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Carcinoid Tumors of the Appendix

Anton Roggo, M.D., William C. Wood, M.D., F.A.C.S., and Leslie W. Ottinger, M.D., F.A.C.S.

From the General Surgical Services, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

Objective

A retrospective study of 41 patients with histologically confirmed diagnosis of appendix carcinoid tumors was undertaken by reviewing the surgical records at Massachusetts General Hospital.

Methods

There were 8 male and 33 female patients (mean age 32 years). Twenty-two patients (54%) presented with signs and symptoms suggestive of acute appendicitis. In 19 patients (46%) the lesions were discovered incidentally. The tumors were located in 32 patients at the tip, in 6 patients in the middle third, and in 3 patients at the base of the appendix. The tumor was less than 1 cm in diameter in 32 patients, between 1 and 2 cm in 7 patients, and was bigger than 2 cm in 2 patients. In 29 patients, the depth of tumor penetration was confined to the submucosa or to the muscle layers of the appendix, and in 8 patients the serosa was involved. In 4 patients, evidence of tumor extension into the meso-appendicular fat was present, including one patient with a tumor bigger than 2 cm and local lymph-node metastases. Forty patients underwent appendectomy alone. One patient with a tumor size bigger than 2 cm in diameter with positive lymph nodes in the mesoappendix underwent secondary right hemicolectomy. Complete follow-up was achieved in 35 patients, and all patients remained free of tumor recurrence.

Conclusions

The authors conclude that appendiceal carcinoids are rare and most often are asymptomatic. Tumors of less than 1 cm are adequately managed by appendectomy alone. The appropriate treatment for tumors of 1 to 2 cm continues to be controversial. Right hemicolectomy is recommended for all tumors larger than 2 cm, whereas preference for an aggressive approach should be given in young patients.

Carcinoid tumors continue to be of interest despite their low incidence in clinical practice.[35] These neoplasms are supposed to be of neuroectodermal origin and are thus classified as part of the other amine precursor uptake and decarboxylation (APUD) neoplasms.[4,37]

Dr. Wood's current address is the Department of Surgery, Emory University School of Medicine, Emory University Hospital, Atlanta, Georgia.

Address reprint requests to Anton Roggo, M.D., Chief Resident, Department of Surgery, University Hospital Zürich, Rämistrasse 100, 8091 Zürich, Switzerland.

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The term "karzinoid" was first used by Oberndorfer[34] in 1907 to described a type of tumor that grew slowly and appeared to be more benign than adenocarcinomas. The description of the malignant carcinoid syndrome dates to Cassidy's report[9] in 1934. The endocrine potential of the carcinoid tumor, and its subsequent relationship with the varied clinical manifestations, however, was recognized after the discovery of serotonin by Rapport et al.[39] in 1948, and the isolation of serotonin from a carcinoid tumor by Lembeck[18] in 1953. In 1954, Thorson and coworkers[51] wrote about the endocrine properties and clinical manifestations of carcinoid tumors (cutaneous flushing and erythema, bronchospasm, diarrhea,

right-sided valvular heart disease). The following year, Page and associates[36] demonstrated the presence of large amounts of a serotonin metabolite, 5-hydroxyindolacetic acid (5-HIAA), in the urine of patients with malignant carcinoid syndrome. Williams and Sandler[55] in 1963 classified carcinoids according to their embryologic site of origin in foregut (respiratory tract, stomach, duodenum, biliary system, and pancreas), midgut (small bowel, appendix, caecum, and proximal colon), and hindgut (distal colon, and rectum). In the last two decades new information about the origin and ultrastructure, as well as the content of amines and peptides have made carcinoid tumors more complex. Most foregut and hindgut tumors lack serotonin-containing cells, these are predominantly found in midgut tumors.[22]

Carcinoids constitute an important group of neoplasms demanding careful assessment and discerning management.[22] While carcinoid tumors of the small bowel are the most common cause of clinical symptoms, carcinoid tumors of the appendix are almost always found incidentally during surgery for appendicitis or other surgical procedures. Most carcinoids outside the appendix metastasize with time, and the median survival time in patients with liver metastases is only 2 to 3 years.[25] Appendiceal carcinoid tumors, however, behave in a benign manner and metastasize in less than 2%. This occurs predominantly in tumors more than 2 cm in diameter. This study reviewed our own experience with appendix carcinoid tumors treated at the Massachusetts General Hospital.

PATIENTS AND METHODS

Data for the present retrospective study was obtained by reviewing the surgical records at Massachusetts General Hospital, Harvard Medical School, Boston, over the period January 1969 to June 1990. The study involved all patients with the histologically confirmed diagnosis of carcinoid tumor of the appendix. Adenocarcinoid tumors, also called goblet cell carcinoid, mucinous carcinoid, and crypt cell carcinoma[7,54] were strictly excluded.

The records analysis comprised of patient age, symptoms, clinical features, tumor location, size, depth of invasion, and metastases, presence of additional carcinoids or neoplasms of other types, and survival. The tumor size was categorized as < 1 cm, 1 to 2 cm, and > 2 cm. Measurements were taken after fixation in formaldehyde. Goblet cell carcinoid, as well as other adenocarcinoid tumors were excluded. Follow-up information was obtained from subsequent follow-up examinations at Massachusetts General Hospital, completed when necessary with telephone interviews.

RESULTS

During the 21½-year period, 41 patients with appendix carcinoid were diagnosed histologically. There were 8 male and 33 female patients. The mean age at presentation was 32 years (range 10–80 yr). The diagnosis of a carcinoid tumor was not made in any patient before the operation. No patient demonstrated symptoms attributable to the carcinoid tumor.

Twenty-two patients (54%) presented with signs and symptoms of an acute abdomen suggestive of acute appendicitis. Possibly the obstruction of the lumen of the appendix by the tumor played a role in signs of acute appendicitis. In 19 patients (46%) the appendiceal lesions were discovered incidentally during another surgical procedure (4 cholecystectomies, 12 hysterectomies and or salpingo-oophorectomies, one colon resection for carcinoma, 2 surgical explorations for urinary bladder carcinoma).

The carcinoid tumors were located in 32 cases at the tip, in 6 cases in the middle third, and in 3 cases at the base of the appendix. The tumor was less than 1 cm in diameter in 32 patients, between 1 and 2 cm in 7 patients, and was bigger than 2 cm in 2 patients. In 29 patients the depth of tumor penetration was confined to the submucosa or to the muscle layers of the appendix, and in 8 patients the serosa was involved. In 4 patients there was evidence of tumor extension into the meso-appendicular fat, including one patient who had a tumor bigger than 2 cm and local lymph-node metastases. Seven patients had second neoplasms at the time of appendectomy (colon and gallbladder each one, urinary bladder 2, uterus 3). No patient had additional carcinoid tumors.

Forty patients were treated by appendectomy alone. The histologic examination of the removed appendix revealed tumor-free margins in all specimens. One patient with a tumor size larger than 2 cm in diameter had positive lymph nodes in the mesoappendix, and underwent secondary right hemicolectomy. There were no distant metastases found. The second patient with a lesion larger than 2 cm underwent no further surgical treatment. The tumor was localized at the tip with mesoappendix infiltration but without local lymph-node metastases. One operative mortality occurred: an 80-year-old male patient, after cholecystectomy and incidental appendectomy, died on the sixth postoperative day (acute myocardial infarction with cardiac arrest). In the late postoperative period, an HIV-positive male patient died due to severe pneumonia 2 months after appendectomy.

The follow-up of one patient has been for such a short period that his current status can not be assessed. Two patients have been lost after a partial follow-up of 4 and 6 years, and one patient was completely lost to follow-up

study. Complete follow-up was achieved in 35 patients for an average length of 9 years (range 1–17 yr). All 35 patients remained free of recurrence of the appendix carcinoid tumor. The patient with right hemicolectomy is doing well after a follow-up period of 15 years. The second patient with a tumor larger than 2 cm in diameter and simple appendectomy remained free of tumor recurrence during a follow-up of 10 years. No patient deaths were related to the carcinoid tumor. One patient died 2 years after incidental appendectomy due to diffuse distant metastases of urinary bladder carcinoma.

DISCUSSION

Incidence

Neoplasms of the appendix can be classified into four main categories: pure carcinoid tumors, adenocarcinomas of the colonic type, malignant mucoceles, and adenocarcinoid tumors. Carcinoids are the most frequently encountered type of appendiceal neoplasms (50–77%), and the appendix is the most frequent site for gastrointestinal carcinoid tumors.[14,21,29,35] In large collective series,[14,32,42] 38 to 44% of the primary carcinoid tumors were appendiceal, 11 to 27% were ileal, and 13 to 19% were rectal. The incidence of appendiceal carcinoid tumors is approximately 3 to 7 in every 1000 appendectomies.[28,40,48,53] However, the exact incidence is not known, and the clinical presentation underestimates the frequency, as many carcinoids remain asymptomatic.[32] Appendiceal carcinoids occur more frequently in women than in men (2–4:1).[1,2,5,14,27,40,44,49] This is confirmed in the present series, and what might be attributed to the greater likelihood of incidental appendectomies in females who have cholecystectomy and/or pelvic surgery.[21] However, a true preponderance in female patients is also possible. In a series of patients younger than 15 years of age, 14 of 18 appendiceal carcinoid tumors were found in girls.[16] In a similar study, 14 of 23 patients ranging in age from 6 to 20 years were female patients.[29]

Diagnosis

Due to the lack of specific symptoms, appendix carcinoid tumors are diagnosed as an incidental finding in 19 to 71%, and routine laboratory tests seem to be of little value in early diagnosis.[1,2,14,22,35,43,44,49] During any abdominal operation, the appendix should be palpated carefully, and the discovery of a firm, bulbar mass should arouse suspicion about the presence of a carcinoid tumor.[38] The tumors occur in up to 70% at the tip of the appendix, and about 70 to 95% are smaller than 1 cm in diameter without evidence of metastases.[2,17,21,24,27,28,38,44] The incidence of tumor size from 1 to 2 cm has varied from 4 to 27%,[5,24,47] and only a few appendiceal carcinoids are larger than 2 cm in diameter.[21,28] The most common primary site for tumor-producing carcinoid syndrome is the small bowel.[26,31] However, the syndrome is rarely observed in carcinoid tumors of the appendix. When it manifests, it is almost always associated with widespread metastases of tumor, predominantly to the liver or retroperitoneum.[12,15,21,26,27,30,33,44,48] Determination of 5-hydroxyindolacetic acid (5-HIAA) in urine is the laboratory diagnostic test most commonly used for follow-up in the later course of the disease, when hepatic metastases are present.[1] However, patients may have a widespread disease without an increase of 5-HIAA, especially in foregut and hindgut tumors.[22,32,50]

Therapy

The metastatic potential of carcinoid tumors depends greatly upon the site of origin, its size, and its depth of penetration.[43] Because of this, there remains much controversy as to the extent of surgery needed for a given tumor.[43] Appendiceal carcinoid tumors of less than 1 cm in diameter have an excellent prognosis and are adequately treated by appendectomy alone.[2,5,28] Carcinoid tumors of less than 1 cm in diameter in the appendix, demonstrate a risk of metastatic disease of almost 0%, in contrast to the the small bowel of 2% to 18%, and in the rectum of 0% to 20%. Moertel[26] found no recurrences and no metastases among 108 patients with a tumor size of less than 1 cm. However, there was a tumor recurrence of 80% in patients with lesions bigger than 2 cm in diameter. Svendson and Bulow[46] reviewed the Danish Cancer Registry and found only eight patients with appendiceal carcinoid tumors of less than 1 cm in diameter that involved the mesoappendix. All were treated by appendectomy alone without recurrence.

Adequate therapy of patients with tumor size from 1 to 2 cm in diameter remains a matter of controversy since a few case reports have appeared describing regional metastases.[5,10,11,47] However, metastases in appendiceal carcinoids from 1 to 2 cm in diameter are extremely rare. In a review of 46 reported metastasizing appendiceal carcinoids, Thirlby et al.[48] found only five patients with a primary tumor size from 1 to 2 cm in diameter who had metastasized to the regional lymph nodes. Their literature review disclosed no reports of tumor recurrences, distant metastases, or deaths after appendectomy for carcinoid tumors of less than 2 cm in diameter. In the long-term experience of Moertel et al.,[28] the authors encountered in 14 patients no tumor recurrence during a follow-up period of more than 25 years, and conclude that appendectomy alone is adequate

treatment in the absence of grossly recognizable metastases.

In the rare cases of tumors measuring more than 2 cm, in whom nodal spread was found at the time of first presentation, aggressive surgery should be considered, due to the definite risk of metastases.[24,28,38] However, the risk is with 30% to 60% compared with 86% to 95% in cases of small bowel carcinoid tumors, and 80% to 100% for carcinoid tumors in the rectum.[3,8,10,13,23,24,27,31,48,52] Almost all appendiceal carcinoid metastases are restricted to regional lymph nodes and are found at the time of first tumor presentation.[2,5,47,48] The two patients in our series with local metastases, had a primary tumor size of more than 2 cm in diameter. Right hemicolectomy has also been advocated as justified aggressive surgical approach in patients with appendiceal carcinoids involving the base of the organ.[47] Thompson[49] in contrast favors partial cecectomy for lesions located at the base of the appendix to ensure clear margins, and describes two patients with disease-free postoperative follow-up of 2.4 and 3 years. On the other hand, Bowman and Ponka describe one patient each in whom the carcinoid was incompletely excised from the base of the appendix. Both patients remained disease free at 17[38] and 30[5] years after appendectomy. Patients with no signs of metastases are probably adequately treated by simple appendectomy alone. Moertel et al.[28] observed only 1 of 12 patients treated in this manner a local tumor recurrence with resectable nodal metastases 29 years after the primary operation. The authors conclude that it would be reasonable to offer right hemicolectomy only to younger patients.

Moertel et al.[28] found no discernible difference between metastatic and nonmetastatic cases in cellular morphology or cellular architecture. The site of the tumor would not appear to bear any relationship to the presence of metastases.[2] In patients with vascular invasion or involvement of the mesoappendix, a more radical approach might be recommended. In the series of Moertel et al.,[28] 2 of 7 patients with metastases had invasion of the mesoappendix, whereas only 4 of 39 patients without metastases had this feature. And vascular invasion was observed again in 2 of 7 patients with metastases, in contrast to 2 of 39 patients without metastases. Syracuse et al.[47] report 2 of 13 patients with tumors 1 to 2 cm in size with extension into the mesoappendix with nodal metastases. Lymphatic invasion alone confined to the appendix is seriously questioned as an indication for extended surgical procedures.[38] Use of muscular invasion, mesenteric invasion and periappendiceal lymphatic involvement as additional criteria for ileocolectomy could not be supported, however, unless there are positive lymph nodes. Bowman and Rosenthal[5] recommend a hemicolectomy if mesoappendicular fat extension *and* subserosal lymphatic invasion are present together. Moertel et al.[24] reply that muscular and lymphatic invasion was an almost universal finding in their series.

For pure appendiceal carcinoid tumors, the guidelines in the authors facilities (Massachusetts General Hospital, and Emory University Hospital [W. C. W.]) are in agreement with Moertel et al.[28] Simple appendectomy is performed for tumors less than 2 cm in diameter, if there is no evidence of local metastases. Right hemicolectomy is recommend in young patients with lesions bigger than 2 cm without lymph node metastases, or in tumors of less than 2 cm with positive lymph nodes due to a known risk for long-term metastases in this age group of patients. However, in older patients due to the fact that the slow growing nature of the tumor, a more conservative approach is recommended.

Prognosis

The prognosis in carcinoid of the appendix with rare exceptions is favorable,[28] and within in the midgut group itself appendiceal carcinoid tumors are reported to have a better prognosis than those arising in other locations.[16,25] Lundqvist and Wilander[20] in 1987 suggested that the different histopathogenesis of appendiceal and small bowel carcinoids might be the reason for. Carcinoids of the appendix mostly develop from the subepithelial-endocrine cells and are immunoreactive for S-100, a protein normally present in Schwann cells, indicating that anatomically they belong rather to the peripheral nervous system and the ectoderm. This is in contrast to the small intestinal carcinoids, which are presumed to arise from intraepithelial endocrine cells and which do not demonstrate the presence of S-100. This type of neuroendocrine cells of the digestive mucosa is supposed to be of endodermal origin, what might somewhat explain the different malignant behavior of these two midgut carcinoid tumors.[19] Shaw[45] supported this statement in his study of analyzing topographical and age distributions of neuroendocrine cells in the normal appendix.

The most significant prognostic indicator is the presence or absence of hepatic metastases at initial operation. Indeed, appendiceal carcinoids rarely metastasize to the liver, as was confirmed in the present study. In contrast, hepatic metastases are recorded in 15 to 22% of patients with small bowel carcinoid of less than 1 cm, and in 58 to 80% while the tumor was larger than 1 cm, almost always metastases occur when the tumor is bigger than 2 cm.[22,27,50] The overall 5-year survival rate for appendiceal carcinoids, including our series, varies from 90 to 100%.[1,6,14,24,35,41] For ileal carcinoids, it is 33 to 62%,[6,14,22,35,50,52] and for rectal carcinoids 83 to 89%.[14,50]

CONCLUSION

We conclude that appendiceal carcinoids are rare and most often are asymptomatic. The size remains a reliable guide to the metastastic potential of carcinoid tumors of the appendix. The diagnosis is excellent, especially if the primary tumor is less than 1 cm and localized or if sites of abdominal dissemination are resectable. Appendiceal carcinoids of less than 1 cm are adequately managed by appendectomy alone. The appropriate treatment for tumors of 1 to 2 cm continues to be a point of controversy, however, appendectomy seems to be appropriate treatment. Right hemicolectomy is recommended for all tumors larger than 2 cm, whereas preference for an aggressive approach should be given in young patients. Radical right hemicolectomy is specially mandatory in patients with positive lymph nodes, and is favored in cases with vascular invasion or involvement of the mesoappendix.

This study was limited to pure carcinoid tumors and the conclusions drawn from the study do not apply to adenocarcinoid tumors of the appendix.

References

1. Andaker L, Lamke LO, Smeds S. Follow-up of 102 patients operated on for gastrointestinal carcinoid. Acta Chir Scand 1985; 151:469–473.
2. Anderson JR, Wilson BG. Carcinoid tumors of the appendix. Br J Surg 1985; 72:545–546.
3. Bates HR. Carcinoid tumors of the rectum: a statistical review. Dis Colon Rectum 1966; 9:90.
4. Beaton HL. Carcinoid tumors of the alimentary tract. CA 1982; 32:92–99.
5. Bowman GA, Rosenthal D. Carcinoid tumors of the appendix. Am J Surg 1983; 148:700–703.
6. Brookes VS, Waterhouse JAH, Powell DJ. Malignant lesions of the small intestine: a ten-year survey. Br J Surg 1968; 55:405–410.
7. Burke AP, Sobin LH, Federspiel BH, Shekitka KM, Helwig EB. Goblet cell carcinoids and related tumors of the vermiform appendix. Am J Clin Pathol 1990; 94:27–35.
8. Caldarola VT, Jackman RJ, Moertel CG, Dockerty MB. Carcinoid tumors of the rectum. Am J Surg 1964; 107:844–849.
9. Cassidy MA. Abdominal carcinomatosis associated with vasomotor disturbances. Proc Roy Soc Med 1934; 27:220–221.
10. Dent TL, Batsakis JG, Lindenauer SM. Carcinoid tumors of the appendix. Surgery 1973; 73:828–832.
11. Dunn JP. Carcinoid tumors of the appendix: 21 cases with a review of the literature. NZ Med J 1982; 95:73–76.
12. Feldman JM, Jones RS. Carcinoid syndrome from gastrointestinal carcinoids without liver metastasis. Ann Surg 1982; 196:33–37.
13. Feldman JM. Carcinoid problems and the carcinoid syndrome. Curr Probl Surg 1989; 12.
14. Godwin JD. Carcinoid tumors: an analysis of 2837 cases. Cancer 1975; 36:560–569.
15. Jaffe BM. Prostaglans and serotonin: nonpeptide diarrheogenic hormones. World J Surg 1979; 3:565–578.
16. Johnson LA, Lavin PT, Moertel CG, et al. Carcinoids: the prognosis effect of primary site histologic type variations. J Surg Oncol 1986; 33:81–83.
17. Jonsson T, Johannsson JH, Hallgrimsson JG. Carcinoid tumors of the appendix in children younger than 16 years. Acta Chir Scand 1989; 155:113–116.
18. Lembeck F. 5-Hydroxytryptamine in a carcinoid tumor. Nature 1953; 172:910–911.
19. Lundqvist M, Wilander E. Subepithelial neuroendocrine cells and carcinoid tumors of the human small intestine and appendix: a comparative immunohistochemical study with regard to serotonin, neuron-specific enolase and S-100 protein reactivity. J Pathol 1986; 148:141–147.
20. Lundqvist M, Wilander E. A study of the histopathogenesis of carcinoid tumors of the small intestine and appendix. Cancer 1987; 60:201–206.
21. Lyss AP. Appendiceal malignancies. Semin Oncol 1988; 15:129–137.
22. Martensson H, Nobin A, Sundler F. Carcinoid tumors in the gastrointestinal tract: an analysis of 156 cases. Acta Chir Scand 1983; 149:607–616.
23. Moertel CG, Sauer WG, Dockerty MB, Baggenstoss AH. Life history of the carcinoid tumor of the small intestine. Cancer 1961; 14:901–912.
24. Moertel CG, Dockerty MB, Judd ES. Carcinoid tumors of the vermiform appendix. Cancer 1968; 21:270–278.
25. Moertel CG, Hanley JA. Combination chemotherapy trials in metastatic carcinoid tumor and the malignant carcinoid syndrome. Cancer Clin Trials 1979; 2:327–334.
26. Moertel CG. Treatment of the carcinoid tumor and the malignant carcinoid syndrome. J Clin Oncol 1983; 1:727–740.
27. Moertel CG. An odyssey in the land of small tumors. (Karnofsky Memorial Lecture) J Clin Oncol 1987; 5:1503–1522.
28. Moertel CG, Weiland LH, Nagorney DM, Dockerty MB. Carcinoid tumor of the appendix: treatment and prognosis. N Engl J Med 1987; 317:1699–1701.
29. Moertel CG, Weiland LH, Telander RL. Carcinoid tumor of the appendix in the first two decades of life. J Pediatr Surg 1990; 25:1073–1075.
30. Nelson JM, Mahoney JP, Ryden SE. Midgut carcinoid tumor with carcinoid heart disease. Its presence in the absence of hepatic metastases—a case report. Arch Pathol Lab Med 1980; 104:428–431.
31. Norheim I, Oberg K, Theodorsson-Norheim E, et al. Malignant carcinoid tumors: an analysis of 103 patients with regard to tumor location, hormone production, and survival. Ann Surg 1987; 206:115–125.
32. Norton JA, Doppman JL, Jensen RT. Cancer of the endocrine system: carcinoid tumors. *In* DeVita VT, Hellman S, Rosenberg SA, eds. Cancer. Principles and Practice of Oncology. Philadelphia: J.B. Lippincott, 1989; 2, pp 1303–1314.
33. Nwiloh JO, Pillarisetty S, Moscovic EA, Freeman HP. Carcinoid tumors. J Surg Oncol 1990; 45:261–264.
34. Oberndorfer S. Karzinoide: Tumoren des Dünndarmes. Frankf Z Pathol 1907; 1:426–432.
35. Olney JR, Urdaneta LF, Al-Jurf AS, Jochimsen PR, Shirazi SS. Carcinoid tumors of the gastrointestinal tract. Am Surg 1985; 51:37–41.
36. Page JH, Corcoran AC, Udenfried S, Szoedsma A, Weissbach H. Argentaffinoma as endocrine tumor. Lancet (letter) 1955; 1:198–199.
37. Pearse AGE. The APUD concept and hormone production. Clin Endocrinol Metab 1980; 9:211–222.
38. Ponka JL. Carcinoid tumors of the appendix: report of thirty-five cases. Am J Surg 1973; 126:77–83.
39. Rapport MM, Green AA, Page IH. Partial purification of the vasoconstrictor in beef serum. J Biol Chem 1948; 174:735–741.
40. Rutledge RH, Alexander JW. Primary appendiceal malignancies: rare but important. Surgery 1992; 244–250.

41. Sanders RJ, Axtell HK. Carcinoids of the gastrointestinal tract. Surg Gynecol Obstet 1964; 119:369–380.
42. Sanders RJ. Carcinoids of the gastrointestinal tract. Springfield, IL: Thomas, 1973.
43. Saha S, Hoda S, Godfrey R, Sutherland C, Raybon K. Carcinoid tumors of the gastrointestinal tract: A 44-year experience. South Med J 1989; 82:1501–1505.
44. Shaw JHF, Canal A. Carcinoid tumors in Auckland, New Zealand. Aust NZ J Surg 1989; 59:229–233.
45. Shaw PA. The topographical and age distributions of neuroendocrine cells in the normal human appendix. J Pathol 1991; 164:235–239.
46. Svendson LB, Bulow S. Carcinoid tumors of the appendix in young patients. Acta Chir Scand 1980; 146:137–139.
47. 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.
48. Thirlby RC, Kasper CS, Jones RC. Metastatic carcinoid tumor of the appendix: report of a case and review of the literature. Dis Col Rect 1984; 27:42–46.
49. Thompson GB, van Heerden JA, Martin JK, et al. Carcinoid tumors of the gastrointestinal tract: presentation, management, and prognosis. Surgery 1985; 98:1054–1063.
50. Thompson JF, Gee DC, Little JM. The carcinoid tumor. Aust NZ J Surg 1979; 49:317–326.
51. Thorson A, Biörck G, Björkman G, Waldenström J. Malignant carcinoid of the small intestine with metastasis to the liver, valvular diseases of the right side of the heart (pulmonary stenosis and tricuspid regurgitation without septal defects), peripheral vasomotor symptoms, bronchoconstriction, and an unusual type of cyanosis. Am Heart J 1954; 47:795–817.
52. Van Sickle DG. Carcinoid tumors — analysis of 61 cases: 11 cases of carcinoid syndrome. Cleve Clin Q 1972; 39:79–86.
53. Wackym PA, Gray GF. Tumors of the appendix: the spectrum of carcinoid. South Med J 1984; 77:288–291.
54. Warkel RL, Cooper PH, Helwig EB. Adenocarcinoid, a mucin producing carcinoid tumor of the appendix. Cancer 1978; 42:2781–2793.
55. Williams ED, Sandler M. The classification of carcinoid tumors. Lancet 1963; 1:238–239.