease in which the family opted to withdraw care. The average length of stay was 8 days.

**Table 1. Clinical presentation of primary tumors of the appendix.**

Symptoms	Number of Patients	%	Pre-operative WBC(K/mcL)
Right Lower Quadrant Pain	18	44	10.1
Diffuse Peritonitis	3	7	23.6
Asymptomatic	9	22	10.9
Other	11	27	9.2



**Figure 1. Distribution of primary tumors of the appendix.**

Adenocarcinoma (N = 16) and carcinoid (N = 15) were the most common pathologic findings. Mucinous cystadenoma (N = 7) and mixed adenocarcinoma and goblet cell carcinoid (N = 3) were also encountered as shown in **Figure 1**. Five percent (N = 2) of patients presented with a synchronous tumor elsewhere in the gastrointestinal tract. Diagnosis was made on colonoscopy when sigmoid adenocarcinomas were found in two patients with synchronous appendiceal adenocarcinomas. As shown in **Table 2**, appendiceal cancer was often discovered incidentally

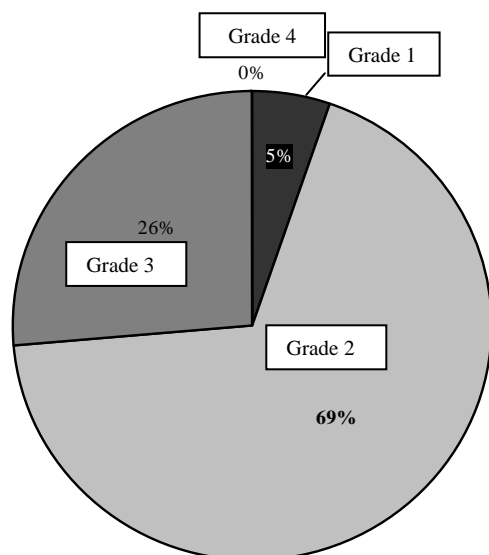
**Table 2. Relationship of the diagnosis of primary appendiceal tumor to the initial operation.**

Operative Findings	Number of patients	%
Incidental finding during another procedure	18	44%
Appendiceal cancer suspected prior to operation	10	24%
Tumor discovered while operating for appendicitis	13	32%

during operation for other symptoms or during an unrelated procedure. Our series found 44% of patients were diagnosed with a primary appendiceal malignancy after undergoing routine colonoscopy or surgical exploration for unrelated symptoms. A large portion of the cohort (41%) was found to have metastatic disease at the time of their initial operation. It should be noted that appendiceal cancer was highly suspected prior to operation in only 24% of the patients who were ultimately found to have an appendiceal malignancy.

Upon further review of the pathologic subsets as shown in **Table 3**, of the 19 patients who presented with either adenocarcinoma or mixed adenocarcinoma and goblet cell carcinoid, 10 were suspected preoperatively, either due to preoperative computed tomography (CT) or while in operating room at the time of the initial operation. Nine of these patients underwent initial right hemicolectomy; one underwent appendectomy with interval right hemicolectomy. The remaining nine patients were diagnosed after histologic examination of the pathologic specimen. Four of these nine returned for right hemicolectomy as a definitive operation. Of the remaining five, one was transferred to another institution upon family request, three refused further operative intervention due to distant metastatic disease, and the last had a lesion located at the tip of the appendix and refused further surgery (**Table 4**). On pathologic review of the tumor grading of the adenocarcinoma tumors, most of the tumors (N = 13) were grade 2 moderately differentiated tumors (**Figure 2**).

In contrast to the patients with adenocarcinomas of the appendix, of the 15 patients diagnosed with carcinoid tumors of the appendix, four underwent curative appen-



**Figure 2. Tumor grading of adenocarcinomas of the appendix.**

dectomy at initial operation, six underwent right hemicolectomy at the initial operation, while five returned for right hemicolectomy secondary to location of the initial lesion near the base of the appendix (**Table 3**). There was one case of carcinoid syndrome secondary to metastatic disease to the liver. When looking at the manner of diagnosis among patients with carcinoid tumors, four patients were found carcinoid tumors at the base of the appendix discovered during colonoscopy. Fifty-three percent (N = 8) of carcinoid patients presented with signs and symptoms of acute appendicitis. One patient presented as an incidental mass palpated during another unrelated procedure and one was diagnosed as an incidental finding on pathologic specimen in a patient undergoing ileocelectomy for Crohn's disease. None of the patients diagnosed with carcinoid tumors subsequently developed metastatic disease and all survived for a minimal two years follow up. The one patient with metastatic disease prior to operation survived 14 months (**Table 3**).

Seventeen percent (N = 7) of patients in our cohort were diagnosed with mucinous cystadenocarcinoma. As seen in **Table 3**, tumor was suspected preoperatively or intraoperatively in 71% (N = 5) of these patients. Three patients underwent initial appendectomy, one of which was followed with a right hemicolectomy while the other four patients underwent right hemicolectomy at the initial operation. The remaining two patients who initially underwent appendectomy developed pseudomyxoma peritonei and did not undergo further surgery. A total of four patients were found to have pseudomyxoma peritonei at the initial operative disease at the time of operation.

Preoperative CT scans were available in 29 of 39 patients. The preoperative interpretation of these scans was obviously suspicious for malignancy in nine of 29 patients. One additional scan was identified as suspicious when reviewed retrospectively. The results of these preoperative CT scans led to changes in treatment in eight patients, preventing an unnecessary second operation in six of these patients and in the institution of non-operative management in another patient.

At the time of diagnosis of a primary tumor of the appendix, metastatic disease was found in 17 of the 41 patients (42%). As shown in **Table 4** these were separated out according to tumor type, and whether or not they received chemotherapy. Among patients with metastatic adenocarcinoma of the appendix 5 of the 10 received chemotherapy with an average survival of 13 months versus 6 months in those without chemotherapy. There were 2 patients with metastatic carcinoid who also opted to receive chemotherapy. Among this group those patients who received chemotherapy had an average survival of 11 months as opposed to 13 months among those who did not receive chemotherapy.

**Table 3. Operative results.**

	Adenocarcinoma	%	Mucinous cystadenocarcinoma	%	Carcinoid	%
Number	19	46	7	17	15	37
Tumor suspected pre-op or intra-op	10	53	5	71	7	47
Appendectomy alone	2	11	2	29	4	27
Right hemicolectomy at initial operation	9	47	4	57	6	40
Right hemicolectomy at second operation	5	26	1	14	5	33
Refusal of further operation	3	16	0	0	0	0
Metastatic disease at initial operation	10	53	4	57	1	7

Twenty four of the 41 patients with primary appendiceal cancers were found to have no evidence of metastatic disease at the time of operation. **Table 5** demonstrates the current survival statistics among this group based on tumor type. At the conclusion of the study all 24 patients without metastatic disease had survived longer than two years. Seventeen of the 24 patients had already survived longer than five years (**Figure 3**). Three

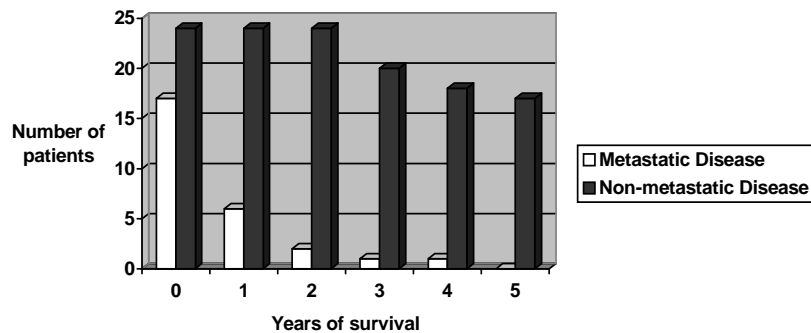
of the 24 patients had deceased, all secondary to non-cancer related illnesses. There were three patients with non-metastatic disease who did choose to receive chemotherapy. Among all patients with non-metastatic disease at the time of initial operation we have seen no cases of tumor recurrence or post-operative development of metastasis.

**Table 4. Metastatic disease based on tumor type.**

	Metastatic disease at initial operation	%	Received chemotherapy	%	Average survival in months with chemotherapy	Average survival in months without chemotherapy
Adenocarcinoma (19)	10	53	5	50	13	6
Mucinous cystadenocarcinoma (7)	4	57	0	0	N/A	21
Carcinoid (15)	3	20	2	67	11	13

**Table 5. Non-metastatic disease based on tumor type.**

	No metastatic disease at initial operation	%	Received chemotherapy	%	Average survival in months with chemotherapy	Average survival in months without chemotherapy
Adenocarcinoma (19)	9	47	3	33	60	65
Mucinous cystadenocarcinoma (7)	3	43	0	0	N/A	104
Carcinoid (15)	102	80	0	0	N/A	139



**Figure 3. 5 years post operative survival.**

#### 4. Discussion

Primary malignant tumors of the appendix are rare, occurring in 0.5% of all appendectomies [3]. The four main types of appendiceal malignancies are carcinoid tumors, mucinous cystadenocarcinomas, adenocarcinomas and adenocarcinoid tumors [4]. Common benign tumors include villous adenomas and mucinous cystadenomas. Once encountered, the management of appendiceal tumors changes patient management from that of traditional causes of appendicitis. As the study has shown, the majority of cases of appendiceal neoplasm are not diagnosed pre-operatively, but rather intra-operatively, or on pathologic review of the specimen post-operatively. The diversity in treatment strategies for appendicitis creates the need for a well-defined treatment algorithm for appendiceal malignancies that will ensure proper treatment in both the acute setting and retrospectively, when diagnosis is made based on the pathologic specimen.

First, gross inspection by the surgeon may reveal atypical findings. A frozen section should be done whenever the appendiceal findings are atypical. A diagnosis of malignancy can be made during surgery and appropriate surgery can be done primarily [4]. Treatment then varies depending on tumor type and location. The treatment of each type of appendiceal neoplasm is well described in the literature. All patients with appendiceal neoplasms should be followed because a second malignancy will develop in 15% to 20% of cases [4].

Consistent with our findings, carcinoid tumors are the second most frequently encountered malignancy of the appendix after adenocarcinoma [5]. Appendiceal carcinoid tumors are typically found in 0.3-0.9 percent of patients undergoing appendectomy [6]. They tend to present with the clinical signs and symptoms of an acute abdomen and frequently coexist with other intestinal neoplasms [5]. The size of the tumor is correlated with prognosis [7]. Diagnosis of a carcinoid tumor less than one centimeter, or according to some sources between one and two centimeters is appropriately treated with appendectomy alone [6]. The same tumor, measuring greater than two centimeters, or associated with mesenteric/lymphatic invasion, should prompt right hemicolectomy [8]. Examination of the histological specimen revealing location at the base of the appendix, rather than at the tip also necessitates right hemicolectomy [6].

Review of the literature reveals that mucinous cystic neoplasms of the appendix continue to engender considerable debate in their diagnosis and management. Abdominal pain is the most common presenting symptom. The recommended treatment of mucinous cystadenocarcinoma is a right hemicolectomy with debulking of any pseudomyxoma peritonei [4]. In the

reported literature, an approximately equal number of patients have been subjected to appendectomy alone versus right hemicolectomy [9].

Primary appendiceal adenocarcinoma is a rare neoplasm that constitutes less than 0.5% of all gastrointestinal neoplasms, yet it is the most common appendiceal neoplasm. Most patients present with either local invasion or metastatic disease often involving the peritoneum or ovaries [10]. In one study, a high frequency of ovarian metastases in women suggested a role for bilateral oophorectomy [11]. One important prognostic factor of primary appendiceal adenocarcinoma appears to be histology, with Park *et al.* [12] reporting improved survival in those patients with mucinous variants. Adenocarcinoma is best treated with right hemicolectomy regardless of size [4]. Survival rate has been shown to be superior after right hemicolectomy versus appendectomy alone [13]. In addition, right hemicolectomy performed as a secondary procedure resulted in the upstaging of 38% of the patients' tumors [13].

Adenocarcinoid tumors have a dual cell origin, sharing the histological features of both carcinoids and adenocarcinomas, and a predilection for developing ovarian metastases. Size and location of the primary tumor is often cited as an indication for hemicolectomy rather than appendectomy. However, other than size greater than two centimeters and base localization, current studies suggest that the presence of mucin producing cells, atypical foci, high mitotic count, or spread beyond the appendix is a further indication for secondary right hemicolectomy [14, 15]. Adenocarcinoid tumor is appropriately treated by right hemicolectomy and oophorectomy in females [4].

Although uncommon, primary appendiceal neoplasms often result in clinical symptoms of appendicitis that may lead to radiographic analysis. As our study and other studies have shown, acute appendicitis is the most common manifestation for most tumor types. Other manifestations include intussusception, a palpable mass, gastrointestinal bleeding, increasing abdominal girth (from pseudomyxoma peritonei), and secondary genitourinary complications [16]. CT can help rule out or confirm an appendiceal tumor and may suggest a more specific diagnosis [16].

#### 5. Conclusions

Operative strategy should be dictated by initial presenting characteristics of the tumor. Tumors should be first differentiated based on pathology. All adenocarcinomas, mixed adenocarcinoids, and mucinous cystadenocarcinomas should undergo right hemicolectomy regardless of size or location on the appendix. With regards to carcinoid tumors, if discovered at initial surgery as a mass larger than two cm,

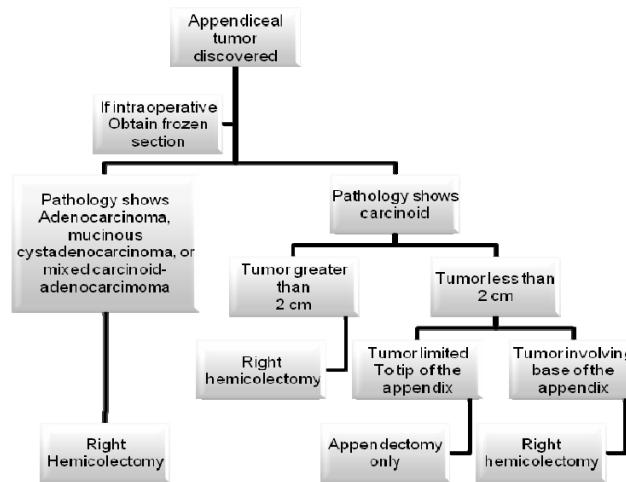


Figure 4. Treatment algorithm for primary tumors of the appendix

a right hemicolectomy should be performed, while tumors less than two cm in size and limited to the tip of the appendix can be treated with appendectomy alone. Tumors detected post-operatively in the histologic specimen should be managed according to the location and pathology of the tumor. Patients with adenocarcinomas and tumors found at the base of the appendix should undergo reoperation with right hemicolectomy or ileocecal resection. Appendectomy alone can be used for a carcinoid tumor limited to the tip of the appendix (Figure 4).

Several key concepts can be gathered from this review. The initial presentation of the patient often dictates management. The presence of carcinoma should be suspected and searched for in patients over 40 presenting with acute appendicitis. The utility of routine perioperative CT scanning in this age group could not be assessed in our study given the time frame of the study and changes in CT technology over this period; however, it may be an important adjunctive test in this cohort and is worth further evaluation in the future.

In the operating room suspicion of an appendiceal neoplasm should prompt a frozen section. Diagnosis of malignancy can be made and the appropriate operation, whether appendectomy or right hemicolectomy, can be done primarily. The propensity of these neoplasms for presentation in the guise of acute appendicitis mandates that the general surgeon be familiar with the appropriate management algorithm, both in and out of the operating room.

## REFERENCES

- [1] J. B. Matthews and R. A. Hodin, "Acute Abdomen and Appendix," In: M. W. Mulholland, *et al*, Eds., *Surgery: Scientific Principles and Practice*, 4th Edition, Williams & Wilkins, Philadelphia, Lippincott, 2006, pp. 1214-1221.
- [2] R. H. Fitz, "Perforating Inflammation of the Vermiform Appendix with Special Reference to Its Early Diagnosis and Treatment," *Transactions of the Association of American Physicians*, Vol. 1, No. 1, 1886, pp. 107-144.
- [3] S. J. Connor, G. B. Hanna and F. A. Frizelle, "Appendiceal Tumors: Retrospective Clinicopathologic Analysis of Appendiceal Tumors from 7,970 Appendectomies," *Diseases of the Colon & Rectum*, Vol. 41, No. 1, 1998, pp. 75-80.
- [4] R. H. Rutledge and J. W. Alexander, "Primary Appendiceal Malignancies: Rare but Important," *Surgery*, Vol. 111, No. 3, 1992, pp. 244-250.
- [5] A. Sandor and I. Modlin, "A Retrospective Analysis of 1570 Appendiceal Carcinoids," *American Journal of Gastroenterology*, Vol. 93, No. 3, 1998, pp. 422-428.
- [6] A. C. Goede, M. E. Caplin and M. C. Winslet, "Carcinoid Tumour of the Appendix," *British journal of Surgery*, Vol. 90, No. 11, 2003, pp. 1317-1322.
- [7] C. G. Moertel, L. H. Weiland, D. M. Nargony and M. B. Dockerty, "Carcinoid Tumor of the Appendix: Treatment and Prognosis," *New England Journal of Medicine*, Vol. 317, No. 27, 1987, pp. 1699-1701.
- [8] C. G. Moertel, M. B. Dockerty and E. S. Judd, "Carcinoid Tumors of Vermiform Appendix," *Cancer*, Vol. 21, 1968, pp. 270-277.
- [9] N. S. Lo and M. G. Sarr, "Mucinous Cystadenocarcinoma of the Appendix. The Controversy Persists: A Review," *Hepatology*, Vol. 50, No. 5, 2003, pp. 432-437.
- [10] G. M. Proulx, C. G. Willett, W. Daley and P. C. Shellito, "Appendiceal Carcinoma: Patterns of Failure Following Surgery and Implications for Adjuvant Therapy," *Journal of Surgical Oncology*, Vol. 66, No. 1, 1997, pp. 51-53.
- [11] R. Cortina, J. McCormick, P. Kolm and R. R. Perry, "Management and Prognosis of Adenocarcinoma of the Appendix," *Diseases of the Colon & Rectum*, Vol. 38, No. 8, 1995, pp. 848-852.
- [12] I. J. Park, C. S. Yu, H. C. Kim and J. C. Kim, "Clinical

- Features and Prognostic Factors in Primary Adenocarcinoma of the Appendix," *Korean Journal of Gastroenterology*, Vol. 43, No. 1, 2004, pp. 29-34.
- [13] S. S. Nitecki, B. G. Wolff, R. Schlinkert and M. G. Sarr, "The Natural History of Surgically Treated Primary Adenocarcinoma of the Appendix," *Annals of Surgery*, Vol. 219, No. 1, 1994, pp. 51-57.
- [14] R. L. Warkel, P. H. Cooper and E. B. Helwig, "Adenocarcinoid, a Mucin-producing Carcinoid Tumor of the Appendix: a Study of 39 Cases," *Cancer*, Vol. 42, No. 6, 1978, pp. 2781-2793.
- [15] J. L. Gouzi, P. Laigneau, J. P. Delalande, *et al.*, "Indications for Right Hemicolectomy in Carcinoid Tumors of the Appendix," *Surgery, Gynecology & Obstetrics*, Vol. 176, No. 6, 1993, pp. 543-547.
- [16] P. J. Pickhardt, A. D. Levy, C. A. Rohrmann Jr. and A. I. Kende, "Primary Neoplasms of the Appendix: Radiologic Spectrum of Disease with Pathologic Correlation," *Radiographics*, Vol. 23, No. 3, 2003, pp. 645-662.