PO Box 2345, Beijing 100023, China
www.wjgnet.com
wjg@wjgnet.com

World J Gastroenterol 2006 November 7; 12(41): 6699-6701
World Journal of Gastroenterology ISSN 1007-9327

RAPID COMMUNICATION

Carcinoid tumor of the appendix: A consecutive series from 1237 appendectomies

Vincent Tchana-Sato, Olivier Detry, Marc Polus, Albert Thiry, Bernard Detroz, Sylvie Maweja, Etienne Hamoir, Thierry Defechereux, Carla Coimbra, Arnaud De Roover, Michel Meurisse, Pierre Honoré

Vincent Tchana-Sato, Olivier Detry, Bernard Detroz, Sylvie Maweja, Etienne Hamoir, Thierry Defechereux, Carla Coimbra, Arnaud De Roover, Michel Meurisse, Pierre Honoré, Department of Abdominal Surgery and Transplantation, University of Liège, CHU Sart Tilman B35, Liège B4000, Belgium
Marc Polus, Department of Gastroenterology, University of Liège, CHU Sart Tilman B35, Liège B4000, Belgium
Albert Thiry, Department of Pathology, University of Liège, CHU Sart Tilman B35, Liège B4000, Belgium
Correspondence to: Dr. Olivier Detry, Department of Abdominal Surgery, CHU Sart Tilman B35, Liège B4000, Belgium. oli.detry@chu.ulg.ac.be
Telephone: +32-4-3667645 Fax: +32-4-3667069
Received: 2006-03-18 Accepted: 2006-09-05

Abstract

AIM: To report the experience of the CHU Sart Tilman, University of Liège, Belgium, in the management of appendiceal carcinoid tumor.

METHODS: A retrospective review of 1237 appendectomies performed in one single centre from January 2000 to May 2004, was undertaken. Analysis of demographic data, clinical presentation, histopathology, operative reports and outcome was presented.

RESULTS: Among the 1237 appendectomies, 5 appendiceal carcinoid tumors were identified (0.4%) in 4 male and 1 female patients, with a mean age of 29.2 years (range: 6-82 years). Acute appendicitis was the clinical presentation for all patients. Four patients underwent open appendectomy and one a laparoscopic procedure. One patient was reoperated to complete the excision of mesoappendix. All tumors were located at the tip of the appendix with a mean diameter of 0.6 cm (range: 0.3-1.0 cm). No adjuvant therapy was performed. All patients were alive and disease-free during a mean follow-up of 33 mo.

CONCLUSION: Appendiceal carcinoid tumor most often presents as appendicitis. In most cases, it is found incidentally during appendectomies and its diagnosis is rarely suspected before histological examination. Appendiceal carcinoid tumor can be managed by simple appendectomy and resection of the mesoappendix, if its size is $\leqslant$ 1 cm.

Key words: Surgery; Digestive cancer; Laparoscopy;

Review

Tchana-Sato V, Detry O, Polus M, Thiry A, Detroz B, Maweja S, Hamoir E, Defechereux T, Coimbra C, De Roover A, Meurisse M, Honoré P. Carcinoid tumor of the appendix: A consecutive series from 1237 appendectomies. *World J Gastroenterol* 2006; 12(41): 6699-6701

http://www.wjgnet.com/1007-9327/12/6699.asp

INTRODUCTION

The appendix is one of the most common single site for carcinoid tumor[1]. Histopathologically, appendiceal carcinoid tumor is mostly enterochromaffin (EC) cell type and derives from a subepithelial cell population, which is different from neuroendocrine tumor in other sites[2]. Although rare and usually detected incidentally in appendectomy, it is considered the most common type of appendiceal primary malignant lesion, and is found in 0.3%-0.9% of patients undergoing appendicectomy[3]. This tumor rarely presents with metastases[4,5]. Despite the fact that it is among the most frequently occurring carcinoids, in surgical practice most surgeons may encounter only one or two such lesions during their career[6]. Therefore, it is important to define a correct management of such a rare tumor. The authors report here a series of 5 appendiceal carcinoid tumors found during appendectomy in a single centre and compared this experience with the recent literature on this subject.

MATERIALS AND METHODS

A retrospective review of all appendectomies was performed from January 2000 to May 2004 in a single department of abdominal surgery in a tertiary referral center (CHU Sart Tilman, University of Liège, Belgium). The data of the patients who were histologically reported to have carcinoid tumor of the appendix were further reviewed for demographic characteristics, clinical presentation, histopathology, operative reports and follow-up.

RESULTS

A total of 1237 patients underwent appendectomy during the study period (991 for acute appendicitis or appendicular syndrome and 246 during other abdominal procedures). Out of these 1237 patients, 5 (0.4%) were found to have

histological evidence of carcinoid tumor of the appendix. There were 4 male and 1 female patients with a mean age of 29.2 years (range: 6-82 years). Acute appendicitis was the clinical presentation for all patients. Open appendectomy was performed in 4 patients and laparoscopic appendectomy in one. Histologically, all tumors were located at the tip of the appendix with a mean diameter of 0.6 cm (range: 0.3-1.0 cm). One patient was reoperated two months later to complete the excision of mesoappendix after histological analysis. All patients were alive and disease-free during a mean follow-up of 33 mo (range: 21-49 mo). Our results are summarized in Table 1.

Table 1 Characteristics of 5 patients with appendiceal carcinoid tumor

Incidence (compared to appendectomy)	0.4%
Sex ratio (M/F)	4/1
Mean age (range) (yr)	29.2 (6-82)
Location	Tip of the appendix (100%)
Mean diameter (range) (cm)	0.6 (0.3-1.0)
Clinical feature	Appendicitis
First procedure	Appendectomy
Second procedure	Resection of mesoappendix (1/5)
Mean follow-up (range) (mo)	33 (21-49)

DISCUSSION

Appendiceal carcinoid tumor is a unique carcinoid tumor and differs from those encountered elsewhere in the gastro-intestinal system characterized by a relatively common frequency, small size of the appendix, usually indolent behavior, occurrence in younger patients and a trend towards female predominance[6,7]. It accounts for 32%-57% of all appendiceal tumors[6,8] in patients with a reported mean age of 42 years[9]. Surprisingly, there is a male predominance in our series (male/female: 4/1). Appendiceal carcinoid tumor lacks specific clinical features and its clinical presentation may not differ from that of acute appendicitis. It is usually diagnosed incidentally during surgery for acute appendicitis and occasionally during other abdominal procedures (colectomy, cholecystectomy, salpingectomy)[5,10]. In our series, the diagnosis of all patients with symptoms of acute appendicitis was made only after histological analysis of the surgical specimen. Appendiceal carcinoid tumor exhibits little metastatic potential and therefore rarely presents with metastases[4,5]. Characteristics of the tumor predicting aggressive behavior include size, histological subtype and mesoappendiceal involvement[3]. The predictive value of tumour size is supported by many studies[4,11,12]. The calculated risk of metastasis from tumors $\leqslant$ 1 cm is zero, while a definite increase of risk occurs with tumor size $\geqslant$ 2 cm, the rate of metastasis ranges from 20%[13] to almost 85%[14]. In the present study, all the tumours were less than 1cm (mean diameter of 0.6 cm) and localized at the tip of the appendix with no evidence of regional or distant metastases. Appendiceal carcinoid tumor usually metastasizes to the regional lymph nodes rather than to the liver[15,16]. Carcinoid syndrome occurs in less than 10% of patients with carcinoid tumor[17]. Clinically, this syndrome develops when vasoactive substances produced by carcinoid tumor escape hepatic degradation and gain access into the systemic circulation. Its clinical features include cutaneous flushing, bronchoconstriction, diarrhea, and right-sided cardiac valvular fibrosis. This syndrome can be seen in appendiceal carcinoid tumor patients with liver metastases (< 2% of all appendiceal carcinoid tumors)[10].

The vast majority of appendiceal carcinoid tumor patients do not require any further procedure or investigation following appendectomy. Those who may benefit from additional screening are patients with high-grade malignant tumor though smaller than 1 cm, patients with tumor of between 1 cm and 2 cm or larger than 2 cm, and patients with incomplete resections and metastatic disease[3]. Plasma chromogranin A is the currently available most accurate blood marker, with its level raised in 80%-100% of neuroendocrine tumor patients[18,19]. Other investigations include 24-h urinary levels of 5-hydroxyindoleacetic acid, computed tomography and ^{111}In-labelled octreotide scintigraphy.

Appendix tumor less than 1 cm in diameter is unlikely to be metastatic and may be managed with simple appendectomy. Our five appendiceal carcinoid tumor patients underwent appendectomy. Reoperation was performed in 1 patient two months later to complete the resection of mesoappendix, since histological analysis of the surgical specimen showed an incomplete mesoappendix. Therefore, consideration should be given to perform a complete mesoappendix resection during appendectomy. Appendiceal carcinoid tumor greater than 2 cm in size demonstrates an increased incidence of regional and distant spread and should be managed with a formal right hemicolectomy[17]. Controversy exists over the management following appendectomy, especially with regard to the role of right hemicolectomy in patients with tumor 1 to 2 cm in size[3]. Acceptable indications for right hemicolectomy in controversial cases have been recently suggested by Goede *et al*[3], including histological evidence of mesoappendiceal extension, tumor at the base of the appendix with positive margins or involvement of the caecum, high-grade malignant carcinoid tumor with a raised tumor prognostic index as measured by mitotic index and Ki67 levels.

The management of metastatic tumors and carcinoid syndrome has focused on cytoreductive chemotherapy and pharmacologic control of the bioactive substances produced by these tumors[17]. Response rates less than 40% have been reported for combined chemotherapy with streptozotocin and 5-fluorouracil or doxorubicin but the response time is short and chemotherapy regimen has significant side effects[20]. Thus, chemotherapy is not the first choice of treatment for patients with carcinoid tumor. Its use has to be discussed in a multidisciplinary approach related to other available treatments. The limited efficacy of systemic chemotherapy underlines the need to restrict its use in progressive cases or in patients with uncontrolled hormone-mediated symptoms despite biological or local treatment[20,21]. Octreotide, a somatostatin analog, is the most effective pharmacologic agent available to improve symptoms associated with carcinoid syndrome with a clinical and biochemical response rate of up to 60%. Available

data on growth control indicate that stabilisation of tumor growth seems to be the most beneficial anti-proliferative effect occurring in up to 50% of patients with slowly growing tumor. Partial tumor regression is marginal and occurs in only 3%-5% of cases. The long-acting somatostatin analogs are actually preferred[22].

Several studies on the antiproliferative effect of interferon-α in metastatic neuroendocrine tumor patients have reported that index hormone is reduced more than 50% in 40%-60% of patients with concomitant improvement of flushing and diarrhea. Stabilisation of tumor growth is observed in 20%-40% and a reduction in tumour size in 12%-15% of patients[23,24]. However, this therapeutic gain must be outweighed by the frequency and severity of toxic reactions[25]. Other treatment modalities such as local therapy and tumor-targeted radiotherapy are available for metastatic carcinoid tumor. Hepatic arterial chemoembolization (HACE) for non-resectable diffuse liver metastases could represent a good therapeutic option if the disease is not under control with other available treatment modalities[26,27]. HACE can be sued as a first line treatment. By targeting somatostatin receptor-positive tumor, it is possible to deliver a tumoricidal dose of radiation with ^{111}In or ^{90}Y coupled to somatostatin analogs. Preliminary studies in end-stage neuroendocrine tumor patients have shown promising results[28,29]. This treatment might be effective in patients refractory to conventional strategies and merits further development.

The prognosis of appendiceal carcinoid tumor is much better than midgut carcinoid tumor[17]. The 5-year survival rate of patients with local disease is reported to be 92% and 81% of those with regional metastases, and 31% of those with distant metastases, respectively[1]. All the patients in our series were alive and disease-free during a mean follow-up of 33 mo.

In summary, appendiceal carcinoid tumor occurs most often as acute appendicitis. In most cases, it is found incidentally during appendectomies and its diagnosis is rarely suspected before histological examination. Although appendiceal carcinoid tumor has an excellent overall prognosis, consideration should be given to screening this group of patients, since the frequency of associated synchronous and metachronous colorectal cancer is high (13%-33%)[1,4,6,8].

REFERENCES

1 **Modlin IM**, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer* 2003; **97**: 934-959
2 **Stinner B**, Rothmund M. Neuroendocrine tumours (carcinoids) of the appendix. *Best Pract Res Clin Gastroenterol* 2005; **19**: 729-738
3 **Goede AC**, Caplin ME, Winslet MC. Carcinoid tumour of the appendix. *Br J Surg* 2003; **90**: 1317-1322
4 **Moertel CG**, Dockerty MB, Judd ES. Carcinoid tumors of the vermiform appendix. *Cancer* 1968; **21**: 270-278
5 **Roggo A**, Wood WC, Ottinger LW. Carcinoid tumors of the appendix. *Ann Surg* 1993; **217**: 385-390
6 **Sandor A**, Modlin IM. A retrospective analysis of 1570 appendiceal carcinoids. *Am J Gastroenterol* 1998; **93**: 422-428
7 **Carr NJ**, Sobin LH. Neuroendocrine tumors of the appendix. *Semin Diagn Pathol* 2004; **21**: 108-119
8 **Connor SJ**, Hanna GB, Frizelle FA. Appendiceal tumors: retrospective clinicopathologic analysis of appendiceal tumors from 7,970 appendectomies. *Dis Colon Rectum* 1998; **41**: 75-80
9 **Modlin IM**, Sandor A. An analysis of 8305 cases of carcinoid tumors. *Cancer* 1997; **79**: 813-829
10 **Spallitta SI**, Termine G, Stella M, Calistro V, Marozzi P. Carcinoid of the appendix. A case report. *Minerva Chir* 2000; **55**: 77-87
11 **Moertel CG**, Weiland LH, Nagorney DM, Dockerty MB. Carcinoid tumor of the appendix: treatment and prognosis. *N Engl J Med* 1987; **317**: 1699-1701
12 **Anderson JR**, Wilson BG. Carcinoid tumours of the appendix. *Br J Surg* 1985; **72**: 545-546
13 **Thompson GB**, van Heerden JA, Martin JK Jr, Schutt AJ, Ilstrup DM, Carney JA. Carcinoid tumors of the gastrointestinal tract: presentation, management, and prognosis. *Surgery* 1985; **98**: 1054-1063
14 **MacGillivray DC**, Heaton RB, Rushin JM, Cruess DF. Distant metastasis from a carcinoid tumor of the appendix less than one centimeter in size. *Surgery* 1992; **111**: 466-471
15 **Syracuse DC**, Perzin KH, Price JB, Wiedel PD, Mesa-Tejada R. Carcinoid tumors of the appendix. Mesoappendiceal extension and nodal metastases. *Ann Surg* 1979; **190**: 58-63
16 **MacGillivray DC**, Synder DA, Drucker W, ReMine SG. Carcinoid tumors: the relationship between clinical presentation and the extent of disease. *Surgery* 1991; **110**: 68-72
17 **Sweeney JF**, Rosemurgy AS. Carcinoid Tumors of the Gut. *Cancer Control* 1997; **4**: 18-24
18 **Oberg K**. Neuroendocrine gastrointestinal tumors--a condensed overview of diagnosis and treatment. *Ann Oncol* 1999; **10** Suppl 2: S3-S8
19 **Stivanello M**, Berruti A, Torta M, Termine A, Tampellini M, Gorzegno G, Angeli A, Dogliotti L. Circulating chromogranin A in the assessment of patients with neuroendocrine tumours. A single institution experience. *Ann Oncol* 2001; **12** Suppl 2: S73-S77
20 **Kvols LK**. Metastatic carcinoid tumors and the carcinoid syndrome. A selective review of chemotherapy and hormonal therapy. *Am J Med* 1986; **81**: 49-55
21 **Cotran RS**, Kumar V, Robbins SL. Robbin's Pathologic Basis of Disease. 5th ed. Philadelphia (PA): WB Saunders, 1994: 818-820
22 **Kvols LK**, Moertel CG, O'Connell MJ, Schutt AJ, Rubin J, Hahn RG. Treatment of the malignant carcinoid syndrome. Evaluation of a long-acting somatostatin analogue. *N Engl J Med* 1986; **315**: 663-666
23 **Moertel CG**, Rubin J, Kvols LK. Therapy of metastatic carcinoid tumor and the malignant carcinoid syndrome with recombinant leukocyte A interferon. *J Clin Oncol* 1989; **7**: 865-868
24 **Eriksson B**, Öberg K. Interferon therapy of malignant endocrine pancreatic tumors. In: Mignon M, Jensen RT, eds. Endocrine tumors of the pancreas, Frontiers of Gastrointestinal research. Basel: Karger, 1995; **23**: 451-460
25 **Oberg K**. Interferon in the management of neuroendocrine GEP-tumors: a review. *Digestion* 2000; **62** Suppl 1: 92-97
26 **Ruszniewski P**, Rougier P, Roche A, Legmann P, Sibert A, Hochlaf S, Ychou M, Mignon M. Hepatic arterial chemoembolization in patients with liver metastases of endocrine tumors. A prospective phase II study in 24 patients. *Cancer* 1993; **71**: 2624-2630
27 **Therasse E**, Breittmayer F, Roche A, De Baere T, Indushekar S, Ducreux M, Lasser P, Elias D, Rougier P. Transcatheter chemoembolization of progressive carcinoid liver metastasis. *Radiology* 1993; **189**: 541-547
28 **Virgolini I**, Smith-Jones P, Moncayo R, Kurtaran A, Wenger M, Raderer M, Havlik E, Angelberger P, Szilvaszi I, Zoboli S, Paganelli G, Riccabona G. 111In / 90Y-DOTA-Lanreotide scintigraphy and therapy: initial clinical results of MAURITIUS. *Eur J Nucl Med* 1998; **25**: 884
29 **Otte A**, Herrmann R, Heppeler A, Behe M, Jermann E, Powell P, Maecke HR, Muller J. Yttrium-90 DOTATOC: first clinical results. *Eur J Nucl Med* 1999; **26**: 1439-1447

S- Editor Wang GP **L- Editor** Wang XL **E- Editor** Liu WF