Published in final edited form as:

Am J Surg. 2014 March ; 207(3): 342–345. doi:10.1016/j.amjsurg.2013.08.038.

Post-Operative Surveillance of Small Appendiceal Carcinoid Tumors

Sara E. Murray, MD¹, Ricardo V. Lloyd, MD, PhD², Rebecca S. Sippel, MD¹, Herbert Chen, MD¹, and Sarah C. Oltmann, MD¹

¹Section of Endocrine Surgery, Department of Surgery, University of Wisconsin, Madison, WI

²Department of Pathology and Laboratory Medicine, University of Wisconsin, Madison, WI

Summary Sentences

Patients with appendiceal carcinoid tumors ≤ 1 cm diagnosed over a 16-year period in a single institution were retrospectively analyzed for disease-specific survival and recurrence. Although there was variation in post-operative surveillance strategies and frequency, there were no cases of tumor recurrence or disease-specific mortality in the follow-up period. Consistent with prior studies, we conclude that post-resection surveillance may not be necessary for tumors ≤ 1 cm after an R0 resection.

Keywords

Appendix; carcinoid; tumor; surveillance; follow-up; recommendation

Background

Carcinoid tumors are the most common primary neoplasm affecting the appendix, comprising 25% to 40% of all appendiceal malignancies according to the Surveillance, Epidemiology, and End Results Program [1,2]. However, overall incidence remains low, with carcinoid found in as few as 0.3% to 0.9% of appendectomy specimens [1,3]. The majority of appendiceal carcinoid tumors are discovered incidentally and are <1 cm in diameter, with metastasis exceedingly rare in tumors of this size [4,5]. As a result, the prognosis is favorable, with a 5-year survival rate of 71% for all appendiceal carcinoids and 81% for localized disease – among the best survival rates recorded for carcinoid tumors at any site [2].

Current surgical management is based on the understanding that tumor size is the best prognostic indicator for appendiceal carcinoids. Consequently, tumors ≤ 2 cm in diameter and confined to the appendix are typically treated with appendectomy alone, whereas a formal right hemicolectomy is recommended for tumors >2 cm [6]. Lymphovascular invasion, mesoappendiceal involvement, location at the appendiceal base, residual disease, and high mitotic indices have been used as indicators for more extensive surgery beyond an appendectomy alone, even in small tumors <2 cm [5,7].

Address for Correspondence: Sarah C. Oltmann, MD, Clinical Instructor, University of Wisconsin, Department of Surgery, Section of Endocrine Surgery, K4/739 Clinical Science Center, 600 Highland Avenue, Madison, WI 53792, USA, Business Tel.: 608-263-1387, Fax: 608-252-0912, oltmann@surgery.wisc.edu.

Presented at the Midwest Surgical Association's Annual Meeting, July 28th to 31st, 2013, Acme, MI.

The post-resection surveillance for appendiceal carcinoid tumors is less clear, and physician practices often differ on the necessity, mode, and frequency of follow-up. Therefore, the objective of this study was to review the post-resection surveillance regimens of appendiceal carcinoid tumors ≤ 1 cm utilized at our institution, in order to determine appropriate follow-up for this patient population.

Materials and Methods

After approval by the Institutional Review Board, patients were identified retrospectively using an institutional pathology database and cases were linked to the corresponding medical record. Only tumors ≤ 1 cm in largest diameter were included in this analysis. Patients who underwent carcinoid resection prior to presentation at our institution were excluded unless the pathology report from the initial procedure was available within the electronic medical record. In these cases, the pathology from the initial resection was utilized for this analysis.

Data extracted from the electronic medical record included the following: patient age, gender, past medical and surgical history, clinical presentation, modality of diagnosis, tumor characteristics, treatment method, complications, follow-up surveillance, recurrence, and survival. Characteristics of tumor pathology included tumor location, tumor diameter and depth of invasion, margin status, lymph node or distant metastasis, and immunohistochemistry if performed. Tumor grade and stage were defined based on the American Joint Committee on Cancer criteria [8]. Patients without clinical or pathologic evidence of lymph node involvement were considered to be negative for lymph node metastasis.

The length of follow-up was calculated from the date of initial tissue diagnosis to the most recent encounter within the electronic medical record. The treating surgeon determined the timing and modality of surveillance after carcinoid resection. For patients that died during the study period, the length of survival was determined from the date of initial tissue diagnosis to the date of death.

Data were analyzed using Stata version 12 software (StataCorp, College Station, TX) and displayed as median with overall range.

Results

Patient characteristics, surgical indications, and intervention

A total of 50 patients with appendiceal carcinoid were identified between January 1994 and December 2010. Thirty-one patients had appendiceal carcinoid tumors ≤ 1 cm, and were included in this analysis. All patients were incidentally diagnosed with carcinoid after operative intervention. Appendicitis and a pelvic mass were the most common indications for surgical intervention (Table 1). Over half of the patients underwent a simple appendectomy for appendicitis (Table 1), 13 patients (81%) underwent a laparoscopic appendectomy, and the remainder underwent open appendectomy via a right lower quadrant incision. After initial appendectomy, 2 patients (tumors 3 mm and 10 mm respectively and located at the appendiceal tip) underwent completion right hemicolectomy.

Fourteen patients (45%) had various pathologies other than appendicitis necessitating an alternate surgical intervention (Table 1). Nine patients (29%) underwent a combination of total abdominal hysterectomy and/or salpingo-oophorectomy for uterine and/or ovarian pathology, 4 of which had uterine or ovarian cancer. In addition, 4 patients (13%) underwent

a laparotomy and total proctocolectomy for ulcerative colitis, and 1 patient with malrotation underwent a laparotomy and cecopexy.

Tumor characteristics

The median tumor diameter was 5 mm (range=1–10 mm), and all tumors were categorized as T1a (Table 1). The location of the tumor was recorded in 21 of the patients' pathology reports, with the most common site being the tip of the appendix (n=16, 76%). Mesoappendiceal invasion was present in 2 (6%) patients. All margins were negative, indicating an R0 resection in all patients. Seven patients had pathologic assessment of regional lymph nodes, including the 2 patients who underwent a completion right hemicolectomy. No pathologic or clinical evidence of regional lymph node or distant metastasis was observed in the series, categorizing all patients as Stage I (Table 1). Lymphovascular invasion and perineural invasion were not present in any tumor. Immunohistochemistry of the tumor was performed on 4 patients; 2 were positive for chromogranin and synaptophysin, 1 was positive for only chromogranin, and 1 was positive for only synaptophysin. Information on mitotic rate and Ki67 labeling was not available.

Follow-up surveillance, recurrence, and survival

The median length of follow-up was 5 years (range=0–15 years), with all but 2 patients having >6 months follow-up. After initial surgical intervention, 14 patients (45%) were given recommendations for carcinoid follow-up surveillance. Physician recommendations varied, including referral to medical oncology, colonoscopy, repeat imaging, or laboratory studies (Table 2). All post-operative imaging, laboratory studies, and colonoscopies were found to be normal in all patients monitored.

Two patients died during the follow-up period, although neither was secondary to carcinoid. One patient died from uterine cancer, the other from breast cancer. In the 29 surviving patients, no carcinoid recurrences were observed during the follow-up period.

Discussion

In this analysis of small (< 1 cm) appendiceal carcinoid tumors, the necessity of post-operative surveillance was examined. In this series of 31 patients, there were no occurrences of regional or metastatic disease, coinciding with previous studies demonstrating a 0% incidence of nodal metastasis in tumors < 1 cm [5,9]. All tumors in this study were effectively treated with surgical resection, most commonly with an appendectomy. There were no recurrences or disease-specific deaths in this cohort of patients with a median follow-up of 5 years, which is consistent with prior studies showing no recurrence at up to 25 years [4,9]. Despite these low recurrence rates and reported 10-year survival rates of 100%, physician practice differs on the necessity and frequency of follow-up surveillance for this patient population [5]. This study demonstrates a broad, inconsistent follow-up regimen utilized by physicians at a large, academic, tertiary referral center. Over half of the patients did not receive any postoperative disease surveillance, whereas the others underwent a variety of interventions, including referral to medical oncology, colonoscopy, imaging, or laboratory studies.

This inconsistent follow-up is a result of the lack of definitive guidelines for postoperative surveillance of small appendiceal carcinoid tumors. The National Comprehensive Cancer Network 2013 Guidelines for appendiceal carcinoids < 2 cm in diameter call for surveillance "as clinically indicated", but offer no specific criteria on which to base this decision [6]. Only for tumors >2 cm is scheduled surveillance recommended. This includes a history and physical 3–12 months post-resection and every 6–12 months thereafter up to 10 years, with

consideration of follow-up imaging or laboratory markers 5-hydroxyindoleacetic acid or chromogranin A.

In 2012 the European Neuroendocrine Tumor Society published consensus guidelines on the follow-up of neuroendocrine tumors, including appendiceal carcinoids [10]. These consensus guidelines state that follow-up investigations are not routinely indicated for appendiceal endocrine tumors <1 cm after simple appendectomy resulting in an R0 resection. Follow-up for carcinoid tumors 1 to 2 cm in diameter and an R0 resection was more controversial, though most participants at the conference suggested no further surveillance was necessary.

The North American Neuroendocrine Tumor Society also released consensus guidelines regarding follow-up and surveillance of gastrointestinal neuroendocrine tumors in 2009 [11]. They concluded that low-grade well-differentiated appendiceal carcinoids <1 cm have a low recurrence risk and require no surveillance. Tumors 1 to 2 cm in size should be followed if poor prognostic factors such as nodal metastasis, lymphovascular invasion, mesoappendiceal invasion, or mixed pathology are identified. Only 2 patients in this series had mesoappendiceal involvement. One underwent an initial total proctocolectomy for ulcerative colitis, with 0 of 12 lymph nodes positive. The other patient had no scheduled follow-up but is alive without clinically symptomatic disease 8 years after resection.

The major limitation of this study is the retrospective methodology. While a prospective study assessing the utility of follow-up in this patient population would be most useful, none have been performed. The low incidence of this tumor type would require a multicenter study over a long period to determine any meaningful difference between follow-up recommendations. Secondly, due to the large time range that this study encompassed, tumor pathology markers evolved and were inconsistently performed, making it difficult to incorporate these into the post-operative surveillance criteria. Thirdly, the small cohort size and inconsistent length of follow-up make it difficult to form broad conclusions regarding follow-up surveillance. However, this study supplements prior reports demonstrating similar findings of low recurrence rates in tumors <1 cm, and thus can be used as further evidence that follow-up in this group is likely unnecessary.

Cancer surveillance is an integral part of oncologic care in the United States, and it is imperative to determine appropriate follow-up surveillance for small appendiceal carcinoid tumors. This is necessary both to reduce unwarranted and costly interventions while still ensuring safe, effective care and patient well-being. The absence of tumor recurrence in this study after resection of small appendiceal carcinoids, consistent with previous studies, leads us to conclude that post-resection surveillance may not be necessary for tumors $\leq$ 1 cm after an R0 resection. This study adds to the small, but growing, evidence base that may motivate updated clinical guidelines on the appropriate post-operative surveillance of small appendiceal carcinoid tumors.

Acknowledgments

University of Wisconsin, Physician Scientist Training in Career Medicine grant, National Institutes of Health T32 CA009614-21.

References

1. Moertel CG, Dockerty MB, Judd ES. Carcinoid tumors of the vermiform appendix. *Cancer*. 1968; 21(2):270–278. [PubMed: 4952505]
2. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer*. 2003; 97(4): 934–959. [PubMed: 12569593]

3. Sandor A, Modlin IM. A retrospective analysis of 1570 appendiceal carcinoids. *Am J Gastroenterol*. 1998; 93(3):422–428. [PubMed: 9517651]
4. Moertel CG, Weiland LH, Nagorney DM, et al. Carcinoid tumor of the appendix: treatment and prognosis. *N Engl J Med*. 1987; 317(27):1699–1701. [PubMed: 3696178]
5. Mullen JT, Savarese DMF. Carcinoid tumors of the appendix: A population-based study. *J Surg Oncol*. 2011; 104(1):41–44. [PubMed: 21294132]
6. [Accessed on May 15, 2013] NCCN Clinical Practice Guidelines v 2.2013. Neuroendocrine tumors. at: https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf
7. Pinchot SN, Holen KD, Sippel RS, et al. Carcinoid tumors. *Oncologist*. 2008; 13(12):1255–1269. [PubMed: 19091780]
8. Edge, SB.; Byrd, DR.; Compton, CC., et al. *AJCC Cancer Staging Manual*, Seventh Edition. New York, NY: Springer; 2010.
9. Roggo A, Wood WC, Ottinger LW. Carcinoid tumors of the appendix. *Ann Surg*. 1993; 217(4): 385–390. [PubMed: 8466309]
10. Arnold R, Chen YJ, Costa F, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: Follow-up and documentation. *Neuroendocrinology*. 2009; 90(2):227–233. [PubMed: 19713715]
11. Boudreaux JP, Klimstra DS, Hassan MM, et al. The NANETS consensus guidelines for the diagnosis and management of neuroendocrine tumors: Well-differentiated neuroendocrine tumors of the jejunum, ileum, appendix, and cecum. *Pancreas*. 2010; 39(6):753–766. [PubMed: 20664473]

Table I

Patient, clinical, and tumor characteristics

Patient characteristics	
Median age at diagnosis, y (range)	36 (20–46)
Female gender, n (%)	27 (87)
Clinical characteristics	
Surgical indication, n (%)	
Appendicitis	17 (55)
Pelvic mass	5 (16)
Ulcerative colitis	4 (13)
Uterine pathology	3 (10)
Other	2 (6)
Initial surgical procedure, n (%) *	
Appendectomy alone	16 (52)
Appendectomy with gynecologic procedure	9 (29)
Total proctocolectomy	4 (13)
Other	1 (3)
Tumor characteristics	
Median carcinoid diameter, mm (range)	5 (3–7)
Mesoappendix invasion, n (%)	2 (6)
Tumor depth, ** n (%)	
T1a (tumor 1 cm or less in greatest dimension)	31 (100)
Regional lymph nodes, n (%)	
NX (regional lymph nodes cannot be assessed)	24 (77)
N0 (no regional lymph node metastasis)	7 (23)
Distant metastasis, n (%)	
M0 (no distant metastasis)	31 (100)
TNM Staging, ** n (%)	
Stage I	31 (100)

* See text for details.

** American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TMN) classification.

Percentages may not add to 100 due to rounding.

Table II

Patients receiving post-resection surveillance

Variable	n (%)
Patients receiving post-resection surveillance	14 (45)
Imaging (computed tomography or ¹¹¹ In-ocreoide scan)	9 (29)
Medical oncology referral	7 (23)
Colonoscopy	5 (16)
Laboratory studies (chromogranin A or 5-hydroxyindoleacetic acid)	5 (16)