

Carcinoid tumors of the duodenum

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Background. Carcinoid tumors of the duodenum are rare, and their natural history has not been defined. Consequently, there is no consensus on the optimal extent of surgical treatment.

Methods. The authors reviewed the records of all patients with primary carcinoid tumors of the duodenum treated at their institution from 1969 through 2004. Patients with primary periampullary tumors and gastrinomas were excluded.

Results. Twenty-four patients had a pathologic diagnosis of duodenal carcinoid tumor. The majority (89%) of tumors measured less than 2 cm in diameter, and most (85%) were limited to the mucosa or submucosa. Lymph node metastases were identified in the surgical specimen in 7 (54%) of 13 patients in whom lymph nodes were examined, including 2 patients with tumors smaller than 1 cm and limited to the submucosa. At a mean follow-up of 46 months, the disease-specific survival rate was 100%, and only 2 patients have had recurrences in regional lymph nodes. No patient has had distant metastases or the carcinoid syndrome.

Conclusions. Carcinoid tumors of the duodenum are indolent. The presence of regional lymph node metastases cannot be predicted reliably on the basis of tumor size or depth of invasion, and their impact on survival is uncertain. (*Surgery* 2005;138:971-8.)

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CARCINOID TUMORS are relatively uncommon neuroendocrine tumors. They arise from enterochromaffin cells and are found most often in the gastrointestinal tract. Primary duodenal carcinoids account for only 2.6% of carcinoid tumors in the United States,¹ although they are increasingly recognized with the more widespread use of upper gastrointestinal endoscopy. Previous studies have suggested that duodenal carcinoid tumors smaller than 2 cm in diameter and confined to the submucosa have limited metastatic potential and, therefore, can be managed by local excision alone.^{2,3} However, these studies consisted of heterogeneous populations of patients, including those with periampullary tumors and gastrinomas (Zollinger-Ellison syndrome, ZES). In addition, these studies included very few patients, with small, superficial tumors, who underwent regional lymph node dissection, and thus the studies may have underestimated the true incidence of lymph node

metastasis in patients with duodenal carcinoids. Accordingly, there are little data concerning the natural history and optimal extent of surgical treatment of duodenal carcinoid tumors.

We reviewed our institutional experience with duodenal carcinoid tumors to more clearly define their biological behavior and to develop guidelines for appropriate surgical therapy.

METHODS

All patients treated at our institution between 1969 (the year of the first diagnosed case) and 2004 who had a pathologic diagnosis of a primary carcinoid tumor of the duodenum were identified. The diagnosis of "carcinoid tumor" was based on light-microscopic histologic criteria established by the World Health Organization in the International Histological Classification of Tumours.⁴ Patients with periampullary carcinoid tumors were excluded, because tumors in this anatomic location are often somatostatin rich and may behave differently than duodenal carcinoids.^{5,6} Patients with primary duodenal gastrinomas were also excluded. Gastrinoma (ZES) was defined as the presence of clinical symptoms of acid hypersecretion, a gastric pH level of 2 or less, and a fasting serum gastrin level of greater than 200 pg/mL (off of acid-suppression therapy).

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Data on patient demographics, presenting symptoms, laboratory studies, diagnostic procedures, and diagnoses of all carcinoid and noncarcinoid tumors were extracted from the records. Pretreatment abdominal computed tomography (CT) and endoscopic ultrasonography (EUS) reports for each patient, if available, were reviewed retrospectively to determine whether the imaging study was able to identify metastatic lymph nodes. Details of the treatment rendered were also recorded. Radical resection was defined as a surgical resection that included the removal of regional lymph nodes. Local excision was defined as a surgical resection that did not include the removal of regional lymph nodes. Pathology reports were reviewed retrospectively for standard pathologic variables including number of tumors, location, size, depth of invasion, immunohistochemical features, presence or absence of vascular and lymphatic invasion, resection margin status, and presence or absence of metastatic carcinoid in the regional lymph nodes. Follow-up data were obtained from the medical records. Recurrences were identified by abdominal CT or endoscopic evaluation. For purposes of this analysis, recurrent disease was defined as local (surgical site), regional (peritoneal cavity), or distant; tissue confirmation was not required for the diagnosis of recurrent disease.

RESULTS

Twenty-four patients (13 men and 11 women) had a pathologic diagnosis of duodenal carcinoid tumor. The histologic diagnosis was confirmed by one of the authors (H.W.) in 19 cases for which the slides were available for re-review; the histologic slides were not available for re-review in the remaining 5 patients. None of the 24 patients had evidence of atypical or poorly differentiated carcinoid histology. The diagnosis of carcinoid tumors was established by endoscopic biopsy in 19 (79%) of 24 patients and at the time of laparotomy for abdominal pain in 2 (8%) patients. The remaining 3 patients' carcinoid tumors were discovered incidentally in the pathology specimens obtained during pancreaticoduodenectomy for adenocarcinoma of the pancreas (2 patients) and subtotal gastrectomy for adenocarcinoma of the stomach (1 patient). The characteristics of all 24 patients are summarized in Table I. The median age at the time of diagnosis was 57 years (range, 36 to 87 years). The most common presenting symptoms were abdominal pain, reflux or dyspepsia, and gastrointestinal bleeding; 11 (46%) of the 24 patients were receiving proton pump

Table I. Patient, tumor, and treatment characteristics in 24 cases of duodenal carcinoid tumors

Characteristic	No. of Patients (%)
Sex	
Male	13 (54)
Female	11 (46)
Symptoms	
Abdominal pain	14 (58)
Reflux/dyspepsia	6 (25)
Gastrointestinal hemorrhage	3 (13)
Asymptomatic	2 (8)
Proton pump inhibitor therapy	
Yes	11 (46)
No	13 (54)
Other tumors	
Another primary malignancy (synchronous or metachronous)	9 (38)
Multifocal carcinoid tumor	1 (4)
Treatment	
Endoscopic resection	6 (25)
Transduodenal excision	4 (17)
Segmental duodenal resection	8 (33)
Pancreaticoduodenectomy	2 (8)
Incomplete resection*	1 (4)
Chromogranin-A level	
Normal (6 to 39 ng/mL)	4 (17)
Elevated (≥ 40 ng/mL)	5 (21)
Not measured	15 (63)
Urinary 5-HIAA level	
Normal (<6 mg/24 hours)	7 (29)
Elevated (≥ 7 mg/24 hours)	0 (0)
Not measured	17 (71)

*Resection of lateral wall of second portion of duodenum, common bile duct, and enlarged retroduodenal and retropancreatic lymph nodes, with unresectable retroperitoneal disease.

inhibitor therapy before their diagnosis. One patient (4%) had multifocal gastrointestinal carcinoid tumors in the rectosigmoid colon. Another synchronous or metachronous primary malignancy was diagnosed in 9 (38%) of 24 patients: adenocarcinoma of the pancreas in 2; adenocarcinoma of the gallbladder, colon, breast, prostate, and stomach in 1 each; and melanoma and soft tissue sarcoma in 1 each. No patient had a diagnosis of neurofibromatosis (von Recklinghausen's disease) or multiple endocrine neoplasia type I.

Urinary 5-hydroxyindoleacetic acid (5-HIAA) levels were measured at the time of diagnosis in 7 patients, and all were normal (<6 mg/24 h). Pretreatment chromogranin-A levels (normal, 6 to 39 ng/mL) were measured in 9 patients, of whom, 5 had an elevated value (range, 59 to 190 ng/mL).

Pretreatment contrast-enhanced abdominal CT was performed in 22 of 24 patients. Abnormal

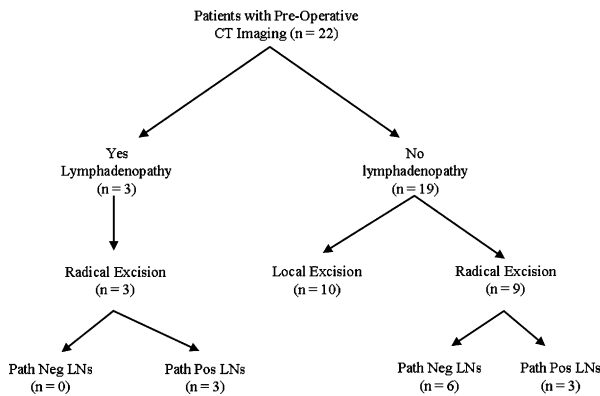


Fig 1. Diagram correlates the findings on pretreatment abdominal CT in 22 patients who had duodenal carcinoid tumors with the findings on pathology (Path) in the 12 patients who underwent radical excision and thus had lymph nodes (LNs) available for analysis. Neg, negative; Pos, positive.

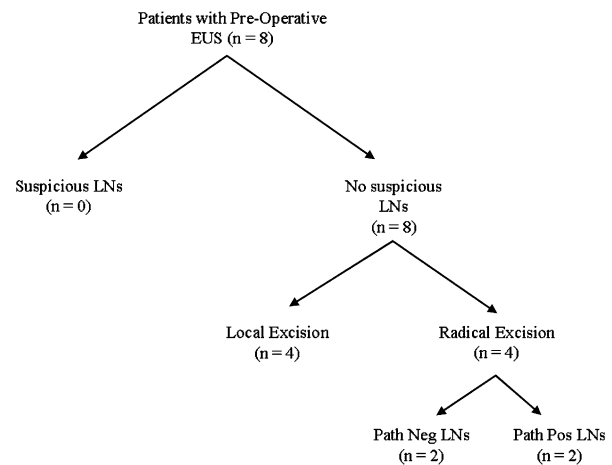


Fig 2. Diagram correlates the findings on pretreatment EUS in 8 patients with duodenal carcinoid tumors who had the findings on pathology (Path) in the 4 patients who underwent radical excision and thus had lymph nodes (LNs) available for analysis. Neg, negative; Pos, positive.

lymphadenopathy was detected in 3 (14%) of the 22 patients; all 3 underwent radical resection and had pathologically confirmed metastatic carcinoid in the resected lymph nodes (Fig 1). Radical resection was performed in an additional 9 patients with no radiographic evidence of lymphadenopathy; 3 had metastatic carcinoid in the resected lymph nodes (Fig 1). Preoperative EUS was performed in 8 patients, and no suspicious lymphadenopathy was identified (Fig 2). Radical resection was performed in 4 of the 8 patients, and 2 of them had metastatic carcinoid tumor in the resected lymph nodes.

The pathologic characteristics of the duodenal carcinoid tumors in this study are summarized in Table II. There were 37 tumors in 24 patients; 4 patients (17%) had multiple duodenal carcinoid tumors (range, 2 to 7 tumors). Thirty (81%) of the 37 tumors were limited to the first portion of the duodenum, 6 tumors (16%) were located in the second portion of the duodenum, and 1 tumor (3%) was located in the distal duodenum (Fig 3). The median tumor size was 0.6 cm (range, 0.2 to 9.0 cm), with 33 (89%) of the 37 tumors measuring less than 2.0 cm in greatest diameter. The depth of invasion was known for 34 of the tumors, of which, 29 (85%) were limited to the mucosa or submucosa. Two tumors invaded the muscularis propria, and 3 tumors, all 2 cm or larger, penetrated through the serosa to involve the pancreas. Immunohistochemical analysis was performed on 17 of the tumor specimens; 16 of 16 specimens stained positively for chromogranin, 8 of 8 for synaptophysin, 3 of 3 for neuron-specific enolase, and 2 of 4 for gastrin.

Lymph nodes were identified in the surgical specimens of 13 patients, and metastatic carcinoid was present in 7 (54%) of the patients, including 2 patients with tumors smaller than 1 cm and limited to the submucosa (Fig 4). Lymphatic or vascular invasion was identified in 5 of 9 patients in whom the status was documented, and 4 of the 5 also had metastatic disease in regional lymph nodes. However, of the 4 patients who had no evidence of lymphatic or vascular invasion in the primary tumor specimen, 2 had positive lymph nodes.

Endoscopic resection of duodenal carcinoid tumors was performed in 6 (25%) of 24 patients; 5 of the tumors were smaller than 1 cm, and the other tumor measured 1.5 cm in greatest diameter. A margin-negative (R0) resection was achieved in all 6 patients. One of these 6 patients, with a 0.6-cm lesion, died of metastatic melanoma, and the other 5 are alive without disease recurrence at a median follow-up of 17 months (range, 3 to 35 months).

Surgical resection was performed in the remaining 18 patients (75%) and included transduodenal local excision (n = 4), segmental duodenal resection (n = 8), pancreaticoduodenectomy (n = 2), and a subtotal radical resection (n = 1) in which residual lymph node disease was left in situ. Duodenal carcinoid was identified incidentally in the pathology specimen after surgery for another disease in the other 3 patients. A margin-negative (R0) resection was achieved in 15 (83%) of 18 patients. Two patients had a microscopically positive margin (R1 resection), including 1 patient

Table II. Pathologic characteristics of 37 duodenal carcinoid tumors

Characteristic	No. of Tumors (%)
Location*	
D1	30 (81)
D2	6 (16)
D3	1 (3)
Size	
Median	0.6 cm
Range	0.2-9.0 cm
<1.0 cm	26 (70)
1.0-1.9 cm	7 (19)
≥2.0 cm	4 (11)
Depth of Invasion	
Mucosa	3 (8)
Submucosa	26 (70)
Muscularis propria	2 (5)
Serosa/pancreas	3 (8)
Unknown	3 (8)
Immunohistochemistry (n = 17)	
Chromogranin-positive	16/16 (100)
Synaptophysin-positive	8/8 (100)
Neuron-specific enolase-positive	3/3 (100)
Gastrin-positive	2/4 (50)
Resection margin status* (n = 24 patients)	
R0	21 (88)
R1	2 (8)
R2	1 (4)

*D1, D2, and D3 = first, second, and third portions of the duodenum.

who had nests of carcinoid tumor at the distal margin of a segmental duodenal resection and 1 patient with a positive cephalad margin after a transduodenal local excision. One patient had gross residual retroperitoneal disease after an incomplete (R2) resection of bulky nodal metastases. At a median follow-up of 44 months (range, 1 to 258 months), 11 (61%) of the 18 patients who underwent surgical resection were alive and free of disease, including 4 patients with positive lymph nodes. Four (22%) of the 18 patients have died of causes unrelated to their carcinoid tumors. Two (11%) patients have had recurrences in regional lymph nodes detected by abdominal CT scan at 13 and 90 months after the initial surgical procedure (Table III). Both of these patients had metastatic carcinoid in regional lymph nodes at the time of the initial operation (complete R0 resection); they have not received further treatment for the lymph node recurrences and are being observed with serial imaging studies, with no evidence of disease progression to date. One patient (6%) is alive with residual nodal disease after a subtotal (R2) resection more than 21 years ago.

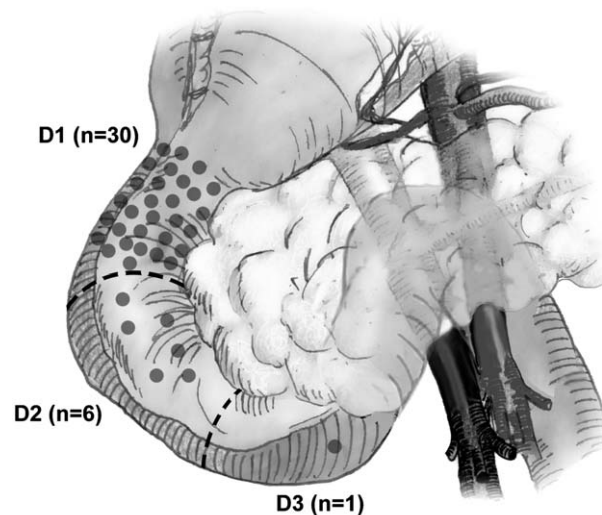


Fig 3. Location of 37 primary duodenal carcinoid tumors in 24 patients. The first, second, and third portions of the duodenum are labeled D1, D2, and D3, respectively.

At a median follow-up of 17 months (range, 1 to 258 months) for the entire cohort of 24 patients, the disease-specific survival rate was 100%. No patient has had distant metastases or the carcinoid syndrome.

DISCUSSION

Langhans is often credited with the first description of a gut carcinoid tumor in 1867⁷; however, it was Oberndorfer in 1907 who first used the term *karzenoide* to describe a carcinomalike small bowel tumor that behaved in a benign fashion.⁸ Although it is true that carcinoid tumors usually exhibit a more benign clinical behavior than epithelial carcinomas of the same anatomic site, the term *carcinoid* represents a diverse group of neoplasms arising from a variety of neuroendocrine cell types and characterized by variable biologic aggressiveness. Carcinoid tumors arise most often within the gastrointestinal tract and are classified traditionally according to their site of origin within the embryologic subdivisions of the gut: foregut, midgut, and hindgut. Given their greater incidence, midgut and hindgut carcinoids have been more extensively studied, and prognostic factors for recurrence and survival after treatment of these tumors have been defined, including tumor size, location, and depth of invasion.⁹⁻¹² Foregut carcinoid tumors, including those of the stomach, pancreas, and duodenum, are less well characterized but have been shown to exhibit substantial differences in clinical behavior depending on the organ of origin.¹³ Indeed, even carcinoid tumors arising

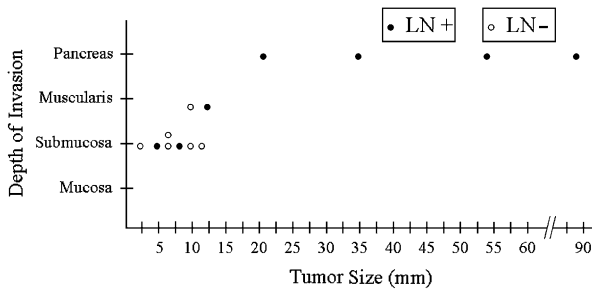


Fig 4. Scatter plot of patients who underwent radical excision with positive (LN +) or negative (LN -) lymph nodes according to the size and depth of invasion of the primary duodenal carcinoid tumor (n = 13).

within the same organ can have a variable biological course, demanding an individualized treatment strategy for each patient. This point is best illustrated in the case of gastric carcinoid tumors, for which 3 subtypes have been defined, each associated with a different biologic behavior.¹⁴

Duodenal carcinoid tumors are uncommon, and so the few large studies of patients with carcinoid tumors of the gastrointestinal tract have included very few patients with duodenal carcinoids.^{9,10} Management recommendations for duodenal carcinoids have, therefore, been extrapolated from the experience with midgut and hindgut carcinoids,^{9,10} as well as from previous studies that have included patients with periampullary carcinoid tumors or duodenal gastrinomas.^{2,9,15} Although the collective experience with periampullary carcinoid tumors is also of modest size, these tumors appear to have a distinctly different, more aggressive biology unrelated to tumor size or mitotic activity and should be considered separately from other duodenal carcinoid tumors.^{5,6} Likewise, gastrinomas arising in the duodenum, although frequently smaller than 1 cm, metastasize to regional lymph nodes in at least 60% of patients and, if left untreated, may metastasize to the liver.¹⁶⁻¹⁸ Duodenal gastrinomas also appear to exhibit a more aggressive biology than nonfunctional duodenal carcinoids and should be considered as a separate entity.

In the largest series of duodenal carcinoid tumors to date, Burke et al² at the Armed Forces Institute of Pathology studied 99 carcinoid tumors of the duodenum in an effort to identify pathologic features that predicted metastasis. The authors identified 3 pathologic features of the primary tumor as independent risk factors for metastasis: invasion of the muscularis propria, size greater than 2 cm, and the presence of mitotic figures. However, this study included 15 patients with ampullary tumors, 5 patients with gastrinomas and

ZES, and 20 patients in whom the exact location of the carcinoid tumor was not known. Given the heterogeneity of this patient population, it may be difficult to draw accurate conclusions about the biologic behavior of a typical, well-differentiated, nonperiampullary carcinoid tumor arising in the wall of the duodenum. In addition, Burke et al included the presence of regional lymph node metastases in their definition of metastatic disease; such patients were grouped with those who had metastatic disease in distant organs (ie, liver and lung).

More recently, Zyromski et al³ from the Mayo Clinic, in a retrospective study of 27 patients with duodenal carcinoid tumors (excluding gastrinomas), concluded that tumors smaller than 2 cm can be treated safely with local excision alone on the basis of the finding that no patient treated with this strategy had a recurrence. However, no patient with a nonperiampullary duodenal carcinoid tumor smaller than 2 cm underwent regional lymphadenectomy, so the rate of lymph node metastasis was not pathologically determined in these patients.

In our single-institution experience, all 4 patients who had duodenal carcinoid tumors 2 cm or larger had histologic evidence of tumor invasion beyond the muscularis propria and had lymph node metastases, in agreement with reports from other investigators.^{2,3} However, we also found that small tumor size and superficial depth of invasion do not reliably predict the absence of lymph node metastasis. Three patients with lymph node metastases had tumors smaller than 1.5 cm, and 2 of the 3 patients had tumors smaller than 1 cm and limited to the submucosa. The risk of lymph node metastasis is thus not limited to patients with tumors larger than 1 cm. Indeed, a previous report from Japan found that 13% of small (less than 1 cm) duodenal carcinoid tumors were associated with regional lymph node metastases.¹⁵

Because most patients with duodenal carcinoids do not have distant organ metastases, it is appropriate to question the clinical relevance of regional lymph node metastases. No patient in our series had liver metastases or died of progressive metastatic carcinoid tumor, including 1 patient who had a subtotal resection of bulky nodal disease more than 21 years ago. Further, the 2 patients who had recurrences in the regional lymph nodes 13 and 90 months after complete surgical resections are currently alive and well and being followed up by serial CT for their low-volume, clinically occult disease. Although other reports have suggested that patients may die of metastatic duodenal

Table III. Clinicopathologic characteristics and outcomes of 7 patients with regional lymph node metastases

Size of tumor(s), cm	Depth of invasion	No. of positive LNs/total LNs resected	Treatment	Recurrence	Status
9.0	Unknown	Unknown	Subtotal radical resection	Residual nodal disease	AWD 258 mo
5.5 and 1	Pancreas & mucosa	2/18	Subtotal duodenectomy, transduodenal excision	Nodal recurrence at 90 mo	AWD 110 mo
3.5	Pancreas	10/23	Pancreaticoduodenectomy	None	NED 52 mo
2.0	Pancreas	4/16	Pancreaticoduodenectomy	None	NED 101 mo
1.2	Muscularis propria	2/15	Segmental resection	None	NED 36 mo
0.8	Submucosa	2/30	Pancreaticoduodenectomy (incidental finding in specimen)	None	NED 2 mo
0.5	Submucosa	1/6	Segmental resection	Nodal recurrence at 13 mo	AWD 13 mo

LN, Lymph node; AWD, alive with disease; NED, no evidence of disease.

carcinoid tumors,^{2,3,13} the majority of patients with duodenal carcinoid tumors die of other causes, confirming the indolent nature of this disease. The impact of lymph node metastasis on survival is thus unclear and may be analogous to the experience with papillary thyroid cancer. Despite the high incidence of clinically and radiographically occult regional lymph node metastasis in “low-risk” patients with papillary thyroid cancer, the survival of these patients is unaffected by the extent of surgery performed, including regional lymph node dissection.^{19,20} The excellent survival rate is owing to the underlying tumor biology; lymph node metastases affect cervical recurrence rates but have little impact on survival duration. Duodenal carcinoid tumors appear to have a similar biologic behavior in which regional lymph node metastases are common but may represent little risk for the development of distant-organ metastases.

Despite the small numbers of patients in this and other series, it is important that we use the available data to develop general treatment recommendations for patients with duodenal carcinoids. First, irrespective of the size of the primary tumor, abnormal lymph nodes detected on pre-treatment imaging studies or at the time of surgery should be resected, because we do not have enough information about the natural history of unresected, grossly evident lymph node metastases to support their nonoperative management. This recommendation is based on the experience with sporadic duodenal gastrinomas, for which surgical resection of lymph node metastases appears to improve survival duration,¹⁶ and the experience with neuroendocrine carcinoma in general, for which surgical resection of clinically or

radiographically evident disease appears to improve outcome.²¹ The majority of our patients had pre-treatment imaging with abdominal CT, and although only 3 patients had suspicious lymphadenopathy, all 3 proved to have pathologically positive lymph nodes after surgical resection (positive predictive value of 100%). Second, for tumors 2 cm in diameter or larger, operative full-thickness excision and regional lymphadenectomy should be performed, even if the results of preoperative imaging are negative, given the high rate of lymph node metastasis with these tumors (4 of 4 cases in this series). The extent of duodenal resection should be based in part on the location of the tumor and the technical issues relating to duodenal reconstruction. For example, segmental duodenal resection with a side-to-side duodenojejunostomy is occasionally preferred (especially for tumors involving D3 or D4) over a local (full-thickness) excision if the options for duodenal closure will result in a tenuous suture line. A regional lymphadenectomy should include the lymph nodes in the following locations: (1) posterior to the duodenum and pancreatic head and anterior to the inferior vena cava, (2) posterolateral to the bile duct and portal vein, and (3) anterior to the common hepatic artery. Third, for tumors 1 to 2 cm in diameter, operative full-thickness excision is preferred. Tumors larger than 1 cm may be difficult to remove completely endoscopically and should be evaluated with EUS before an attempt at endoscopic resection owing to their potential for invasion beyond the submucosa (Fig 4).²² A full-thickness excision helps avoid the possibility of a positive deep margin with the potential for delayed identification of a

local recurrence because of the mucosa being closed over the remaining tumor. In patients who undergo laparotomy for primary tumor resection, a regional lymphadenectomy should be performed at that time. Although the benefit of regional lymphadenectomy, if one exists, will likely be in regional tumor control, information regarding the presence or absence of lymph node metastases in patients with tumors smaller than 2 cm may affect the risk of recurrence and thus the clinician's schedule of postoperative surveillance. Namely, node-positive patients should undergo continued radiographic surveillance even if the primary tumor measured less than 2 cm. Further, the small sample size in this and other series should convey a level of caution in the direct application of such natural history data to patient care. The experienced clinician will incorporate a variety of patient and tumor characteristics into the assessment of the risk for recurrence and then devise an appropriate follow-up strategy. Fourth, endoscopic excision of a primary duodenal carcinoid tumor seems most appropriate for tumors 1 cm or smaller.

Despite the discovery and characterization of carcinoid tumors nearly 100 years ago, the unique biology of these tumors remains a mystery. Although investigators are beginning to elucidate the molecular events in the malignant evolution of small bowel carcinoid tumors,²³ today we still rely on parameters such as tumor size and depth of invasion to estimate the likelihood of metastatic spread. Natural history data as presented in this manuscript are critically important to the development of appropriate treatment algorithms. Although we do not know why carcinoid tumors behave in such an unusual fashion, their biologic behavior is becoming more accurately defined, allowing for the development of stage-specific treatment recommendations.

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DISCUSSION

Dr Henning Dralle (Halle, Germany). I have 2 questions for this excellent study on a remarkable number of duodenal carcinoid tumors. You mentioned 2 terms, radical and local excision. Please explain a little

more about what the differences were from the surgical point of view. The other question would be, did the exact location, supra- or infrapapillary, have an influence on your surgical decision making?

Dr John Mullen. The only difference between a local excision and a radical excision (as defined in this report) is whether a regional lymphadenectomy was performed. We used the term *local excision* if regional lymph nodes were not removed, and we used the term *radical excision* to indicate that regional lymph nodes were removed with the primary tumor specimen.

First, the management of periampullary carcinoid tumors is not addressed in this study, because these tumors have been shown to exhibit a more aggressive behavior than other duodenal carcinoid tumors and thus may warrant a more extensive surgical resection. The management of nonampullary duodenal carcinoid tumors in proximity to the ampulla is dictated by the size and depth of invasion of the primary tumor as well as the general health of the patient. For tumors smaller than 1 cm in diameter and limited to the mucosa or submucosa, endoscopic excision is reasonable. If this is not technically possible, a local excision is appropriate, especially for the patient with significant medical comorbidities in whom pancreaticoduodenectomy is best avoided. For tumors larger than 2 cm with invasion of the muscularis propria, a pancreaticoduodenectomy with regional lymphadenectomy should be performed given the significant risk of lymph node metastases with such tumors as well as the technical concerns of resecting a tumor larger than 2 cm in proximity to the ampulla.

Dr Janice L. Pasiaka (Calgary, Alberta, Canada). You said you reviewed this according to the World Health Organization classification. Were these all well-differentiated neuroendocrine tumors or well-differentiated endocrine carcinomas? Do you have any data on the

proliferative index, ie, the Ki-67 index, in these patients and did that make any difference in terms of their ability to metastasize or recur?

Dr John Mullen. We did not look at proliferative indices. All of the tumors in this study were well-differentiated carcinoids; we excluded atypical carcinoids and neuroendocrine carcinomas.

Dr Subash Patel (Chicago, Illinois). In looking at these 24 patients that had histologically confirmed duodenal carcinoid tumor, did the presence of other neuroendocrine tumors, eg, MEN-1, have any influence on the presence or absence of lymphadenopathy? Second, did the recurrence of disease have any impact on patient's quality of life?

Dr John Mullen. Only 1 patient had another neuroendocrine neoplasm, a rectal carcinoid tumor, which was managed by local excision. Nine patients had a history of another synchronous or metachronous malignancy, most commonly an adenocarcinoma.

In answer to your second question, 2 patients have recurred in regional lymph nodes, 1 after a relatively short follow-up and another after more than 7 years. Both of these patients underwent radical resections with extensive regional lymphadenectomies. Their lymph node recurrences were small and asymptomatic and have not progressed on serial imaging studies; these patients have not undergone reoperation.

Dr Orlo H. Clark (San Francisco, California). Because these are foregut carcinoids, did you look for either menin germline or somatic mutations?

Dr John Mullen. No, we did not perform routine genetic analyses on our patients to exclude those patients with a possible subclinical diagnosis of multiple endocrine neoplasia. However, all the patients were of an age at which the phenotypic expression of MEN-1 should have been apparent.