Annals of Surgical Oncology, **12**(1): 72–80
DOI: 10.1245/ASO.2005.03.013

Lymph Node Metastasis in Epithelial Malignancies of the Appendix With Peritoneal Dissemination Does Not Reduce Survival in Patients Treated by Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy

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Background: Peritoneal dissemination of appendiceal malignancy combined with regional lymph node metastasis is an unusual combination of patterns of cancer dissemination.

Methods: A database of 501 appendiceal malignancy patients, all with documented peritoneal seeding, was used to identify 25 patients with involvement of the regional lymph nodes. All patients were uniformly treated with cytoreductive surgery plus perioperative intraperitoneal chemotherapy with mitomycin C and 5-fluorouracil. The clinical and pathologic features of the lymph node–positive patients were compared with those of the lymph node–negative patients. The effect of regional lymph node involvement on survival was determined. Within the group of lymph node–positive patients, clinical and pathologic features were tested for their effect on survival.

Results: When compared with patients with no apparent lymph node positivity, patients with positive lymph nodes were more likely to have an acute abdomen as the initial presentation ($P < .001$). The intestinal (nonmucinous) histological type was more common ($P < .001$), and the disseminated peritoneal adenomucinosis histology was less common ($P < .001$). Survival with the aggressive treatment strategy used in these patients was not different for lymph node–positive as compared with lymph node–negative patients ($P = .15$ by univariate and $P = .38$ by multivariate analysis).

Conclusions: Appendiceal malignancy with dissemination to the lymph nodes has a more acute onset and a more frequent nonmucinous histology. With aggressive treatment strategies, lymph node–positive patients did not show a statistically significantly diminished survival.

Key Words: Appendix neoplasms—Pseudomyxoma peritonei—Mucinous adenocarcinoma—Lymphatic metastasis—Peritoneal carcinomatosis.

The prognosis of patients with gastrointestinal malignancy depends on three major factors: diagnosis in an asymptomatic versus symptomatic state, regional lymph node involvement, and presence versus absence of distant metastases. Although this is true in colon, gastric, and pancreatic cancer, some of these prognostic criteria may not be applicable to appendiceal malignancy. Appendiceal epithelial malignancies show a distinct pathobiology. They are mostly mucinous, and peritoneal seeding occurs early in the natural history; this is usually present at clinical presentation. Comprehensive management requires cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. [1] The survival of ap-

Received March 11, 2004; accepted August 26, 2004.
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TABLE 1. *Demographic features of 501 patients with appendiceal epithelial malignancy with peritoneal dissemination*

Variable	Positive lymph nodes (n = 25)	Negative lymph nodes (n = 95)	Lymph nodes not detected (n = 381)	*P* value
Sex, n (%)				
Male	9 (36)	39 (41.1)	176 (46.2)	
Female	16 (64)	56 (58.9)	205 (53.8)	.44[a]
Age at initial diagnosis (y)				.12[b]
Mean (SD)	45.4 (8.94)	45.96 (11.02)	48.31 (11.60)	
Median	46	44	47	
Age when first treated at our center (y)				.05[b]
Mean (SD)	46.8 (8.75)	48.15 (10.79)	50.66 (11.62)	
Median	46	49	49	

[a] Chi-square.
[b] Analysis of variance.

pendiceal malignancy patients treated in this manner is not consistent with that of patients with other digestive cancers with peritoneal seeding.[2,3] Related to this prolonged survival is an infrequent involvement of regional lymph nodes. Previously published reports on lymphatic metastases of appendix epithelial cancer range from 4% to 18%.[4–13] The purpose of this study was to characterize clinically and pathologically lymph node–positive appendix epithelial cancer and to assess the prognostic significance of lymph node involvement for patient survival.

PATIENTS AND METHODS

Five hundred one patients (224 men and 277 women; mean age, 47.72 years) with appendiceal epithelial malignancies were surgically treated by the senior author (P.H.S.) between December 1983 and December 2000. Three hundred eighty-one patients had no apparent involvement of their regional lymph nodes. In 183, no right colectomy was performed, and in 198, the pathologist did not detect or sample nodes in a right colectomy specimen. In 95 patients, negative regional lymph nodes were histologically documented. In 25 patients, involvement of regional lymph nodes by the tumor was histologically documented. A statistical analysis of the demographic features of patients in whom no lymph nodes were detected, patients with negative lymph nodes, and patients with positive lymph nodes is given in Table 1.

Clinical Presentation

Patients were placed in one of three groups for an assessment of their clinical presentation. Patients with an acute abdomen had symptoms and signs compatible with acute appendicitis. The second group had symptoms and signs compatible with diffuse peritoneal involvement. These patients had one or more of the following: increasing abdominal girth, subacute and diffuse abdominal pain, weight loss, clinical and radiological signs of ascites, or palpable abdominal masses. In the third group of patients, the appendiceal malignancy was diagnosed incidentally during clinical investigations for a condition apparently not related to appendiceal malignancy.

Assessment of the Extent of Prior Surgery

A prior surgical score (PSS) was used to assess the extent of surgery performed before referral.[14] Briefly, a PSS of 0 indicated biopsy only; a PSS of 1 indicated exploratory laparotomy with operation in one or two abdominopelvic regions; a PSS of 2 indicated previous operation involving two to five abdominopelvic regions; and a PSS of 3 indicated prior surgical dissection in more than five regions. The abdominopelvic regions were defined by two sagittal planes through the mid clavicle and two transverse planes: one through the anterior superior iliac spines and the other through the most caudad point of the costal margins.

Treatment

Once under our care, all patients were treated by a uniform management plan consisting of cytoreductive surgery with the intention to clear as completely as possible all visible tumor from the abdomen and pelvis, combined with perioperative intraperitoneal chemotherapy.[15,16] Cytoreductive surgery, including peritonectomy procedures, was used in an attempt to clear the abdomen of all visible evidence of tumor. All patients received perioperative intraperitoneal

mitomycin C, and a majority received early postoperative intraperitoneal 5-fluorouracil. Normothermic intraperitoneal mitomycin C was given on the first postoperative day in 83 patients. The mitomycin C was given heated in the operating room, with manual distribution of the drug in 413 patients. Mitomycin C was not used in five patients. Treatment with 5-fluorouracil was withheld if there was a small volume of intraperitoneal disease or if small bowel loops could not be separated to allow the uniform distribution of the chemotherapy solution. Eighty-five patients were not treated with 5-fluorouracil. Recurrences after this treatment were treated with second-look surgery and the same perioperative intraperitoneal chemotherapy regimen.[17] In patients with positive lymph nodes, systemic chemotherapy was recommended after recovery from surgery.

The completeness of cytoreduction was assessed by the size of the peritoneal tumor deposits remaining at the completion of cytoreductive surgery (CC score).[14] The possible categories for this variable were as follows: no visible tumor deposits (CC-0), deposits <2.5 mm in greatest diameter (CC-1), deposits between 2.5 mm and 2.5 cm (CC-2), and deposits >2.5 cm in greatest diameter (CC-3). For appendix cancer, CC-0 and CC-1 were considered complete cytoreductions, whereas CC-2 and CC-3 were considered incomplete cytoreductions.

Pathology

Light Microscopy

Appendiceal tumors were histologically classified as mucinous type if there was extracellular mucin in $>50\%$ of the lesion and as intestinal type if this component was present in $\leq 50\%$ of the lesion. The histological appearance of the latter is similar to that of typical colorectal adenocarcinoma.[18] The presence or absence of a signet ring cell type was determined.

The peritoneal mucinous tumor deposits were morphologically categorized according to Ronnett et al.[19] and Yan et al.[20] Briefly, disseminated peritoneal adenomucinosis was characterized by multifocal mucinous tumors adherent to but not invading visceral and parietal peritoneal surfaces. Mucinous adenocarcinoma (peritoneal mucinous carcinomatosis) was characterized by invasive peritoneal lesions composed of abundant epithelium with glandular or signet ring morphology and architectural and cytological atypia. This category was also further subdivided into well-differentiated, moderately differentiated, and poorly differentiated adenocarcinoma depending on the degree of cell atypia and architectural irregularity. Hybrid tumors predominantly demonstrated histological features of adenomucinosis; however, focal ($<5\%$ of the tumor cells) areas of well-differentiated adenocarcinoma were identified in the peritoneal lesions.

Ki-67 Immunohistochemistry (Proliferative Index)

Immunohistochemical staining with anti Ki-67 (Zymed Laboratories, San Francisco, CA) was performed in the formalin-fixed paraffin-embedded tissue sections to assess the proliferative activity of the tumor. Anti−Ki-67 is a murine monoclonal antibody that reacts with the human Ki-67n nuclear antigen, which is expressed in all human proliferating cells.[21] The fixed tissues were stained with anti−Ki-67 after trypsin digestion, followed by heat-induced antigen recovery. Quantitative determination of the fraction of cells positively stained gives an estimation of the cell proliferation index in tumor cells and is used as a prognostic indicator in solid tumors.

The stained tissues were blindly evaluated by two different pathologists. The relative number of cells positive for this marker were recorded as negative (no cells stained), 1+ ($<25\%$ of cells stained), 2+ ($25\%-75\%$ of cells stained), or 3+ ($>75\%$ of cells stained). In case of discrepancy between pathologists, the higher reading was the one recorded for the study.

Flow Cytometry

Flow cytometry analysis of the fixed specimens was performed to assess DNA nuclear content (diploid or aneuploid).[22–24] In cases with an aneuploid component, the percentage of aneuploid cells and the percentage of cells in S-phase were recorded as well.

Study Design

In the first evaluation, the 25 lymph node−positive patients were compared with 95 patients with negative lymph nodes and 381 patients in whom lymph nodes were not assessed. The clinical and pathological data of these patients were retrieved from a prospectively recorded database.

Collected data included information regarding patients' age and sex, initial clinical presentation, treatment before referral to our center (number of operations, surgical procedures performed, PSS, and prior chemotherapy administration), presence versus absence of distant metastases, presence versus absence of regional lymph node involvement, management at our service (number of cytoreductions,

surgical procedures performed, and completeness of cytoreduction), and tumor pathology (intestinal vs. mucinous, presence vs. absence of signet ring cells, and morphology of the peritoneal lesions).

In the second part of the evaluation, the effects of clinical and pathologic variables on survival among the 25 lymph node–positive patients were assessed in an attempt to recover further prognostic information in this group. The end point in all analyses was disease-specific survival.

Follow-up time was recorded in years elapsed from the time of initial diagnosis to the closing date of this study (May 1, 2001), the death of the patient, or the date of the last available clinical information. Patients' vital status by the last available follow-up was categorized as alive with no clinical evidence of disease, alive with clinical evidence of disease, dead of disease, or dead of other causes. This information was obtained from correspondence; from direct contact with the referring physicians, patients, or their families; or from an Internet search through the Social Security Death Index.

Statistical Analysis

Death caused by the disease was considered the terminal event for the survival analyses. Survival was estimated by the Kaplan-Meier method. Five-year survival, 10-year survival, and median survival were assessed. Ninety-five percent confidence intervals are provided for each median survival estimate.

Univariate comparison of survival curves was performed by the log-rank test. The Cox proportional hazard regression model was used to assess the influence of lymph node status on survival, adjusted by the other clinical and pathologic variables recorded. The χ^2 test was used to analyze statistical relationships between pairs of variables. Two × two tables were analyzed by Fisher's exact test if the expected count was less than five in more than one cell. Differences were considered statistically significant when the P value was $\leq .05$.

RESULTS

Incidence of Lymph Nodal Involvement in Epithelial Tumors of the Appendix

Twenty-five patients were found to have tumor involving regional lymph nodes. This accounts for 5% of the global series of 501 cases. In patients who had histopathologic node sampling, lymph node metastases were detected in 21%. In 95 patients, right colic or appendiceal lymph nodes were sampled and determined to be negative. In 198 patients, no lymph nodes were detected in the resected right colon specimen in a gross anatomic study by the pathologist. In 183 cases, no enlarged lymph nodes were palpated by the surgeon at the time of cytoreduction, and no right colectomy was performed.

Follow-Up and Overall Survival for Lymph Node–Positive Patients

The mean age at initial diagnosis of the malignancy for the 25 lymph node–positive patients was 45.4 years (median, 46 years; range, 33–68 years). Nine patients were women (36%), and 16 (64%) were men.

None of these patients was lost to follow-up. Fourteen patients remained alive at the time of the last available follow-up; their mean follow-up time was 5.4 years.

At the time of the last available follow-up, patients' vital status was distributed as follows: 9 patients (36%) had no clinical evidence of disease, 5 (20%) were alive with clinical evidence of disease, and 11 (44%) were dead of disease. None died of causes other than their appendix malignancy.

Clinical and Pathologic Comparison of Lymph Node–Positive, Lymph Node–Negative, and Lymph-Nodes-Not-Detected Groups of Patients

The most common clinical presentation of lymph node–positive patients was an acute abdomen with typical signs and symptoms of acute appendicitis. This occurred in 15 patients (60%). Two patients (8%) were asymptomatic, and their appendiceal tumor was found incidentally in the course of a surgical exploration indicated for a condition not related directly to the appendix (one for infertility and the other for resection of colonic polyps). The remaining eight patients presented with signs and symptoms of diffuse peritoneal involvement. To determine whether lymph node–positive patients had distinct clinical and pathologic features, this group was compared with patients with documented negative lymph nodes and patients in whom lymph nodes were detected. Statistically significant differences were found in initial clinical presentation. These comparisons are listed in Table 2. An acute abdomen was statistically significantly more common in the lymph node–positive patients when these patients were compared with both lymph node–negative and lymph-nodes-not-detected groups ($P < .001$).

TABLE 2. *Clinical and pathologic comparison of lymph node–positive, lymph node–negative, and lymph-nodes-not-detected patients*

Variable	Positive lymph nodes (n = 25)		Negative lymph nodes (n = 95)		No lymph nodes detected (n = 381)		*P* value (I/II)
	n	%	n	%	n	%	
Initial clinical presentation							
Acute abdomen (n = 127)	15	60.0	42	44.2	70	18.3	.32/.0006
Incidental (n = 101)	2	8.0	16	16.8	83	21.8	
Diffuse disease (n = 272)	8	32.0	37	38.9	227	59.6	
Peritoneal surface dissemination at initial diagnosis							
Absent (n = 50)	8	32.0	19	20.0	23	6.0	.27/.0010
Present (n = 418)	16	64.0	73	76.8	329	86.4	
Tumor histology							
Mucinous (n = 495)	21	84.0	95	100.0	379	99.0	.0015/ < .0001
Intestinal (n = 6)	4	16.0	0	.0	2	.1	
Morphological type							
DPAM (n = 244)	4	16.0	40	42.1	200	52.4	< .0001/ < .0001
Hybrid (n = 80)	2	8.0	17	18.0	61	16.0	
PMCA (n = 140)	15	60.0	30	31.6	95	24.9	
PCA (n = 5)	4	16.0	0	.0	1	.2	
Signet ring cells							
Absent (n = 443)	22	88.0	77	81.0	344	90.3	.56/1.0
Present (n = 58)	3	12.0	18	18.9	37	9.7	

DPAM, disseminated peritoneal adenomucinosis; PMCA, peritoneal mucinous carcinomatosis; PCA, peritoneal carcinomatosis from nonmucinous cancer.

Comparison I provides the *P* value for positive lymph nodes versus negative lymph nodes. Comparison II provides the *P* value for positive lymph nodes versus both negative lymph nodes and no lymph nodes detected.

There was a statistically significant predominance of the intestinal type as compared with the mucinous type of appendiceal tumors ($P < .001$). Four of 25 patients with positive nodes had an intestinal type of malignancy, compared with 0 with negative lymph nodes.

The morphological type of appendiceal tumor differed significantly between groups. Only 16% of lymph node–positive patients had disseminated peritoneal adenomucinosis, as compared with 42% of lymph node–negative patients. The incidence of peritoneal mucinous carcinomatosis was higher in the node-positive group (60%; $P < .001$). There was no statistically significant difference in the incidence of signet ring cells.

Comparison of Survival Among Lymph Node–Positive, Lymph Node–Negative, and Lymph-Nodes-Not-Detected Patients

In the series of 501 patients, lymph node status did not have a statistically significant effect on mean survival, either by univariate ($P = .15$; Fig. 1) or multivariate ($P = .38$) analysis. Median survival for the lymph node–positive group was 7 years (95% confidence interval, 3.86–10.14 years); 5-year survival was 50.73%, and 10-year survival was 40.58%. For the group without pathologic assessment of their regional lymph nodes, the median survival was 13 years (95% confidence interval, 9.0–17.0 years); 5-year survival was 71.97%, and 10-year survival was 55.57%. Median survival had not yet been reached for the group with documented negative regional lymph nodes; their 5-year survival was 78.17%, and their 10-year survival was 55.72%.

Dissemination of Lymph Node–Positive Tumors

Four (16%) of the 25 lymph node–positive patients developed distant metastases during the disease process. One already had distant disease at the time of initial diagnosis (malignant pleural effusion), and in the other three it was detected at follow-up. When compared with the other 476 appendiceal malignancy patients (with a 5.88% rate of distant dissemination), the influence of regional lymph node status on the subsequent development of distant metastases was not statistically significant ($P = .098$ by Fisher's exact test). The remaining 21 patients (84%) with regional node involvement did not have distant metastases at presentation, nor were there signs of subsequent tumor progression or spread to extra-abdominal sites up to the last available follow-up.

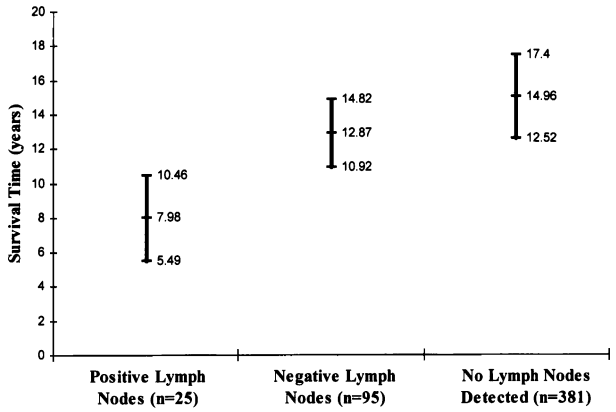

FIG. 1. Mean survival with standard error by lymph node status of 501 patients with epithelial appendiceal tumors ($P = .15$).

The incidence of disease spread to extra-abdominal sites for lymph node–positive patients was greater for the ones with intestinal (25%) than for those with mucinous (10%) tumors, but this difference was not statistically significant (Fisher's exact test; $P = .44$). Among the regional lymph node–positive patients whose disease progressed at distant sites, two did so in the pleura with cytologically confirmed malignant pleural effusion (one case with a mucinous-type tumor and the second case with an intestinal-type one), and the third did so in the lung with parenchymal metastases (mucinous-type tumor).

None of these three patients was specifically treated for their distant disease component. At the last available follow-up, the first two patients died of their disease during the year that followed the detection of the distant metastases, and the third one was alive 9 months afterward.

Survival Analysis by Clinical and Pathologic Variables in Lymph Node–Positive Patients

Of the pathological variables studied in this group of 25 patients, only 2 affected survival. The presence versus absence of signet ring cells showed a significant decrease in survival ($P = .002$). Also, the presence versus absence of distant metastases at the time of presentation resulted in a significant decrease in survival ($P = .01$).

The ploidy by flow cytometry and the Ki-67 proliferation index by immunochemical stain did not have a statistically significant effect on the survival of the group of 16 patients in whom tissue was available for study ($P = .86$ and $P = .43$, respectively). For the aneuploid tumors, the percentage of aneuploid cells and that of cells in S-phase did not affect the survival of these patients ($P = .07$ and $P = .84$, respectively).

DISCUSSION

Knowledgeable treatment of a rare disease such as appendix cancer has not been possible for years because of the lack of large series of patients that would allow the formulation of statistically valid conclusions. Most of the series published in the past included patients treated in several different centers and by various surgeons with heterogeneous treatment plans.[4–13] We have accumulated experience with 501 cases of appendiceal malignancy with peritoneal dissemination over a 17-year period treated by a consistent management plan by the same surgeon.

The low incidence of regional lymph node involvement in patients with appendix epithelial tumors has been pointed out by other authors. The larger published series have an incidence that ranges from 4% to 30% of the reported cases (Table 2). There are definite anatomical and tumor biologic considerations that may assist in understanding the unusual natural history presented by appendiceal epithelial malignancy. From an anatomical perspective, the vermiform appendix has a thin wall with areas of absent muscularis propria. This brings the serosal and submucosal layers closer together than in other portions of the intestine. In this anatomical situation, full-thickness invasion of the appendiceal wall is likely, and peritoneal seeding by a mucinous epithelial neoplasm should be expected. Another anatomical consideration is the narrow lumen of this structure along with its blind end. A mucosal growth, regardless of its capacity for invasion, may cause an accumulation of debris distal to the adenoma or the carcinoma. Under the pressure of continued mucinous secretions, first distention as a mucocele and then appendiceal perforation will result. Dissemination of epithelial cells in a mucinous matrix into the free peritoneal cavity will occur.

A valid criticism of the data in this study involves the 381 patients (76%) who did not have lymph nodes studied by histopathology. Three causes for this can be cited. First, in the past, in performing appendectomy for a malignant mucocele, most surgeons (ourselves included) did not purposely dissect the mesoappendix to sample lymph nodes. Presently, this is recommended in every patient. Second, the right colectomy specimen is usually only part of a much greater tumor mass covered by a large volume of mucinous tumor nodules. Presently, with orientation

TABLE 3. *Incidence of lymph node involvement in appendiceal cancer in published series with sample size greater than four cases*

Reference	No. cases	Mucinous tumors	Intestinal tumors	LN (+) cases	Global LN (+) incidence	LN (+) incidence, mucinous	LN (+) incidence, intestinal
Hilsabeck et al.[4]	41	29	12	3	7.3%	3.4%	16.7%
Hesketh[5]	95 (87 operated)	0	95 (87 operated)	4	4.6%	NA	4.6%
Wolff and Ahmed[6]	24	2	22	4	16.6%	NA	18.2%
Panton et al.[7]	5	NA	NA	1	20%	NA	NA
Gilhome et al.[8]	10	3	7	3	30%	NA	NA
Schlatter et al.[9]	23 (20 operated)	NA	NA	8	4%	NA	NA
Conte et al.[10]	15	13	2	1	6.7%	NA	NA
Nitecki et al.[11]	94	52	42	17	18.1%	0%	40%
Proulx et al.[12]	23	15	8	3	13.04%	NA	NA
Hananel et al.[13]	22	NA	NA	1	12.5%	NA	NA
Gonzalez-Moreno et al.[26]	501	495	6	25	5%	4.2%	66.7%

LN (+), lymph node positive; NA, not available.

by the surgeon, pathologic lymph node sampling is recommended in every patient. In the past, only enlarged nodes would be taken for histological study, and enlarged nodes were seldom palpated in processing the specimen. Third, many of these patients came to us on a referral after prior right colectomy at an outside institution. Often these patients were thought to have a terminal condition, so a diligent search for lymph nodes in these patients with carcinomatosis may not have been thought necessary (Table 3).

In colon cancer, perforation occurs after the invasive primary tumor has progressed to invade through all layers of the bowel wall. This occurs late in the natural history of the cancerous process. In appendiceal cancer, when perforation occurs, it happens early in the natural history of the disease—usually before lymph node or hematogenous dissemination. This may be a major reason for the low incidence of hematogenous or lymphatic metastases with a diagnosis of appendiceal cancer. Because of the copious mucus production by a mucinous tumor, the pressure that causes perforation with an obstructed appendiceal lumen may occur more readily than with an intestinal (nonmucinous) cancer type.

The mechanism of presentation is in large part dependent on the invasive character of the cancer and its production or lack of production of mucus. With an invasive malignancy, more often seen with lymph node–positive tumors, sclerosis of the surrounding tissues causes a segmental closure of the appendiceal lumen. If perforation occurs, bacterial-containing debris distal to the obstruction disseminates into the free peritoneal cavity because of obstruction of the appendiceal lumen. In patients with lymph node–positive disease, appendicitis is expected to be a common presenting clinical feature and occurred in 60% of our patients (Fig. 2). However, in patients who have an adenoma of the appendix, a malignant mucocele will develop, and a gradual expansion of the appendix occurs. Only with pressure from an accumulation of copious mucinous secretions will the "blowout" occur. In this situation, the appendiceal leakage is of mucus-containing adenomatous epithelial cells. Before any symptoms of inflammation, the mu-

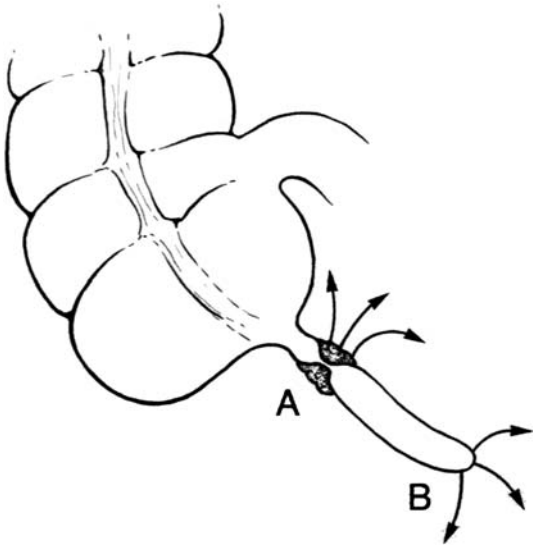

FIG. 2. Appendicitis as a result of an invasive intestinal-type appendiceal malignancy. If the tumor biology is such that the thin appendiceal wall is invaded by cancer, then a perforation develops, and there is acute inflammation as a result of bacterial soilage of the right lower quadrant (perforation at site A). Alternatively, appendicitis could be caused by a constriction of the narrow lumen and a distal appendiceal perforation (perforation at site B). In either situation, the high-grade and invasive malignancy results in symptoms compatible with appendicitis. In this situation, the peritoneal seeding occurs at the time of the perforation. Carcinomatosis will be clinically apparent months later as the cancer cells in the right lower quadrant and pelvis cause symptoms or radiological findings.

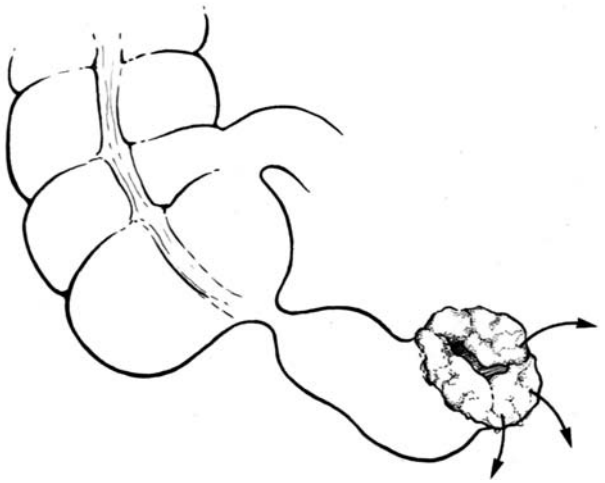

FIG. 3. Appendiceal perforation as a result of an adenoma. If the tumor of the appendiceal epithelium is minimally aggressive, it will not result in an acute perforation of the appendiceal wall. Rather, it will produce large quantities of mucus that is contaminated by adenomatous epithelial cells. This results in a malignant mucocele. Over the course of many months and even years, the mucocele expands in size and will eventually cause the characteristic "horn of plenty" defect of the distal appendix. Large quantities of mucoid fluid contaminated by tumor cells extrude from the appendix. Usually this mucus is not infected and does not result in symptoms of acute appendicitis. The mucoid fluid does distribute itself in a characteristic fashion beneath the right hemidiaphragm and within the pelvis, replacing the omentum. This is the pseudomyxoma peritonei syndrome.

coid fluid disseminates itself widely and in a characteristic fashion around the peritoneal cavity and results in the pseudomyxoma peritonei syndrome (Fig. 3).

A surprising finding in this study was the lack of a significant effect of lymph nodal status on patient survival. Patients with lymph node involvement did have a shorter median survival than the rest of the patients, but this was without statistical significance (Fig. 1). It is possible that this lack of significance would change with a larger sample size. This is unique among gastrointestinal malignancies, where lymph node involvement is one of the major determinants of survival. The explanation for this is probably multifactorial. From a tumor biology perspective, a limited number of positive nodes is associated with a better survival than many nodes. These patients usually had limited nodal involvement. A second explanation may be treatment related. The incidence of locoregional cancer recurrence is greater in gastrointestinal cancer patients with positive as compared with negative lymph nodes. Nearly all of these patients had perioperative intraperitoneal chemotherapy treatment of the entire abdominal and pelvic surface before the ileocolic or any other anastomosis. Tumor cell leakage from transected lymphatic channels that results in locoregional recurrence should be effectively managed by this treatment. These data may have implications for the development of clinical trials in gastrointestinal cancer patients. In a study of primary gastric cancer patients treated with intraperitoneal chemotherapy, there was a marked improvement in the survival of lymph node–positive patients as compared with patients treated by surgery alone.[25]

If a malignant process gains access to regional lymph nodes, connections between the lymphatic system and the systemic circulation make it more likely that disease at distant sites will occur. The development of clinically detectable distant metastases in our patients with positive lymph nodes did not occur with significantly greater frequency than in patients without them. It occurred in 16% of the patients, a much lower incidence than would be expected in lymph node–positive patients with other digestive malignancies. These findings suggest that lymph node–positive appendix epithelial cancer might not be as aggressive a process as one might expect or that these mucinous cancer cells are highly metastatically inefficient.

From this analysis of lymph node–positive cases, we can better characterize this stage of appendiceal malignancy. Lymph node involvement is significantly more likely to occur in the rare intestinal-type tumors than in the more prevalent mucinous ones. Also, lymph node–positive tumors had the invasive morphology of peritoneal mucinous carcinomatosis in 60% of patients; lymph node–negative tumors had half that incidence of peritoneal mucinous carcinoma.

Several pathologic prognostic variables in the patients with positive lymph nodes were explored in an attempt to identify patients who would develop progressive disease despite this maximal locoregional treatment effort. Determination of the proliferative index and ploidy in the subset of lymph node–positive appendix cancer patients did not add further valuable pathologic information. A diploid DNA content or a negative proliferative index does not help to predict accurately the survival of patients with lymph node–positive appendix epithelial cancers. However, the small sample size may warrant further studies. The presence of the signet ring morphology did correlate with a significantly worsened prognosis.

The low incidence of lymph node positivity in patients with appendiceal malignancy and peritoneal dissemination may have implications for the optimal management of this group of patients. Right colectomy, currently a standard of practice, may not be the treatment of choice in this situation. Previous studies have shown that right colectomy does not

improve survival in this group of patients.[26] Therefore, generous sampling of the appendiceal lymph nodes in this clinical situation by using the sentinel node concept was advocated. Only if the appendiceal lymph nodes were determined positive by cryostat sectioning or if the margin of resection on the base of the appendix was inadequate was the right hemicolectomy procedure recommended. This would be a marked deviation from the current standard of practice with this disease.

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