Primary appendiceal cancer is a rare neoplasm. We analyzed the clinicopathologic characteristics and clinical outcomes of patients with primary appendiceal cancer treated at Buddhist Tzu Chi General Hospital in Eastern Taiwan. We reviewed the medical records of patients who had appendectomy at our hospital over a 10-year period and studied those who had histologically proven malignant appendiceal neoplasms. We treated eight such patients: seven males and one female. Their median age was 66 years (range, 59–78 years). There were three mucinous adenocarcinomas, two colonic type adenocarcinomas, and three adenocarcinoids. No patient was diagnosed correctly before surgery, and five (62.5%) had a preoperative diagnosis of acute appendicitis. Operative procedures included right hemicolectomy or partial colectomy in four, debulking and right hemicolectomy in three, and appendectomy only in one. With a mean follow-up of 64 months (range, 3–132), patients with adenocarcinoid lesions had better prognosis than those with adenocarcinomas. The important prognostic factors of primary appendiceal cancer included histologic subtypes and the extent of dissemination. In our series, palliative resection for disseminated lesions with or without additional chemotherapy resulted in long-term survival.

Key Words: adenocarcinoid, appendiceal cancer, colonic type adenocarcinoma, mucinous cystadenocarcinoma, pseudomyxoma peritonei

staging, and their follow-up status. The diagnostic studies used in these patients included abdominal CT and double contrast barium enema. Histologic subtypes were determined by hematoxylin-eosin stain, mucin stain (to differentiate mucinous and nonmucinous adenocarcinoma), argyrophil, argentaffin stain, and immunohistochemical stain using anti-neuron specific enolase (NSE) antibody for adenocarcinoid tumors. Follow-up information was obtained by telephone or interview. The mean duration of follow-up was 64 months (range, 3–132 months).

RESULTS

During the 10-year study period, 2,841 appendectomies were performed. The incidence of appendiceal cancer was 0.28% (8/2,841). Among the eight patients with primary appendiceal cancer, seven were male and one was female. Their median age was 66 years (range, 59–78 years). The individual clinicopathologic characteristics of our patients, operative and follow-up information are summarized in the Table. Six patients (75%) presented with right lower quadrant (RLQ) pain, among whom five (62.5%) also had fever (operated on with presumptive impression of acute appendicitis). The other two patients presented with abdominal distension: one had chronic abdominal pain and the other, massive ascites with pseudomyxoma peritonei.

Some of our patients had abdominal CT and double contrast barium enema before their operations. Double contrast lower GI series showed an annular ulcerative filling defect at the pericecal region with irregular outline of the appendix (case 5). Patients with pseudomyxoma peritonei had several pathognomonic findings on abdominal CT: irregular peritoneal wall thickening, a metastatic nodular lesion at segment 8 of the liver and prominent ascites, and omental cake formation in the lower abdomen (case 1). CT study showed a spiculated mass in the infracecal region with adjacent soft tissue stranding and small periaappendiceal lymph nodes (case 4).

Simple appendectomy was performed in three cases initially because appendiceal cancers were not suspected by the operating surgeons (cases 3, 6, 8). Two patients (cases 6, 8) required a second operation, at which time a right hemicolectomy was performed. Case 3 had an appendectomy for a benign mucocele. Eight years later, pseudomyxoma peritonei was encountered during a herniorrhaphy. Thus, five patients had right hemicolectomy initially, two later, and one had partial colectomy. Excluding the case initially diagnosed as benign mucocele, one of our patients had a stage I tumor, three had stage II tumors, and three had stage IV tumors according to the TNM system of the American Joint Committee on Cancer (AJCC 6th edition).

The pathologic findings of colonic type adenocarcinoma of the appendix are illustrated in Figure 1. Grossly, the tumor arises from the appendix with cecal invasion (Figure 1A). Microscopically, the tumor is composed of adenocarcinoma arising from the mucosa of the appendix (Figure 1B). The pathologic findings of mucinous cystadenocarcinoma are shown in Figure 2. Grossly, it shows a unilocular cyst containing mucin and a yellowish-white mural nodule (Figure 2A). Microscopically, the mural nodule is composed of adenocarcinoma with stromal invasion and mucin pool formation in the cystic wall (Figures 2B–D). The pathologic findings of adenocarcinoid are presented in Figure 3. Microscopically, the tumor is composed of signet ring cells with glandular formation (Figure 3A). The argyrophil stain shows numerous blackish granular substances in the cytoplasm (Figure 3B). The mucin stain shows positive mucin in the cytoplasm (Figure 3C). The immunohistochemical stain shows positive NSE in the cytoplasm (Figure 3D).

Follow-up information showed that these eight patients survived from 3 months to 12 years. Three patients, all with adenocarcinoid, are still alive without any evidence of recurrence (at 8, 117 and 118 months after resection). Four patients died at various intervals. Two died of the disease itself (at 3–9 months). The other two died without recurrent disease from esophageal carcinoma and cerebrovascular accident (at 2 and 12 years, respectively). Patients with intraperitoneal dissemination at operation and synchronous liver metastasis have poorer prognosis. Overall, our patients had a 2-year survival rate of 62.5%, and a 5-year survival rate of 50%.

DISCUSSION

Primary appendiceal adenocarcinoma is very rare. According to Collins, the incidence is only 0.08% among 71,000 appendix specimens [1]. The mean age
Table. Clinicopathologic characteristics of patients with appendiceal cancers (1995–2005)

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex/age (yr)</th>
<th>Symptom(s)</th>
<th>Preoperative diagnosis (AJCC stage)</th>
<th>Postoperative diagnosis</th>
<th>Operation performed</th>
<th>Follow-up information</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/68</td>
<td>Ascites, abdominal distension</td>
<td>Pseudomyxoma peritonei, liver metastasis</td>
<td>Disseminated mucinous adenocarcinoma and liver metastasis (IV)</td>
<td>Right hemicolecotomy and debulking resection of pseudomyxoma</td>
<td>DOD 3 mo later</td>
</tr>
<tr>
<td>2</td>
<td>M/59</td>
<td>RLQ pain, fever</td>
<td>Acute appendicitis</td>
<td>Ruptured mucinous adenocarcinoma of appendix (II)</td>
<td>Partial colectomy and debulking resection of pseudomyxoma</td>
<td>Alive and well 87 mo later</td>
</tr>
<tr>
<td>4</td>
<td>M/71</td>
<td>RLQ pain, fever</td>
<td>Acute diverticulitis or appendimoma</td>
<td>Colonic type adenocarcinoma of appendix (II) (2 years later, diagnosis of esophageal cancer)</td>
<td>Right hemicolecotomy</td>
<td>Died of esophageal cancer 28 mo later</td>
</tr>
<tr>
<td>5</td>
<td>F/65</td>
<td>RLQ pain</td>
<td>Suspected cecal cancer with liver metastasis</td>
<td>Colonic type adenocarcinoma of appendix and liver metastases (IV)</td>
<td>Right hemicolecotomy</td>
<td>DOD 9 mo later</td>
</tr>
<tr>
<td>6</td>
<td>M/60</td>
<td>RLQ pain, fever</td>
<td>Acute appendicitis</td>
<td>Adenocarcinoid of appendix (I)</td>
<td>Appendectomy before right hemicolecotomy</td>
<td>Alive and well 118 mo later</td>
</tr>
<tr>
<td>7</td>
<td>M/74</td>
<td>Chronic abdominal pain and distension</td>
<td>Mechanical ileus</td>
<td>Adenocarcinoid of appendix (II)</td>
<td>Right hemicolecotomy</td>
<td>Alive and well 117 mo later</td>
</tr>
<tr>
<td>8</td>
<td>M/64</td>
<td>RLQ pain, fever</td>
<td>Acute appendicitis</td>
<td>Adenocarcinoid of appendix, disseminated (IV)</td>
<td>Appendectomy before right hemicolecotomy, debulking resection and HIOC</td>
<td>Alive and well 8 mo later</td>
</tr>
</tbody>
</table>

AJCC = American Joint Committee on Cancer; M = male; F = female; DOD = died of disease; RLQ = right lower quadrant; CVA = cerebrovascular accident; HIOC = hyperthermic intraoperative chemotherapy.
at presentation is around 60 years. More than 70% of patients were considered to have acute appendicitis before surgery and some presented with abdominal mass, which may be confused with Crohn’s disease, intussusception, hydronephrosis, cecal carcinoma, or ovarian carcinoma. Primary appendiceal cancer is diagnosed in 0.9–1.4% of appendectomy specimens [1,2]. The incidence of appendiceal cancer was 0.28% in our hospital.

These rare tumors are seldom suspected before surgery and less than one half of cases are diagnosed intraoperatively [4]. Most are mistaken for acute...
appendicitis. In our series, six of eight patients (75%) presented with RLQ pain, and five (62.5%) had a pre-operative diagnosis of acute appendicitis. No patient was diagnosed before surgery or during surgery. Three cases were not suspected by the operating surgeon and a simple appendectomy was performed initially.

Appendiceal malignancy were classified histologically into five categories: mucinous adenocarcinoma (37%), colonic type adenocarcinoma (25%), signet ring cell carcinoma (4%), malignant carcinoid (20%), and goblet cell carcinoid or adenocarcinoid (14%) [8].

We had three cases of mucinous cystadenocarcinoma in our series. Case 1 presented with abdominal distension and much ascites. Pseudomyxoma was confirmed by peritoneocentesis. Abdominal CT revealed irregular surface of liver, cecum, appendix, peritoneum, and omental cake formation and metastatic lesions in the liver. Although right hemicolecction and debulking resection of pseudomyxoma was performed, the patient died of this disease 3 months later. Case 2 had a perforated mucocele and localized pseudomyxoma found during surgery, through a McBurney’s incision. The RLQ wound was closed and converted to midline laparotomy. Partial colectomy and debulking resection of pseudomyxoma were done and he is still alive 87 months after surgery. Case 3 underwent an appendectomy initially, and a benign mucocele was reported. Eight years later, ventral hernia and pseudomyxoma peritonei were found. Hernioplasty and debulking surgery were performed and most pseudomyxoma lesions were removed. Scanty adenocarcinoma components were found in the pseudomyxoma.

Among 73 patients with appendiceal mucocele, Higa et al reported that 24.7% were hyperplasia, 63.0% were mucinous cystadenoma, and 12.3% were mucinous cystadenocarcinoma [9]. Accurate preoperative diagnosis of mucocele is important in order to avoid rupture at surgery with the development of pseudomyxoma peritonei [10]. Most cases of pseudomyxoma peritonei from primary tumors in the appendix are usually low grade. On CT scan, the typical mucocele appears to be a well-encapsulated cystic mass in the

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**Figure 3.** Adenocarcinoid of the appendix. (A) Microscopic photo shows that the tumor is composed of signet ring cells with glandular arrangement (hematoxylin and eosin; 100×). Three other stains show that the cytoplasm of the cancer cells stain positive for: (B) numerous blackish granular substances (argyrophil; 200×); (C) mucin (200×); and (D) neuron specific enolase (LSAB stain; 200×), indicating goblet adenocarcinoid.
appendiceal area. Detection of enhancing nodules in the mucocele wall suggests cystadenocarcinoma [10]. According to our experience, the prognosis of malignant mucocele with dissemination and the presence of liver metastasis is poor, while perforation of mucocele with localized pseudomyxoma does not influence the clinical outcome.

From a clinicopathologic analysis of 107 cases, Misdraji et al suggested that appendiceal mucinous neoplasm can be classified as either low-grade mucinous neoplasms or mucinous adenocarcinoma [11]. This distinction is of prognostic significance. Bulky peritoneal tumor has worse prognosis. The prognosis of pseudomyxoma peritonei found in the setting of mucinous cystadenocarcinoma of the appendix is poor, with a 5-year survival rate of 50%. Generalized pseudomyxoma peritonei is best treated by aggressive surgical debulking of all apparent mucinous tissues and to achieve complete cytoreduction. This approach significantly improves survival and decreases the rate of recurrence compared to appendectomy alone. Additional intraperitoneal chemotherapy with mitomycin C and postoperative 5-fluorouracil have also been used to further improve the survival rate and reduce the rate of disease relapse [12,13]. However, our cases 2 and 3 survived 7–12 years with cytoreductive surgery only.

Cases 4 and 5 of this series had colonic type adenocarcinoma. Case 4 presented with repeated RLQ pain and fever. Abdominal CT revealed an inflammatory lesion in the pericecal region. Initially, he was thought to have acute diverticulitis or an appendimoma, and his symptoms improved after 2 weeks of antibiotic therapy. However, pain and fever recurred 2 months later, and a right hemicolectomy was performed. The lesion was very bulky, involved both the cecum and appendix, and adhered to the retroperitoneum, but without metastasis to regional lymph nodes. Unfortunately, another metachronous primary esophageal cancer developed 2 years later. Even with chemoradiation, he died of esophageal cancer without recurrence of the appendiceal cancer 28 months after right hemicolectomy. Case 5 had multiple liver tumors revealed by abdominal sonography and an irregular filling defect in the cecum revealed by barium enema. After a right hemicolectomy and debulking surgery, she died of progressive disease 9 months later.

Goblet cell carcinoids or adenocarcinoid of the appendix have distinct morphologic features characterized by the presence of numerous goblet cells [14]. We encountered three patients with adenocarcinoid in our series, including two localized types and one disseminated type. Case 6 had an appendectomy for a beefy red appendix. After pathologic diagnosis of cancer, he underwent a subsequent right hemicolectomy at another hospital. Case 7 presented with chronic abdominal pain and distension, and underwent laparotomy with the impression of mechanical ileus. Because of marked desmoid reaction at the ileocecal junction and stricture of the terminal ileum, a right hemicolectomy was performed. Both of these patients are still alive and have been disease-free for nearly 10 years. This is in agreement with other reports that adenocarcinoid, when localized, has an excellent prognosis (5-year survival about 99%) [15].

However, the subtype of mixed carcinoid and adenocarcinoma can spread widely [16], with more than 14% mortality in reported cases [15]. Bak and Asschenfeldt reviewed 108 cases from the literature and found that the metastatic rate of these tumors was 22.4% [17]. It is obvious that appendectomy alone is not enough to achieve long-term survival. Warkel et al proposed three characteristics to predict the aggressiveness of adenocarcinoid and recommended right hemicolectomy for high-risk cases [18]. The three characteristics are: (1) evidence of tumor spread beyond the appendix; (2) atypical microscopic foci; and (3) mitotic count of two or more mitotic features/10 high power field.

Case 8 presented with RLQ pain and fever, and initial appendectomy was done at another hospital. After tissue was proven to be adenocarcinoid, a subsequent right hemicolectomy and peritonectomy was done at our hospital because disseminated tumors were found in the peritoneal cavity. Intraoperative chemohyperthermia with mitomycin C and postoperative chemotherapy with 5-fluorouracil were given. The patient is still alive 8 months later. Glehen et al [19], and Esquivel and Sugarbaker [20] suggested that second-look surgery with repeated aggressive cytoreduction plus intraperitoneal chemohyperthermia might be of benefit for peritoneal surface spread of appendiceal malignancy. Their 5-year survival rate of 74% obtained with second-look surgery in this group of patients is far superior to that reported with colon or ovarian cancers.

The leading factor that influenced the outcome of primary appendiceal cancer in this series was histologic type. However, we do agree with an aggressive
approach in patients with pseudomyxoma peritonei because death from mucinous low-grade tumor is usually secondary to mechanical or functional bowel obstruction.

Appendiceal cancer has a high incidence of synchronous and metachronous malignancy of other parts of the GI tract [7]. We had two patients with metachronous lesions in other parts of the GI tract, including one with sigmoid colon cancer (case 3) and one with esophageal cancer (case 4). Therefore, diagnosis of adenocarcinoma of the appendix at the initial operation should prompt the surgeon to survey other parts of the GI tract for the possibility of a synchronous or metachronous neoplasm. Careful intraoperative search and postoperative endoscopic surveillance of the alimentary tract would be prudent.

In summary, the diagnosis of appendiceal cancer is rarely made preoperatively. As appendiceal cancer is prevalent in elderly patients, abdominal CT may be beneficial for the differentiation of disease other than acute appendicitis. If a mass is unexpectedly found in the appendix and appendiceal cancer is confirmed by frozen section, right hemicolectomy and aggressive cytoreduction, especially for mucinous cystadenocarcinoma of the appendix. A re-evaluation of appendiceal “mucocele,” Cancer 1973;32:1525–41.


原發性腫瘤：臨床病理研究

陳華宗¹ 倪雨珠¹ 周紹賓² 吳永康¹ 尹文耀¹ 李明哲¹ 許永祥³
花蓮慈濟醫院 ¹外科 ²放射科 ³病理科

原發性腫瘤是很稀有腫瘤。我們分析在花蓮慈濟醫院這種罕見病症之臨床病理特性及預後。我們分析十年來本院腫瘤手術病例中經病理診斷為腫瘤惡性腫瘤個案。本研究共有 8 位病人：7 個男性及 1 位女性，平均年齡 66 歲 (59－78 歲)。3 位是黏液性腺瘤，2 位大腸型腺癌及 3 位胃癌。沒有 1 位在術前診斷，而有 5 位術前診斷為急性腫瘤炎。手術方式包括 4 位接受右側大腸切除術或部份大腸切除術，3 位接受右側大腸切除術及腹部腫瘤根除術而另一位只作腫瘤切除術。我們平均追蹤 64 個月 (3－132 個月)，發現腺瘤癌預後比起腺癌有較好預後。我們研究資料顯示原發性腫瘤重要預後指標包括組織病理分型及腫瘤分佈範圍。在我們研究系列發現不管有無接受化學治療，姑息性切除及放療都能夠延長病人壽命。

關鍵詞：腺類癌，腫瘤癌，大腸型腺癌，黏液性腺癌，偽黏液性腹膜炎

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