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ORIGINAL ARTICLE

Clinicopathological features and the outcome of surgical management for adenocarcinoma of the appendix

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Abstract

AIM: To present a comprehensive analysis of incidence, clinicopathological features, appropriateness of surgical procedures, and survival for adenocarcinoma of the appendix.

METHODS: A retrospective case analysis was conducted for the 10-year period 1998-2008. All patients diagnosed with adenocarcinoma of the appendix were analyzed for their demographics details, clinical features, tumor incidence and characteristics, tumor stage, surgical procedures performed, and their survival.

RESULTS: Nine thousand three hundred and twenty-three patients underwent appendectomies during the study period, and of these, 10 (0.1%: 8 men and 2 women with a mean age of 53.1 years, age range 21-83 years) were found to have primary adenocarcinoma of the appendix. Appendicular neoplasia was not suspected pre-operatively in any of the patients. Six (60%) patients underwent secondary right hemicolectomy. Four (40%) cases had appendectomy alone, and two of them died, whereas all those who underwent right hemicolectomy are alive and disease free. Five (50%) were reported to have grade 1 disease, three (30%) grade 2, and two (20%) grade 3 with mean survival of 34, 48, and 22 mo, respectively. Six (60%) patients presented with advanced disease (Duke's C and D). At the end of follow up (mean period: 37.9 mo), eight patients are alive and disease free at the end of follow up. Overall mean survival was 36.3 mo (confidence interval; 16%-56%) with 41.3 and 16 mo for men and women, respectively. Mean survival for those with and without lymph node involvement was 33.6 and 40.2 mo, respectively. Right hemicolectomy gave better results than appendectomy alone, although the difference was not statistically significant due to the small number of cases.

CONCLUSION: Adenocarcinoma of the appendix is extremely rare neoplasm with varied presentations, and is usually advanced when diagnosed. Right hemicolectomy is the treatment of choice for such tumors.

Key words: Adenocarcinoma of the appendix; Appendectomy; Appendicitis; Right hemicolectomy

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INTRODUCTION

Primary adenocarcinoma of the appendix accounts for 0.4%-1% of all gastrointestinal malignancies[1] and 4%-6% of primary appendiceal neoplasms[2]. It is found in only 0.9%-1.4% of appendectomy specimens with an age-adjusted incidence of 0.12 cases per million people per year[3]. The diagnosis of appendiceal adenocarcinoma is rarely established pre-operatively and less than half of

cases are diagnosed intra-operatively during acute or elective abdominal operations[4,5]. Most tumors are identified only after histological examination of the removed specimens[6]. The rarity of adenocarcinoma of the appendix has made it difficult to clearly understand the natural history of the disease and to amass extensive data on which to base therapeutic and diagnostic decisions. A review of the current literature regarding the optimal treatment for noncarcinoid appendiceal cancer reveals variability in the recommendations for optimal surgical treatment.

Our study presents a review of the clinical presentations, various therapeutic modalities, and the outcome of surgical treatment for adenocarcinoma of the appendix.

MATERIALS AND METHODS

A retrospective review was performed of the medical files of all consecutive patients who underwent appendectomies, in a single university based center, over the period 1998-2008. The records of patients with histologically established adenocarcinoma of the appendix were analyzed for their demographics, clinical features, operative procedures, histopathological reports, and the final outcome. Pathological specimens were categorized by the type of neoplasm, grade, and the lymph nodes status. Tumor stage was evaluated using the SEER staging system (localized, regional, and distant), which corresponds to Stage Ⅰ-Ⅱ, Ⅲ, and Ⅳ, respectively, of the American Joint Committee on Cancer 5th TNM staging system[1]. The data was statistically analyzed by a SPSS 13.0 software package (SPSS Inc., Chicago, IL). Survival plots were generated using Kaplan-Meier analysis and prognostic variables were determined using log-rank, Breslow, and Tarone-ware tests. There were too few patients for a multivariate analysis.

RESULTS

Nine thousand three hundred and twenty-three patients were incorporated in this series and of these, 10 cases (0.1%: 8 male and 2 female patients with a mean age of 53.1 years, age range 21-83 years) were reported to have primary adenocarcinoma of the appendix (Table 1). No patient was pre-operatively diagnosed to have appendicular carcinoma. Appendicitis was reported to be the most frequent presenting complaint. Based on the histological diagnosis of appendiceal cancer, six (60%) patients underwent a secondary right hemicolectomy (3 laparoscopic and 7 open) following appendectomy and all are alive and disease-free. Four (40%) cases underwent appendectomy alone and two of them died after two and seventeen months, respectively. Eight (80%) patients had colonic type and 2 (20%) cystic type adenocarcinoma of the appendix. Three (30%) patients were found to have stage Ⅰ-Ⅱ disease, 3 (30%) stage Ⅲ, and 4 (40%) stage Ⅳ. Five (50%) patients had grade 1lesions, three (30%) grade 2 and two (20%) grade 3. Patients with positive lymph nodes received systemic chemotherapy which consisted of 5-fluorouracil either alone or in combination with other agents.

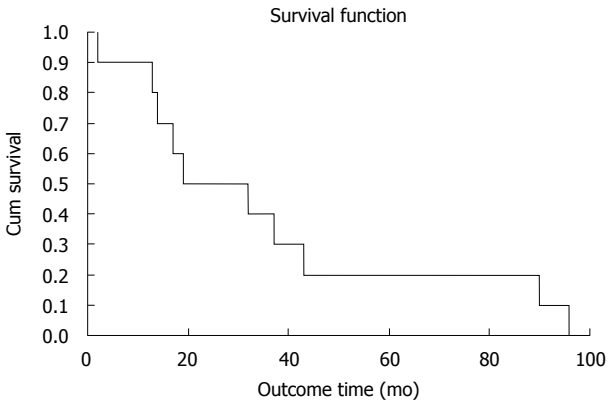

Figure 1 Survival analysis of final outcome.

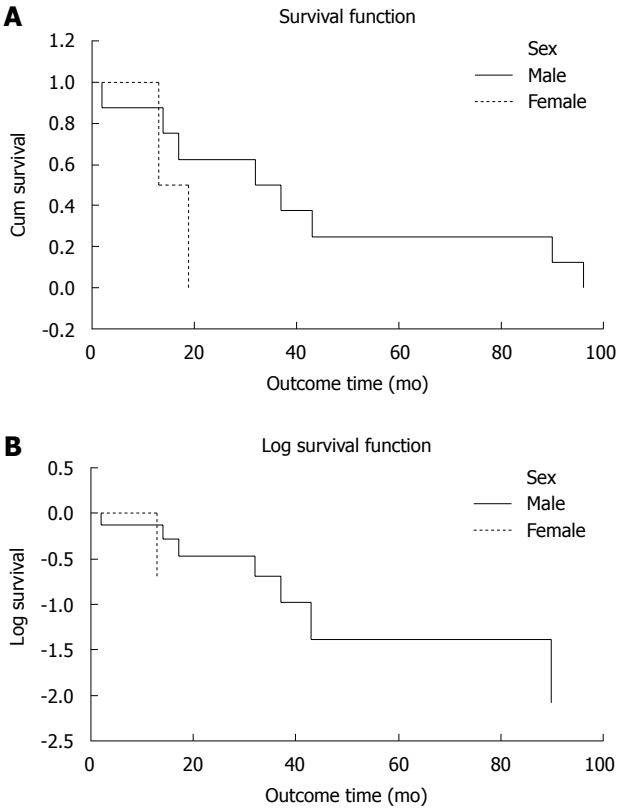

Figure 2 Survival analysis of outcome (A) and log survival function curve (B) for male and female patients.

After a mean follow up time of 37.9 mo, eight patients are alive and disease free. Mean survival in this series was 36.3 mo (Figure 1) with a 95% confidence interval (95% CI) of 16.27%-56.33%. Mean survival for male and female patients was 41.3 and 16 mo, respectively (95% CI 17.44%-31.65% and 10.12%-21.88%) (Figure 2A and B). The results of Log Rank, Breslow, and Tarone-ware statistical tests for the equality of survival distributions for sex showed 1.86 (significance 0.1729), 1.33 (significance 0.2482), and 1.58 (significance 0.2081), respectively. The median survival of patients with grade 1, 2, and 3 tumors was 34, 48 and 22 mo, respectively (Figure 3A and B). Mean survival for patients without lymph node involvement was 40.25 mo (95% CI: 77.42) whereas mean sur-

Table 1 Summary of patients with adenocarcinoma of appendix (n = 10)

No.	Age (yr)	Sex	Preoperative diagnosis	Operation	Histopathology				Final outcome
					Type	Duke's	Grade	LN	
1	76	M	Appendicitis	Appendectomy	Colonic	A	1	-	Died, 17 mo
2	83	M	RIF mas	App→RH	Colonic	D	3	+	Alive, 3 yr, 1 mo
3	68	M	PR bleeding	App→RH	Colonic	C	1	-	Alive, 4 yr
4	48	M	Appendicitis	Appendectomy	Cystic	A	1	-	Alive, 14 mo
5	21	F	Appendicitis	Appendectomy	Colonic	A	1	-	Alive, 19 mo
6	49	M	Appendicitis	Appendectomy	Cystic	A	2	+	Died, 2 mo
7	65	M	RIF mas	App→RH	Colonic	D	2	+	Alive, 8 yr
8	69	M	Appendicitis	App→RH	Colonic	C	2	+	Alive, 7 yr, 6 mo
9	37	F	Appendicitis	App→RH	Colonic	C	1	+	Alive, 13 mo
10	80	M	Cecal cancer	App→RH	Colonic	C	3	+	Alive, 3 yr, 7 mo

RIF: Right iliac fossa; PR: Per rectal; App: Appendectomy; RH: Right hemicolectomy; LN: Lymph node.

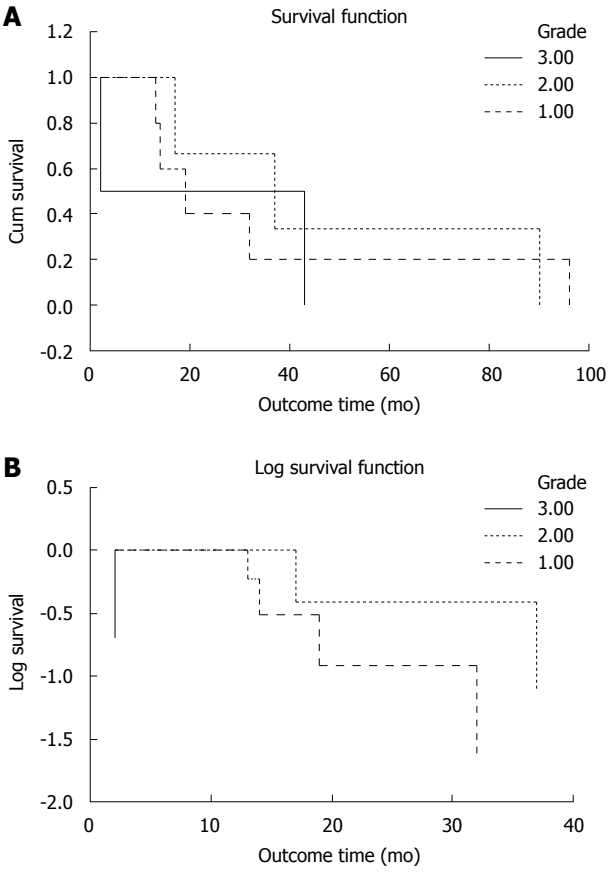

Figure 3 Survival analysis of outcome (A) and log survival function (B) for different grades of adenocarcinoma of appendix.

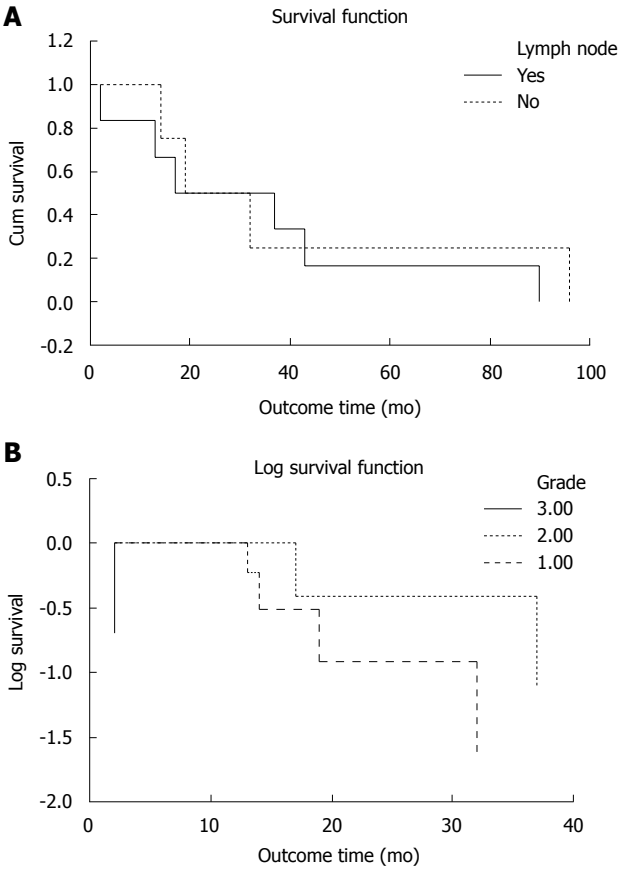

Figure 4 Survival analysis of outcome (A) and log rank function (B) for lymph node involvement by adenocarcinoma of appendix.

vival for those patients with involved lymph nodes was 33.67 mo (95% CI: 58.92) as shown in Figure 4A and B.

DISCUSSION

Primary adenocarcinoma of the appendix is exceedingly rare with a reported incidence of 0.08%-0.2% of appendectomies[7]. Carcinoid tumors are the most common primary lesions arising from the appendix, comprising 32%-85% of all appendiceal tumors[8,9], with adenocarcinomas accounting for a further 4%-6% of tumors[10]. A slight male predominance is documented in the literature[11,12] which is in contrast to our results which showed significantly greater number of affected male patients. The published mean age of presentation is in the 5th or 6th decade with a reported range of 17-89 years[13], similar to our results.

Most symptomatic appendiceal tumors present as acute appendicitis or a palpable mass[14-16]. Rarer presentations include masquerading as primary bladder cancer[17], pelvic mass causing urinary frequency[18], fever and hydronephrosis[19], Crohn's disease[20], vaginal bleeding[21], cecal intus-

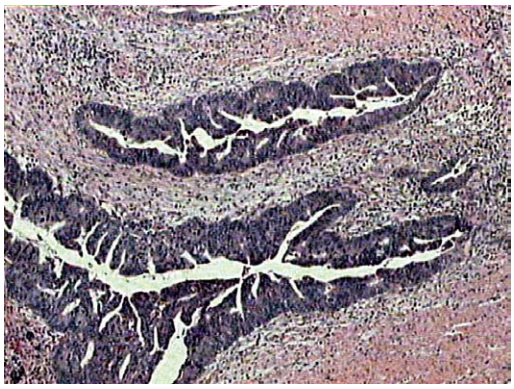

Figure 5 A well-differentiated adenocarcinoma of the appendix in which the glands demonstrate intense hyperchromatism, and the stroma is surrounded by lymphocytes.

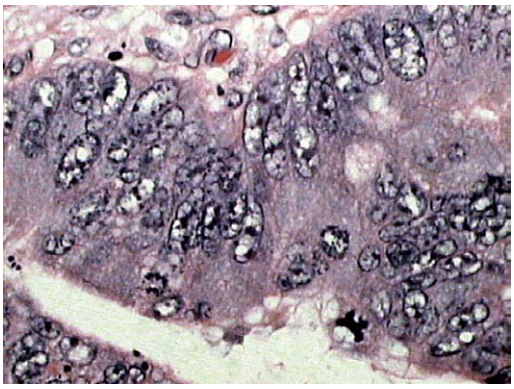

Figure 6 The high power microscopy of adenocarcinoma cells showing hyperchromatisn, pleomorphism abnormal mitotic figures, prominent nucleoli and regular thickening of nuclear membrane.

susception[22], and anemia[23]. Our study revealed 6 (60%) patients presented with the clinical impression of acute appendicitis. There are no symptoms specific to appendiceal cancer. Most symptoms result from associated disease such as, acute appendicitis, chronic recurrent appendicitis or peritonitis from perforation of the appendix[24]. In none of our patients was an objective diagnosis of appendiceal cancer made pre operatively, in agreement with the published reports[12,25]. This is attributed mainly to the lack of definite diagnostic, clinical, sonographic or radiological features characteristic of this disease[26]. Investigations such as ultrasound, computed tomography-scan, and magnetic resonance imaging of the abdomen might be advantageous in making the diagnosis before surgery[27], but are seldom performed for logistic reasons[28]. Sakamoto *et al*[29] achieved the first ever pre-operative diagnosis of intramucosal adenocarcinoma of the appendix by colonoscopy. The tumor was also removed by the endoscope. However, resection is not appropriate for appendiceal lesions as an intussuscepted appendix can sometimes mimic a polyp[30], and because accurate evaluation of the base of the lesion is difficult. The appendix must always be subjected to histological examination as, otherwise, an appendiceal malignancy can be easily missed[31].

Adenocarcinoma of the appendix arises in pre-existing adenomas, with either a cystic or colonic growth pattern. Cystic-type appendiceal carcinoma is a mucin-producing tumor which tends tending to rupture and spread through the peritoneal cavity, resulting in pseudomyxoma peritonei. Less common is the colonic-type of tumor that develops from a tubular or a tubulovillous adenoma[5]. Our study revealed a greater number[8] of colonic-type appendiceal adenocarcinomas (Figures 5 and 6). A narrow appendiceal diameter predisposes to neoplastic luminal occlusion early in the course of a colonic-type tumor[32], leading to appendicitis and a rupture rate as high as 56%[12]. Adenocarcinoma of the appendix is the most frequently perforating carcinoma of the gastrointestinal tract[33]. Anatomically there appears to be several reasons for this: (1) an extremely thin subserosal and peritoneal coat; (2) a delicate vascular submucosa supplied by a terminal artery; and (3) extremely thin longitudinal and circular muscular layers of the appendix. Interestingly, perforation had no significant effect on reported outcomes[15]. With the colonic-type of appendiceal adenocarcinoma, the perforated neoplastic cells have a low survival potential and less tendency to peritoneal implantation. The same authors also documented that patients with perforation faired better than those without perforation (74% *vs* 69% at 5 years and 48% *vs* 40% at 10 years) although there was no statistical difference ($P = 0.14$ and $P = 0.08$, respectively). In our study, no patient presented with perforated appendix. Adenocarcinoma of the appendix, like carcinoma of the colon, spreads via local invasion, lymphatic vessels, and the bloodstream. The most common metastatic location is the peritoneal cavity, followed by lymph nodes, liver, ovaries, abdominal wall, and lungs[34].

Controversy still prevails concerning the preferred surgical treatment for adenocarcinoma of the appendix. Cortina *et al*[15] concluded in their series that patients who underwent right hemicolectomy had a better prognosis for survival than patients who had appendectomy alone, although the difference was not statistically significant. Several other reports agree with this management strategy[35,36]. On the other hand, Murphy *et al*[1] suggested that appendectomy is appropriate for tumors found incidentally at operation, if the tumor was confined to the appendix, smaller than 2 cm, without evidence of mesoappendiceal involvement, and not extending to base of the appendix. For an optimal outcome, any neoplasm greater than 2 cm and involving the base of the appendix or mesoappendix should be considered for immediate right hemicolectomy. However, diminished tactile feedback during laparoscopic appendectomy potentially makes the detection of a cecal or appendiceal base lesion extremely difficult. Hata *et al*[37] suggested that early adenocarcinoma of the appendix rarely has lymph node metastases, and that well-differentiated adenocarcinoma invading the submucosa, or adenocarcinoma of any differentiation confined to the mucosa, may potentially be treated by simple appendectomy. On the other hand, poorly differentiated cancer is quite likely to be associated with lymph node metastases and secondary right hemicolectomy with

lymph node dissection should be considered in patients with: (1) lymphatic and/or venous invasion; (2) poorly differentiated adenocarcinoma; and (3) massive invasion of the submucosa. In patients with Duke's C stage, adjuvant chemotherapy, with 5-fluorouracil and levamisole may improve the survival, although another report found no benefit in survival from the use of systemic chemotherapy[38]. Hesketh[39] reported that the 5-year survival rate was 20% with appendectomy alone, while it was 63% with right hemicolectomy. Hopkins *et al*[40] reported rates of 20 and 45%, respectively. Our series substantiates these reports that right hemicolectomy is the treatment of choice for appendiceal adenocarcinoma, although the results are not statistically significant owing to a small number of cases. In our study, 6 (60%) underwent secondary right hemicolectomy, and all are still alive and disease free. On the other hand, two of the four patients had appendectomy alone died due to extensive metastases. Adenocarcinoma of the appendix often metastasizes to the ovaries and bilateral oophorectomy is recommended, especially if post menopausal, for staging and to eliminate metastatic spread to the ovaries[12]. A 5-year survival rate of 55% for appendiceal adenocarcinoma with a deteriorating prognosis correlating with an increasing Duke's staging has been established[12,41]. Colorectal cancers have 3%-5% risk of synchronous and 2%-3% metachronous tumors of the appendix, and a recent report[42] has observed similar incidences of synchronous and metachronous tumors of the appendix.

To conclude, adenocarcinoma of the appendix presents with diverse clinical features and the surgeon should maintain a high level of suspicion especially when managing patients with questionable appendicitis in older age groups. For optimal outcome, right hemicolectomy should be performed in all patients.

COMMENTS

Background

Primary adenocarcinoma of the appendix accounts for 0.4%-1% of all gastrointestinal malignancies and 4%-6% of primary appendiceal neoplasms. It is found in only 0.9%-1.4% of appendectomy specimens with an age-adjusted incidence of 0.12 cases per million people per year. The diagnosis of appendiceal adenocarcinoma is rarely established pre-operatively and less than half of cases are diagnosed intra-operatively during acute or elective abdominal operations. Most tumors are identified only after histological examination of the removed specimens.

Research frontiers

The rarity of adenocarcinoma of the appendix has made it difficult to clearly understand the natural history of the disease and to amass extensive data on which to base therapeutic and diagnostic decisions.

Innovations and breakthroughs

This study presents a review of the clinical presentations, various therapeutic modalities, and the outcome of surgical treatment for adenocarcinoma of the appendix.

Applications

The authors concluded that the adenocarcinoma of the appendix is extremely rare neoplasm with varied presentations, and is usually advanced when diagnosed. Right hemicolectomy is the treatment of choice for such tumors.

Peer review

The authors give us some interesting and important data with morphologic correlation and the readability of the article is high.

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