PAPER

Is Right Hemicolectomy for 2.0-cm Appendiceal Carcinoids Justified?

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Hypothesis: We believe right hemicolectomy (RHC) is not necessary in patients with an appendiceal carcinoid greater than 2.0 cm.

Design: A retrospective review of patients with a histologically confirmed appendiceal carcinoid from April 1, 1980, to February 28, 2005, and an analysis of the literature.

Setting: Tertiary care referral center.

Patients: Forty-eight patients (34 females and 14 males) with a histologically confirmed diagnosis of appendiceal carcinoid were included in the study. Appendiceal carcinoid was diagnosed incidentally in all 48 patients. Patient ages ranged from 11 to 86 years (mean age, 41 years). Postoperative follow-up and disease-free survival were confirmed in 33 patients via medical record review.

Main Outcome Measures: We assessed the relationship between survival, tumor size, and the role of RHC vs appendectomy alone.

Results: Four patients in our series underwent secondary RHC and lymph node dissection for tumors greater than 2.0 cm, and none had positive lymph nodes. Following review of the literature, we were unable to find any recent evidence of distant metastasis from carcinoids in patients already treated by appendectomy. There seem to be no conclusive data to support the notion that RHC confers a survival benefit over appendectomy for carcinoids greater than 2.0 cm.

Conclusion: Appendiceal carcinoids greater than 2.0 cm can be managed effectively with simple appendectomy, given their low malignant potential and slow growth, obviating the need for RHC in this group of patients without affecting overall survival.

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Carcinoid tumors are among the most common primary malignant lesions arising from the appendix, accounting for up to 60% of all appendiceal tumors.[1] They are present in approximately 0.3%[2] of patients undergoing appendectomy and are often found incidentally during surgery for other indications. Although most appendiceal carcinoids are clinically silent and behave benignly, they do have the potential to metastasize. Extensive investigation into the molecular, biological, and clinical characteristics of the tumor since its recognition early in the 20th century has resulted in a management algorithm that has seen little change since initial proposals were made in landmark articles by Moertel and colleagues in 1968[2] and 1987.[3] Surgical resection remains the mainstay of treatment and the only means by which complete cure may be achieved.

During the past decade, there has been extensive investigation into the importance of characteristics other than tumor size that might have an association with metastasis and poorer prognosis. The prognostic data on characteristics such as vascular, muscular, mesoappendiceal, and periappendiceal lymphatic invasion have been conflicting.[4] Tumor size, in contrast, is considered the most important prognostic factor, with a proposed increase in the risk of metastasis for tumors greater than 2.0 cm.[3] The accepted treatment of such tumors is a primary right hemicolectomy (RHC) or an interval RHC following appendectomy and histological confirmation of a carcinoid greater than 2.0 cm.

Although there have been reports of recurrent disease in patients with tumors greater than 2.0 cm treated by simple appendectomy alone, the literature[3,5] suggests that recurrence occurs as late as 25 years after the initial diagnosis, and death from metastases occurs even later. This raises the question of whether RHC should be considered for appendiceal carcinoids greater than 2.0 cm in diameter. To our knowledge, there is no study that demonstrates a survival benefit for RHC over simple appendectomy in patients with carcinoids greater than 2.0 cm in diameter. The risks associated with a more radical operation vs the risks of tumor recurrence and its effect on patient survival need to be assessed.

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Table. Type of Operation Performed on Patients With an Appendiceal Carcinoid in Relation to Tumor Size*

Type of Operation	Tumor Size (Maximal Diameter), cm				Postoperative Complications
	≤1.0	1.1-2.0	>2.0	Total	
Simple appendectomy	16	3	1	**20**	0
Right hemicolectomy					
Secondary†	0	2	4	**6**	3
Primary	2	0	0	**2**	2
Appendectomy‡	10	10	0	**20**	0
Total	**28**	**15**	**5**	**48**	**5**

*Data are given as number of patients.
†The primary procedure in all of these patients was appendectomy.
‡Refers to patients in whom appendectomy was incidental and the indication for surgery was gynecology related.

METHODS

The hospital records of patients treated for appendiceal carcinoid at Massachusetts General Hospital, from April 1, 1980, to February 28, 2005, were reviewed. The diagnosis of appendiceal carcinoid was confirmed in every patient following histological analysis of the surgical specimen. We excluded patients with an uncertain diagnosis, concurrent malignancies, and tumors with an admixture of mucus-producing or adenocarcinoma elements, such as adenocarcinoids. The final study population included 48 patients (34 females and 14 males).

Information gathered from the medical records included standard demographic data, length of hospitalization, postoperative complications, and disease-free survival. Operative reports were reviewed for type of resection performed and intraoperative findings. Light microscopy and routine hematoxylin-eosin stains of the surgical specimens established the diagnosis of pure carcinoid tumors, which were measured at their greatest diameter and categorized as 1.0 cm or less, 1.1 to 2.0 cm, or greater than 2.0 cm. In cases that included colonic specimens, the presence of metastatic disease and the number of positive nodes within the resected lymph node basins were recorded. The length of stay for the complication and complication-free groups of patients was determined for all the patients studied. For patients undergoing a secondary hemicolectomy, only the length of stay for the secondary procedure was noted. Readmissions for complications related to a surgical procedure were included in length-of-stay calculations. Survival duration was measured from the time of diagnosis to the last follow-up examination or documentation of death. The cause of death, when available, was also noted. Patients for whom there was no follow-up information were not included in analyses of disease-free survival. The data from our study were compared with similar data from studies already published in the literature.

RESULTS

Most patients with appendiceal carcinoid were women (34 [71%] of 48 patients). The median age of the patients was 38.5 years (age range, 11-86 years; average age, 41 years). The surgical indications included gynecologic disease in 20 patients, acute appendicitis in 26 patients, and recurrent diverticulitis in 2 patients. Most tumors of the appendix were small, with 28 (58%) of 48 being 1.0 cm or less; 15 (31%), between 1.1 and 2.0 cm; and 5 (10%), greater than 2.0 cm in maximal diameter (percentages do not total 100 because of rounding). Of the 28 patients with tumors less than 1.0 cm, 16 were treated by simple appendectomy for signs and symptoms consistent with appendicitis. Of the remaining 12 patients, 10 underwent more extensive surgical procedures, most of which were gynecologic procedures, and 2 underwent primary RHC for recurrent diverticulitis.

Of the 28 patients with tumors less than 1.0 cm, 2 (7%) were found to have died by the time of follow-up: 1 died 26 years postoperatively of lung cancer and the other died 9 years postoperatively of prostate cancer. There was no clinical evidence of carcinoid recurrence in either of these patients at death. Of the remainder of the group with tumors that were 1.0 cm or less for whom follow-up information was available, 100% were alive and disease free with a mean follow-up of 18 years (range, 1-25 years).

The **Table** illustrates the surgical approach adopted for tumors based on size. Of the 15 tumors between 1.1 and 2.0 cm, 10 were incidentally removed during gynecologic surgery that included appendectomy. The appendectomy and gynecology patients were all alive and disease free (100% survival) after a mean postoperative follow-up of 19 years (range, 1-25 years). The 2 patients treated by secondary RHC for tumors measuring 1.8 and 1.9 cm, respectively, had no histological evidence of metastatic disease in their surgical specimens and were alive and disease free (100% survival) at follow-up intervals of 7 and 8 years, respectively.

Of the 5 patients with tumors greater than 2.0 cm, 1 was treated by appendectomy alone and 4 by secondary RHC following appendectomy. There was no evidence of metastatic disease in any of the surgical specimens. The appendectomy patient refused secondary RHC and was alive and disease free 8 years postoperatively. Of the 4 patients treated by secondary RHC, survival was 100% with a mean follow-up of 10 years (range, 1-15 years).

Postoperative complications occurred in 5 (10%) of the 48 patients. Gastrointestinal tract–related complications occurred in 4 patients who underwent RHCs. They included an ileus in 3 patients and an anastomotic stricture in 1 patient, which was detected 3 years after undergoing a primary RHC for recurrent diverticulitis. Two cases of pneumonia occurred, one in a 37-year-old woman who underwent a bilateral salpingo-oophorectomy in addition to an appendectomy and the other in a patient with a 1.8-cm carcinoid who underwent a secondary RHC for unclear indications. The average length of stay was 4 days for the complication-free group when compared with 8

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days for the group that experienced a complication (such as primary and secondary hemicolectomies and gynecologic procedures in which the appendix was removed).

COMMENT

Our results are consistent with those in the articles published by Moertel and colleagues in 1968[2] and 1987,[3] in which none of the 122 patients with carcinoids less than 2.0 cm experienced lymph node or distant metastases over a follow-up of up to 25 years.

For localized tumors larger than 2.0 cm with a presumed increase in metastatic potential, Moertel and colleagues[2,3] reported that 1 of 12 such patients treated by appendectomy alone had a local recurrence with resectable nodal metastasis 29 years later. This patient underwent a secondary RHC and was alive and disease free for 17 years thereafter. The remaining 11 patients were free of recurrence after a median follow-up of 28 years. In the same study, 7 patients with tumors larger than 2.0 cm were treated primarily with an RHC. Two of them had microscopic metastases in the regional lymph nodes, but all remained disease free after an 11-year median follow-up.[2,3] Our surgical approach for tumors greater than 2.0 cm is based on findings from a cohort in the 1950s in which 2 of 7 patients had micrometastasis, none of whom had prolonged survival when compared with 12 patients treated by appendectomy alone.[2]

A French cooperative study[6] reported close to 20% regional lymphatic spread in resection specimens for tumors greater than 2.0 cm. When considering this relatively high percentage, it is important to note that this study failed to exclude adenocarcinoid tumors, which are known to be more aggressive, and also included patients with concurrent carcinoids and adenocarcinomas elsewhere in the gastrointestinal tract. Our data suggest that the percentage of pure appendiceal carcinoids greater than 2.0 cm with lymphatic spread is significantly lower and that those with distant metastasis are rarely seen. Furthermore, the indolent nature of these tumors suggests that even in the presence of local or regional metastases, patient survival would not be affected. Thus, although a formal RHC for advanced tumors greater than 2.0 cm may be of value as a staged procedure, the relatively low malignant potential of these tumors and unproved effect of this procedure on overall patient survival suggest that it may be an aggressive treatment strategy.

Right hemicolectomy is a significant abdominal procedure with associated risks. Elderly patients and those with multiple comorbidities face significant perioperative risks, resulting in mortality and morbidity as high as 30% in some studies.[7] A small subset of patients will have permanent motility issues after the loss of their ileocecal valve. Respiratory tract and cardiovascular complications predominate, placing the elderly population, in particular, at risk.[7] Of the 5 postoperative complications that occurred in our study, 4 were in patients undergoing RHC, resulting in a 100% increase in the average length of stay when compared with patients without any postoperative complications.

Most patients with malignant appendiceal carcinoids are alive and disease free for many years after their diagnosis, and those with metastases on presentation have had normal life spans following resection.[2,5] Modlin et al,[8] in their analysis of 13 715 midgut carcinoids in the small bowel, appendix, and proximal colon regions, reported 5-year survival rates of 92% for patients with local disease, 81% for those with regional metastases, and 31% for the few with distant metastases. To our knowledge, there have been no studies looking specifically at appendiceal carcinoids to compare whether RHC and removal of regional lymph nodes positive for metastatic disease confer a survival advantage or any improvement in symptom control over patients treated by appendectomy alone. We thus believe that the risk-benefit analysis tips the scale in favor of simple appendectomy for appendiceal carcinoids greater than 2.0 cm, especially in the elderly population in whom life expectancy in the absence of disease may not exceed the time it takes for metastases to become clinically evident.

To help minimize the risks that might be associated with a more conservative approach to tumors greater than 2.0 cm, patients could be observed periodically to screen for recurrent disease by 1 of the many surveillance options available, including surveillance computed tomographic scans, periodic plasma chromogranin A levels, 24-hour urine 5-hydroxyindoleacetic acid levels, or indium In 111 pentetreotide–labeled octreotide scintigraphy in cases of suspected recurrent disease. The measurement of neuroendocrine markers in the urine and plasma has become an important cost-effective adjunct in the postoperative follow-up period for patients with carcinoid tumors.[9-11] In studying the prognostic factors and indications for RHC for appendiceal carcinoids, Safioleas et al[12] found that the only patient to develop tumor recurrence among their 28 study patients had it picked up postoperatively using indium In 111 pentetreotide scintigraphy. A clinically occult lung metastasis was detected, which was subsequently treated with somatostatin analogues with good effect.[12]

Unlike appendiceal carcinoids, patients with adenocarcinoids of the appendix fare much worse. The 10-year survival rate for these tumors of 60%[13,14] supports the fact that they are biologically more aggressive than appendiceal carcinoids and are associated with a poorer prognosis and higher rates of recurrence.[15,16] Although there are no clear criteria on when to perform an RHC on patients with these tumors, there is no doubt that they need to be managed more aggressively than their pure carcinoid counterparts. Part of the difficulty in shifting from the current paradigm of treating appendiceal carcinoids greater than 2.0 cm via RHC stems from the fact that many of the existing studies have failed to distinguish the difference between pure appendiceal carcinoids and their adenocarcinoid variants. This has led to the false perception that the malignant potential of appendiceal carcinoids is similar to that of adenocarcinoids, and so their treatment approaches have remained similar. Some researchers[17] regard the mere presence of an adenocarcinoid as an indication for RHC.

While we understand that there are only 5 patients in this study with tumors greater than 2.0 cm, the results from our study are consistent with collective data reported by other investigators. Larger studies[2,3] in which patients have

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been followed up for extended periods report that deaths attributable to appendiceal carcinoids have occurred only in patients with distant metastases at presentation. To further validate our findings, a multi-institutional collaborative study is needed in which a larger sample of patients with tumors greater than 2.0 cm is followed up over an extended period. When considering the younger patient population with localized tumors larger than 2.0 cm, an RHC may be appropriate. These patients generally have longer life expectancies and face lower perioperative risks for an RHC and may, therefore, benefit from a more extensive resection. In addition, there are some data to suggest that this population subset can harbor more aggressive carcinoid tumors when compared with their older counterparts.[3]

In assessing the risks of RHC and studying the survival figures for patients treated with appendectomy alone for tumors smaller than 2.0 cm, there is little doubt that a conservative surgical approach is the appropriate choice. In contrast, the optimal surgical management for appendiceal carcinoids larger than 2.0 cm has been, and continues to remain, a debated issue. Carcinoid tumors differ substantially from conventional adenocarcinomas and adenocarcinoid tumors in their pathophysiological features and outcome. In defining the appropriate surgical strategy, we believe that our proposed approach not only obviates the risks associated with more extensive resections but does so without affecting overall patient survival and quality of life.

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DISCUSSION

David Clark, MD, Portland, Me: I was intrigued by the statistical aspects of basing your recommendation on essentially 4 cases, which is to say that if you flip a coin 4 times the chances it is going to come up heads each time is still greater than 5%. This suggests that even if the risk of carcinoid appearing was 50% in 4 cases, you would have a *P* value greater than .05 that you would not find any in your series of 4 cases. Do you care to comment on the small sample size?

Dr Bamboat: Your point is very well taken. Part of the difficulty in studying these tumors is, one, that appendiceal carcinoids in general tend to be relatively rare and carcinoid tumors larger than 2 cm in particular even more rare. What ideally needs to be done is some sort of collaborative review involving multiple centers in which people get together and gather all the data for carcinoid tumors larger than 2 cm and study whether or not this finding is consistent. It needs to be done, but the other very important point that needs to be stressed in this case is that of all the existing studies that have been conducted thus far, there has been none that has shown that performing a right hemicolectomy for local disease or even in the presence of lymph node metastases confers any survival advantage at all.

Steven Yood, MD, New Haven, Conn: In follow-up to that question, did you do a sample size or power calculation to determine how many patients you would need to be able to determine if there was a difference? Second, you would probably need to do a multi-institutional study over a long period of time. How would you deal with calendar-time bias?

Dr Bamboat: That is another one of the difficulties. Given the indolent nature of these tumors, often if the tumor is to develop local or distant metastases, of the existing literature that is out there, that tends to occur many years later, often greater than 20 years later and so following these patients over that time period would be difficult.

To answer your first question, we did not conduct any studies to assess power for our particular patient group.

John Welch, MD, Hartford, Conn: If we encounter a carcinoid incidentally at an operation, would you propose that we do frozen section and would a pathologist be able to tell an adenocarcinoid from a carcinoid reliably? Could we depend on his decision on frozen section?

Dr Bamboat: In a lot of these studies, the carcinoid was found incidentally and discovered at the time of histological assessment of the sample on frozen section. I am unaware as to whether or not on frozen section the pathologist will be able to differentiate between carcinoid and adenocarcinoid, but there are clear histological variances between the two. I do not know if frozen section would be able to assess those differences.

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