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Surgical Treatment of Appendiceal Adenocarcinoid (Goblet Cell Carcinoid)

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Abstract
Adenocarcinoid of the appendix is an infrequent tumor with histologic features of both adenocarcinoma and carcinoid tumor. Although its malignant potential remains unclear, adenocarcinoids seem to be biologically more aggressive than conventional carcinoids. The aim of this study was to analyze long-term results of surgical treatment for appendiceal adenocarcinoid. A retrospective review (1991–2003) identified seven patients (median age 72, range 27–81 years) treated for appendiceal adenocarcinoid. The clinical data of these patients were reviewed. Follow-up was complete for all patients (median 60 months, range 24–108 months). Most cases presented with associated acute appendicitis (71%). First intention surgery consisted of appendectomy (m = 6) and right hemicolectomy (m = 1). In three patients, additional surgical procedures were performed (right colectomy). Indications for colectomy were tumor size (three cases) associated with appendectomy margin invasion in one case. One patient with lymph node and peritoneal involvement experienced recurrence 9 months after hemicolectomy and died of the disease at 2 years. One patient subsequently died of colon carcinoma 6 years after adenocarcinoid treatment. Five patients were alive without disease at the time of the last follow-up. Synchronous or metachronous colon carcinomas developed in three patients (43%). Our results suggest that appendectomy alone could be used for appendiceal adenocarcinoid provided that the tumor (1) is less than 1 cm; (2) does not extend beyond the appendix adventitia; (3) has less than 2 mitoses/10 high power fields; and (4) has surgical margins that are tumor free. Otherwise, carcinologic right colectomy seems to be indicated. The risk for developing colorectal adenocarcinoma seems to be extremely high in patients treated for appendiceal adenocarcinoid and warrants close follow-up with colonoscopic screening.

Adenocarcinoid, alternatively named goblet cell carcinoid, of the appendix is an uncommon tumor. It was first described as a specific entity in 1969 by Gagne et al.[1] and eventually coined "adenocarcinoid" by Warkel et al.[2] Although adenocarcinoids share histologic features with adenocarcinoma and carcinoid tumor, it is biologically distinct from both. The aggressiveness of the adenocarcinoid is still unclear.[3] but is probably more aggressive than the carcinoid and less so than colorectal adenocarcinoma.[4–6] In particular, adenocarcinoid has a propensity for ovarian metastasis and principally peritoneal carcinomatosis.[3,7]

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Debates continue as to whether the appendiceal adenocarcinoid should be treated by appendectomy alone, as for most carcinoids, or if right hemicolectomy is indicated as for the appendiceal adenocarcinoma.[7] This study was undertaken to review the long-term results of surgical

Table 1.
Adenocarcinoid histologic features, treatment, and follow-up.

Tumor size (cm)	Appendix wall invasion	Lymph node invasion	Mitosis/10 high power fields	Appendectomy margins invaded	Surgical treatment	Follow-up status
0.7	Adventitia	No	0	No	Appendectomy	NED at 87 months
0.7	Adventitia	No	0	No	Appendectomy	NED at 84 months
0.9	Adventitia	No	0	No	Appendectomy	NED at 36 months
1.2	Mesoappendix	No	0	Yes	Appendectomy and hemicolectomy	NED at 35 months
1.5	Adventitia	No	1	No	Appendectomy and hemicolectomy	NED at 60 months
2.5	Peritoneum	Yes	3	No	Appendectomyand hemicolectomy	DOD at 24 months
3.0	Mesoappendix	No	0	No	Hemicolectomy	DFD at 75 months

NED: no evidence of disease; DFD: died free of disease; DOD: died of disease

treatment of appendiceal adenocarcinoids and evaluate the role of appendectomy alone in selected cases.

MATERIALS AND METHODS

A retrospective review identified seven patients treated for appendiceal adenocarcinoid in a single institution between January 1991 and December 2003. An experienced pathologist reviewed the histologic diagnoses. Three of these cases were previously reported in an article on surgical treatment of appendiceal tumors.[8] Preoperative, postoperative, and long-term follow-up information was obtained from patients' charts, family physicians, and questionnaires. Follow-up was complete for all patients.

RESULTS

Study Population and Pathologic Diagnosis

Appendiceal adenocarcinoid were diagnosed in seven patients. The median follow-up was 60 months (range 24–87 months). The median age was 72 years (range 27–81 years). The male/female ratio was 6:1. Most patients presented with clinical symptoms of acute appendicitis, and tumors were not suspected in any of them preoperatively. Associated acute appendicitis was confirmed by pathology examination in 71% of the resected specimen. Appendix perforation was detected in two patients (29%) with acute appendicitis.

Adenocarcinoid localization along the appendix was the apex (m = 4), middle third (m= 1), and proximal third (m = 2). The median tumor size was 1.1 cm (range 0.7–3.0 cm). In four cases (57%) the tumor was more than 1 cm in diameter. One case presented peritoneal invasion and a positive lymph node in the mesoappendix. Tumor characteristics are summarized in Table 1.

Surgical Treatment

First intention surgery was open appendectomy in six cases. In one patient the diagnosis of an appendiceal tumor was suspected peroperatively, and a right hemicolectomy was performed. This patient had a 3 cm adenocarcinoid in the absence of associated acute appendicitis. All patients with an adenocarcinoid >1 cm underwent subsequent carcinologic right colectomy, except the one who had a first intention colectomy. Among these three patients, one had invaded the appendectomy margin, and one had appendiceal peritoneal surface invasion and lymph node invasion in the mesoappendix.

Long-term Follow-up

The median follow-up was 60 months (range 24–87 months). The overall 5-year actuarial survival was 83%. The three patients who underwent appendectomy for a < 1 cm tumor were all alive without evidence of disease at a median follow-up of 84 months (range 36–87 months). Two patients among those who presented with a tumor > 1 cm underwent right colectomy and are alive without recurrence 3 and 5 years after surgery, respectively. One patient with a 2.5 cm adenocarcinoid presented with peritoneal carcinomatosist 9 months after right hemicolectomy and died of the disease at 2 years. The last patient developed subsequent metachronous colorectal adenocarcinoma and died 6 years after adenocarcinoid resection.

Associated Cancer

Three patients (43%) developed an associated colorectal cancer during follow-up for their adenocarcinoid tumor. Synchronous colon cancer (adenocarcinoma) was discovered in one patient (14%), and metachronous colon carcinomas were encountered in two patients (29%). Their

Table 2.
Published series reporting clinical outcomes of appendiceal adenocarcinoids.

		Appendectomy		Extended resection		
Study	Cases	Total	Failure[a]	Total	Failure[a]	Recommendations
Subbuswamy et al.[12]	12	8	0	3	1	AP alone if no cecal invasion
Wolf and Ahmed[13]	2	1	0	0	0	Treated as appendiceal adenocarcinoma
Haqqani and williams[14]	6	5	1	0	0	AP alone if no invasion, ER if cecal invasion
Warkel et al.[2]	39	14	2	13	0	ER if spread beyond appendix, ≥ 2 mitoses/10 HPF
Chen and Qizilbash[15]	5	3	0	2	0	AP alone if no cecal invasion
Olsson and Ljunberg[16]	4	3	0	1	1	ER if spread beyond appendix, ≥ 2 mitoses/10 HPF
Edmonds et al.[17]	10	3	0	3	1	ER for all adenocarcinoids
Watson and Alguacil[18]	6	0	0	2	0	No recommendation
Bak and Asschemfeldt[19]	20	8	0	6	0	ER if spread beyond appendix, ≥ 2 mitoses/10 HPF
Park et al.[20]	10	7	1	3	1	ER for all adenocarcinoids
Rutledge and Alexander et al.[6]	3	1	0	2	0	ER for all adenocarcinoids
Butler et al.[21]	9	3	0	1	0	AP alone if no cecal invasion, oophorectomy for females
Li et al.[22]	11	3	0	5	0	ER if MiB1 > 3%, TNM N1 or M1
Aizawa et al.[10]	2	1	0	1	0	ER if spread beyond appendix, ≥ 2 mitoses/10 HPF
This series	7	3	0	4	1	See discussion
Total	146	63	4 (6.3%)	46	5 (11%)	

AP: appendectomy; ER: extended resection; HPF: high power field; MiB1: proliferation index.
[a]Failure is defined as adenocarcinoid recurrence or metastatic disease

median age was 72 years (range 60–81 years). In none of these patients were there known predisposing factors or pathologic conditions for colorectal carcinoma.

DISCUSSION

We analyzed the long-term results of surgical treatment for appendiceal adenocarcinoids. Our data indicate that appendectomy alone is curative for patients presenting with small adenocarcinoids (< 1 cm) not expanding beyond the appendix and with a low mitosis rate. Otherwise, extended resection (i.e., right colectomy) should be proposed.

Adenocarcinoids and goblet cell carcinoids share histologic features of both conventional carcinoids and colonic type adenocarcinomas.[9] Its most frequent site of occurrence is the appendix. Although 40 years after its first description.[1] the histologic characteristics of this tumor have been well described.[4] its biologic behavior is still not clearly defined.[10] Its malignant potential has been reported as between that of a carcinoid and a colonic adenocarcinoma.[4–6] Adenocarcinoid have a propensity for ovarian metastasis and peritoneal carcinomatosis.[3,7] Recently, the natural history of peritoneal carcinomatosis from appendiceal adenocarcinoid has been shown to be similar to that of adenocarcinoma.[3] Clinically, adenocarcinoid is a relatively indolent neoplasm not associated with carcinoid syndrome.[2] which is usually discovered in association with acute appendicitis, as was the case in 70% of patients in our series.

No consensus has been determined for appendiceal adenocarcinoid treatment in the world literature because of the low prevalence of this pathology, with experience based only on small series.[7] There is still debates as to whether they should be treated by appendectomy alone, as for most carcinoids, or it right hemicolectomy is indicated as for appendiceal adenocarcinoma.[7,11] Moreover, no definitive staging system has been validated for appendiceal adenocarcinoid, and the value of the TNM staging system has never been tested. The malignant potential of appendiceal adenocarcinoids is evaluated similar to appendiceal carcinoids: tumor size and mitosis rate. The results of published series on surgical treatment of adenocarcinoid.[2,6,10,12–22] are summarized in Table 2. In accordance with these data, our results support the idea that appendectomy alone is associated with good results in patients with a small (< 1 cm) adenocarcinoid not expanding beyond the appendix and a low mitosis rate. By contrast, adenocarcinoids > 1 cm in size, with a mitosis

count of > 2/10 HPF, and/or spreading beyond appendiceal adventitia are probably better treated with an extended resection (i.e., right colectomy in accordance with Varisco et al..[7] Although experience with adjuvant treatment of adenocarcinoid is sparse, two recent reports have shown encouraging results for peritoneal carcinomatosis treatment: cytoreduction and intraperitoneal chemotherapy.[3] or for metastatic cases Folfox chemotherapy.[23]

Patients treated for appendiceal tumors, including carcinoids, have an increased risk of a second cancer.[8,24] The high risk for developing synchronous or metachronous colorectal adenocarcinoma in patients with adenocarcinoid is intriguing. In our series, three of seven (43%) patients treated for appendiceal adenocarcinoid developed colorectal adenocarcinoma. None of these patients had a known pathologic condition predisposing to colorectal carcinoma. Thus colonoscopic examination plays an important role in patients with incidentally discovered appendiceal adenocarcinoid; this diagnostic modality seems to be particularly indicated in patients in their sixth to eighth decades. Moreover, patient follow-up should include an endoscopic surveillance program, coloscopy every 5 years, after appendiceal adenocarcinoid treatment.

CONCLUSIONS

According to our results and the literature, it appears that appendectomy alone may be curative for appendix adenocarcinoids provided the tumor is < 1 cm, does not extend beyond the appendix adventitia, has less than 2 mitoses/10 HPF, and the surgical margins are free of tumor. For all other patients a right colectomy is indicated. Because of a high risk of synchronous and metachronous colorectal adenocarcinoma in patients with adenocarcinoids, we recommend postoperative and follow-up screening for all patients with coloscopy.

REFERENCES

1. Gagne F, Fortin P, Dufour V, *et al.* Tumors of the appendix associating histologic features of carcinoid and adenocarcinoma. Ann. Anat. Pathol. 1969;14:393–406.
2. Warkel R, Cooper P, Helwig E. Adenocarcinoid, a mucin-producing carcinoid tumor of the appendix: a study of 39 cases. Cancer 1978;42:2781–2793.
3. Mahteme H, Sugarbaker P. Treatment of peritoneal carcinomatosis from adenocarcinoid of appendiceal origin. Br. J. Surg. 2004;91:1168–1173.
4. Hirsch I, Kasper H, Bradender J, et al. Adenocarcinoid of the appendix vermiformis. Pathologe 2004.
5. McCusker M, Cote T, Clegg L, *et al.* Primary malignant neoplasms of the appendix: a population-study from the surveillance, epidemiology and end-results program, 1973–1998. Cancer 2002;94:3307–3312.
6. Rutledge RH, Alexander JW. Primary appendiceal malignancies: rare but important. Surgery 1992;111:244–250.
7. Varisco B, McAlvin B, Dias J, *et al.* Adenocarcinoid of the appendix: is right hemicolectomy necessary? A meta-analysis of retrospective chart reviews. Am. Surg. 2004;70:593–599.
8. Bucher P, Mathe Z, Demirag A, *et al.* Appendix tumors in the era of laparoscopic appendectomy. Surg. Endosc. 2004;18:1063–1066.
9. Levendoglu H, Cox C, Nadimpalli V. Composite (adenocarcinoid) tumors of the gastrointestinal tract. Dig. Dis. Sci. 1990;35:519–525.
10. Aizawa M, Watanabe O, Naritaka Y, *et al.* Adenocarcinoid of the appendix report of two cases. Surg. Today. 2003;33:375–378.
11. Gonzalez-Moreno S, Sugarbaker P. Right hemicolectomy does not confer a survival advantage in patients with mucinous carcinoma of the appendix and peritoneal seeding. Br. J. Surg. 2004;91:304–311.
12. Subbuswamy S, Gibbs N, Ross C, *et al.* Goblet cell carcinoid of the appendix. Cancer 1974;34:338–344.
13. Wolff M, Ahmed N. Epithelial neoplasms of the vermiform appendix (exclusive of carcinoid). Cancer 1976;37:2493–2510.
14. Haqqani M, Williams G. Mucin producing carcinoid tumors of the vermiform appendix. J. Clin. Pathol. 1977;30:473–480.
15. Chen V, Qizilbash A. Goblet cell carcinoid tumor of the appendix: report of five cases and review of the lterature. Arch. Pathol. Lab. Med. 1979;103:180–182.
16. Olsson B, Ljunberg O. Adenocarcinoid of the vermiform appendix. Virchows Arch A Pathol. Anat. Histol. 1980;386:201–210.
17. Edmonds P, Merino M, LiVolsi V, *et al.* Adenocarcinoid (mucinous carcinoid) of the appendix. Gastroenteroloy 1984;86:302–309.
18. Watson P, Alguacil-Garcia A. Mixed crypt cell carcinoma: a clinicopathological study of the so-called (goblet cell carcinoid). Virchows Arch. A. Pathol. Anat. Histol. 1987;412:175–182.
19. Bak M, Asschenfeldt P. Adenocarcinoid of the vermiform appendix: a clinicopathological study of 20 cases. Dis. Colon Rectum 1988;31:605–612.
20. Park K, Blessing K, Kerr K, *et al.* Goblet cell carcinoid of the appendix. Gut 1990;31:840.
21. Butler J, Houshiar A, Lin F, *et al.* Goblet cell carcinoid of the appendix. Am. J. Surg. 1994;168:685–687.
22. Li C, Hirokawa M, Qian Z, *et al.* Expression of cadherine, B-caterin, an Ki-67 in goblet cell carcinoids of the appendix. Endocr. Pathol. 2002;13:47–58.
23. Garin L, Corbinais S, Boucher E, *et al.* Adenocarcinoid of the appendix vermiformis: complete and persistent remission after chemotherapy (folfox) of a metastatic case. Dig. Sci. 2002;47:2760–2762.
24. Tichansky D, Cagir B, Borrazzo E, *et al.* Risk of second cancer in patients with colorectal carcinoids. Dis. Colon. Rectum 2002;45:91–97.