

Lymph Nodes and Survival in Pancreatic Neuroendocrine Tumors

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Hypothesis: Lymph node metastases decrease survival in patients with pancreatic neuroendocrine tumors (pNETs).

Design: Prospective database searches.

Setting: National Institutes of Health (NIH) and Stanford University Hospital (SUH).

Patients: A total of 326 patients underwent surgical exploration for pNETs at the NIH (n=216) and SUH (n=110).

Main Outcome Measures: Overall survival, disease-related survival, and time to development of liver metastases.

Results: Forty patients (12.3%) underwent enucleation and 305 (93.6%) underwent resection. Of the patients who underwent resection, 117 (35.9%) had partial pancreatectomy and 30 (9.2%) had a Whipple procedure. Forty-one patients also had liver resections, 21 had wedge resections, and 20 had lobectomies. Mean follow-up was 8.1 years (range, 0.3-28.6 years). The 10-year overall survival for patients with no metastases or

lymph node metastases only was similar at 80%. As expected, patients with liver metastases had a significantly decreased 10-year survival of 30% ($P < .001$). The time to development of liver metastases was significantly reduced for patients with lymph node metastases alone compared with those with none ($P < .001$). For the NIH cohort with longer follow-up, disease-related survival was significantly different for those patients with no metastases, lymph node metastases alone, and liver metastases ($P < .001$). Extent of lymph node involvement in this subgroup showed that disease-related survival decreased as a function of the number of lymph nodes involved ($P = .004$).

Conclusions: As expected, liver metastases decrease survival of patients with pNETs. Patients with lymph node metastases alone have a shorter time to the development of liver metastases that is dependent on the number of lymph nodes involved. With sufficient long-term follow-up, lymph node metastases decrease disease-related survival. Careful evaluation of number and extent of lymph node involvement is warranted in all surgical procedures for pNETs.

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PANCREATIC NEUROENDOCRINE tumors (pNETs) are clinically rare and comprise a heterogeneous group of neoplasms.^{1,2} Pancreatic neuroendocrine tumors can be classified as hormonally functional or nonfunctional.³ Despite recent advances in medical therapies for pNETs,⁴⁻⁶ surgical resection remains the only curative therapy.^{3,6,7} Pancreatic neuroendocrine tumors are more indolent than exocrine pancreatic cancer; however, most patients with metastatic tumor ultimately die of their disease.⁸⁻¹¹

See Invited Critique at end of article

Except for insulinoma, pNETs are malignant in 50% to 90% of cases.³ Although

the significance of hepatic metastases on patient survival is well established,^{8,11-22} the importance of lymph node metastases on survival is unclear. This is in marked contrast to results with a number of nonendocrine gastrointestinal tumors (eg, pancreatic, esophageal, gastric, and colon)²³⁻²⁶ and other endocrine tumors (eg, follicular or medullary thyroid)^{27,28} in which the presence and number of lymph node metastases have important prognostic significance and influence the surgical approach.

Prior studies have reported that the presence of lymph node metastases is not a significant determinant of survival,^{19,20,29-43} not associated with recurrence after resection,^{44,45} or not related to disease progression.⁴⁶ In contrast, others report that lymph node involvement adversely affects survival and is associated with recurrence after resection or progres-

sive disease.⁴⁷⁻⁵¹ As such, the true effect of lymph node involvement in pNETs on patient survival remains poorly understood and controversial. This lack of knowledge has clinical implications because the presence of lymph node metastases could affect the surgical approach and the follow-up if the lymph nodes were found to have prognostic significance. Consequently, we sought to further define the significance of lymph node metastases on survival of patients with pNETs by analyzing results from a large number of patients with long-term follow-up.

METHODS

Two prospective databases of patients with functional or nonfunctional pNETs who underwent surgical exploration for cure as previously described⁵² were reviewed. In one, surgery was performed at Stanford University Hospital (SUH) since 1996, and in the other, at the National Institutes of Health (NIH) since 1981. In total, 326 patients underwent operations for pNETs. Two hundred sixteen operations were performed at the NIH and 110 at the SUH. The main outcome measures were overall survival, disease-related survival, and time to development of liver metastases.

The diagnosis of hormonally functional and nonfunctional tumors has been previously described in detail.^{3,53,54} After their diagnosis was confirmed, patients underwent detailed localization imaging studies as previously described.^{52,55-58} Patients were invited to undergo surgery to remove the tumor if they had no comorbid medical condition that markedly limited life expectancy, had an apparently operable tumor, and, if multiple endocrine neoplasia 1 was present, had a tumor of 2.5 cm or greater in diameter.^{11,22,55} Patients with potentially completely resectable liver metastases were also included as previously described.⁸ Multiple endocrine neoplasia 1 was established by assessing plasma hormone levels (eg, parathyroid hormone [intact and mid-molecule], prolactin, insulin, proinsulin, and glucagon), serum calcium (eg, ionized and total), and glucose, as well as from personal and family history.^{55,59,60}

The operative techniques have been previously described.^{11,15,22,55,61} Briefly, pNETs in the head of the pancreas were enucleated unless they were large (>3 cm) or had bulky lymph node metastases, in which case a Whipple pancreaticoduodenectomy was performed, duodenal tumors were excised with a full-thickness duodenal excision, and tumors in the body and tail were excised with a distal pancreatectomy plus splenectomy. For duodenal tumors or tumors in the head of the pancreas that were enucleated, a systematic adjacent lymph node sampling was performed. Postoperatively, patients underwent evaluation for disease-free status immediately after surgery (ie, 2 weeks after resection), within 3 to 6 months after resection, and then yearly.^{11,15,22,55,61} A recurrence after resection was defined as previously reported.⁵⁵

All continuous variables were reported as mean (SEM). Survival analysis was performed using the Kaplan-Meier method and 2-group comparisons using log-rank tests. Proportions were compared statistically by the Fisher exact test. Statistical analysis was performed by means of the SAS statistical software package (SAS Institute, Inc), and significance was defined as a 2-tailed $P < .05$.

RESULTS

Three hundred twenty-six patients were analyzed, and the complete demographic characteristics are listed in

Table 1. Demographic Characteristics of the 326 Study Patients

Characteristic	Value
Male sex, No. (%)	178 (54.6)
Race, No. (%)	
White	171 (79.2) ^a
Black	34 (15.7) ^a
Hispanic	8 (3.7) ^a
Asian	3 (1.4) ^a
Age at diagnosis, mean (SEM) [range], y	45.7 (0.8) [14-69] ^a
Age at surgery, mean (SEM) [range], y	49.9 (9.9) [14-94]
Type of pNET, No. (%)	
Nonfunctional	115 (35.3) ^b
Functional	250 (76.7)
Gastrinoma	218 (66.9)
Insulinoma	26 (8.0)
VIPoma	3 (0.9)
Somatostatinoma	1 (0.3)
Glucagonoma	3 (0.9)
Other ^c	8 (2.5)
Presenting symptoms, No. (%)	
Pain	165 (76.4) ^a
Other functional pNET symptoms ^d	78 (36.1) ^a
MEN1 present	64 (19.6)
Duration of functional pNET symptoms at diagnosis, mean (SEM) [range], y	5.8 (0.5) [0.01-34.60] ^a
Hormone elevation, fold increase, median (range)	6.4 ^{a,e} (1.1-5500) ^a

Abbreviations: MEN1, multiple endocrine neoplasia 1; pNET, pancreatic neuroendocrine tumor; VIPoma, vasoactive intestinal peptide-producing tumor.

^aData available only for the National Institutes of Health cohort (n = 216); data from Stanford University Hospital were not available.

^bThirty-nine patients with MEN1 with functional pNETs also had nonfunctional pNETs identified.

^cOther functional syndromes include ectopic Cushing syndrome (n = 5), carcinoid syndrome (n = 2), and parathyroid hormone-related peptide-secreting tumor (n = 1).

^dOther functional pNET symptoms include Zollinger-Ellison syndrome (eg, gastrointestinal reflux disease or diarrhea), insulinoma hypoglycemic symptoms, carcinoid syndrome, or ectopic Cushing syndrome.

^eFasting hormone level elevation over normal preoperatively in patients with functional pNETs.

Table 1. The primary tumor was localized preoperatively in 210 patients (64.4%) (**Table 2**). Primary tumors and distant metastases were seen in 106 patients (32.5%), whereas lymph node metastases were localized in 85 (26.1%). Fifty-two patients (16.0%) had limited liver metastases. Positive results were found in 51.9% of patients by computed tomography, 27.1% by abdominal ultrasonography, and 56.9% by magnetic resonance imaging. Somatostatin-receptor scintigraphy accurately identified primary tumors 75.3% of the time, whereas hormonal gradient studies revealed positive results in 79.5% of patients in which it was used.

Surgical findings are summarized in **Table 3**. Primary tumors were located in the pancreas (112 [34.4%]), duodenum (178 [54.6%]), and other locations (34 [10.4%]). Fifty-eight patients (17.8%) had multiple primary tumors. The mean primary tumor size was 2.6 cm (range, 0.3-15 cm). For the Stanford cohort, the mean sizes of the primary tumors were 2.5 cm for patients without metastases, 4.6 cm for patients with lymph node metastases, 4.5 cm for patients with liver metastases, and 6.6 cm for patients with lymph node and liver metastases.

Table 2. Preoperative Tumor Features Assessed by Localization Studies

Characteristic	Value
Tumor extent, No. (%)	
Primary localized	210 (64.4)
Primary and metastases	106 (32.5)
Possible lymph node metastases	85 (26.1)
Liver metastases, limited ^a	52 (16.0)
Liver metastases in 1 lobe	4 (1.8) ^{a,e}
Liver metastases in >1 lobe	7 (3.2) ^{a,e}
Primary tumor, mean (SEM) [range]	3.1 (2.4) [0.3-15]
Preoperative primary location, No. (%) ^b	
Pancreatic head or duodenum ^c	199 (61.0)
Pancreatic body	32 (9.8)
Pancreatic tail	59 (18.1)
Other ^d	7 (2.1)
Preoperative study positive, No. (%) ^e	
CT	110/212 (51.9)
Ultrasonography	55/203 (27.1)
MRI	91/160 (56.9)
Any conventional imaging study	140/216 (64.8)
Selective angiogram	111/201 (55.2)
SRS	116/154 (75.3)
Hormonal gradient positive ^f	128/161 (79.5)

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; SRS, somatostatin-receptor scintigraphy.

^aLimited liver metastases refers to patients without diffuse liver metastases and liver metastatic disease thought to be completely resectable.

^bNine patients with multiple endocrine neoplasia 1 had multiple pancreatic neuroendocrine tumors identified preoperatively.

^cImaging studies frequently could not clearly differentiate between the pancreatic head or duodenum.

^dOther tumor locations include primary pancreatic neuroendocrine tumor localized in the heart, lung, liver, ovary, common bile duct, and mesentery.

^eData are available only for the National Institutes of Health cohort (n = 216); data from Stanford University Hospital were not available.

^fRefers to positive hormonal gradient with portal venous sampling or intra-arterial secretin injection (gastrinoma) or calcium (insulinoma) with hepatic venous sampling.

ses. At initial surgery, 181 patients (55.5%) had metastatic disease, of whom 171 (52.5%) had lymph node involvement and 41 (12.6%) had liver metastases. Patients had a mean of 4.4 lymph nodes positive for tumor (range, 0-58). A total of 155 patients (47.5%) did not have positive lymph nodes, 68 (20.9%) had 1 positive lymph node, 45 (13.8%) had 2 positive lymph nodes, 40 (12.3%) had 3 to 5 positive lymph nodes, 11 (3.4%) had 6 to 10 positive lymph nodes, 4 (1.2%) had 11 to 20 positive lymph nodes, and 3 (0.9%) had more than 20 positive lymph nodes. Within the Stanford cohort, 30 patients (27.3%) had a lymph node ratio greater than 0.20 and 59 (53.6%) had a ratio of 0.20 or less. The extent of tumor at initial surgery was also analyzed. At the time of surgery, 145 patients (44.5%) had only a primary tumor, 154 (47.2%) had a primary tumor with lymph node involvement, 41 (12.6%) had synchronous liver metastases with or without lymph node metastases, and 17 (5.2%) had only lymph node involvement.

Surgical procedure and results, follow-up, and complications are summarized in **Table 4**. There were 78 stage I (23.9%), 68 stage II (20.9%), 139 stage III (42.6%), and 41 stage IV tumors (12.6%). Of the 326 patients who underwent surgical exploration, 318 (97.5%) had tumors enucleated or resected. Eight pa-

Table 3. Surgical Findings for the 326 Study Patients

Characteristic	Value ^a
Primary pNET location and size at surgery, No. (%)	
Location	
Pancreas	112 (34.4)
Duodenum	178 (54.6)
Other	34 (10.4) ^b
>1 Primary tumor	58 (17.8) ^c
Primary tumor size, mean (SEM) [range], cm	2.6 (2.4) [0.3-15]
Mean for primary only	2.5 ^d
Mean for primary plus lymph node metastases	4.6 ^d
Mean for primary plus liver metastases	4.5 ^d
Mean for primary plus lymph node and liver metastases	6.6 ^d
Metastases found at surgery, No. (%)	
Any metastases found	181 (55.5)
Lymph node involvement	171 (52.5)
Liver metastases, initial surgery	41 (12.6)
Lymph node metastases	
No. positive per patient, mean (SEM) [range]	4.4 (3.6) [0-58]
No. of positive lymph nodes per patient	
0	155 (47.5)
1	68 (20.9)
2	45 (13.8)
3-5	40 (12.3)
6-10	11 (3.4)
11-20	4 (1.2)
>20	3 (0.9)
Lymph node ratio	
>0.20	30 (27.3) ^d
0-0.20	59 (53.6) ^d
Tumor extent at surgery, No. (%)	
Primary only	145 (44.5)
Primary plus lymph node involvement	154 (47.2)
Liver involvement with or without lymph node involvement	41 (12.6)
Lymph node metastases only ^e	17 (5.2)

Abbreviation: pNET, pancreatic neuroendocrine tumor.

^aThe number of patients undergoing surgery was used as 100% in this table.

^bOther refers to primary pNETs located in the ovary, liver, mesentery, heart, lymph node, and lung.

^cMore than 1 primary pNET primarily occurred in patients with multiple endocrine neoplasia 1 (n = 45) or with multiple functional pNETs (n = 9).

^dData are available only for the Stanford University Hospital cohort (n = 110); the National Institutes of Health data were not available.

^ePatients from the National Institutes of Health cohort with gastrinoma involving lymph nodes and no identifiable primary as previously described.⁶¹

tients had either unresectable disease or a negative laparotomy result. Forty patients (12.3%) had enucleation alone. A total of 178 (54.6%) had tumor excised from the duodenum. A total of 305 patients (93.6%) underwent resection, 117 (35.9%) had distal pancreatectomy and 30 (9.2%) had a Whipple pancreaticoduodenectomy. Forty-one patients also had liver resections, of which 21 were wedge resections and 20 were hepatic lobectomies. In all the patients, 1 surgical death occurred, and 66 (20.2%) had postoperative complications. At last follow-up, 249 of the 326 patients (76.4%) were alive, and 77 deaths (23.6%) had occurred, of which 51 (15.6%) were disease related. The mean duration from surgery to disease-related death was 6.2 years (range, 0.5-28.6 years). The time from diagnosis to last follow-up averaged 13 years (range, 0.9-44.4 years), and

the time from surgery to last follow-up averaged 8.1 years (range, 0.1-28.6 years). During the follow-up period, 68 patients (20.9%) developed liver metastases. The mean time to developing liver metastases was 4.1 years (range, 0.2-18 years). One hundred fourteen patients (35.0%) developed new lesions during follow-up. In the NIH cohort of 216 patients, 32 patients (14.8%) underwent other antitumor treatments during the follow-up period, including chemotherapy in 21 (9.7%), somatostatin analogues in 20 (9.3%), and interferon alfa or peptide receptor radionuclide therapy in 16 (7.4%).^{55,62}

A comparison of results in surgical patients with primary pNETs only, primary plus lymph nodes only, or liver metastases is given in **Table 5**. A total of 145 patients had primary-only lesions, 140 had primary and lymph node involvement, and 41 had primary and liver metastases. The mean postoperative follow-up was 7.5 years (range, 0.3-26.5 years) for patients with primary-only lesions, 10.1 years (range, 0.3-28.6 years) for patients with primary and lymph node involvement, and 5.0 years (range, 0.6-12.2 years) for patients with liver metastases. At last follow-up for the primary-only group, 130 of the 145 patients (89.7%) were alive, 15 (10.3%) died of other causes, and no patients had disease-related deaths. In the primary and lymph node group of 140 patients, 107 patients (76.4%) were alive at last follow-up, 33 (23.6%) died of other causes, and 27 (19.3%) had disease-related deaths. Disease-related deaths were significantly greater in the primary plus lymph node group (19.3%) compared with the primary-only group (0%, $P = .005$). The primary and liver metastases group had 12 patients (29.3%) alive at last follow-up and 29 patients (70.7%) dead, all of disease-related causes. This finding was significantly greater than the primary-only group and the primary plus lymph node group ($P < .001$). All 41 patients in the primary and liver metastases group developed disease recurrence, and 28 patients (68.3%) developed new liver lesions after initial resection. This finding contrasted with the primary-only group, in which 12 patients (8.3%) developed new lesions and 3 (2.1%) developed metachronous liver metastases. The primary and lymph node group had intermediate results, with 61 patients (43.6%) developing new lesions and 37 (26.4%) developing metachronous liver metastases. Each group was significantly different from the other groups ($P < .001$). At 10 years, the probability of developing liver metastases was 100% for the primary and liver metastases group, 30% for the primary and lymph node group, and 1% for the primary-only group. The 3 groups were significantly different from each other ($P < .001$).

For the combined cohort, the overall survival was not significantly different between patients with lymph node involvement and those without lymph node metastases (**Figure, A**). Furthermore, we analyzed the databases for functional status of pNETs (functional vs nonfunctional). No difference was found in overall survival or liver metastases-free survival between patients with functional tumors and those with nonfunctional tumors. We compared the behavior of the duodenal and pancreatic gastrinomas and found a similar percentage with lymph

Table 4. Type and Result of Surgery, Follow-up, and Complications

Result	Value
pNET stage, No. (%)	
I	78 (23.9)
II	68 (20.9)
III	139 (42.6)
IV	41 (12.6)
Tumor resected or enucleated, No. (%)	318 (97.5) ^a
Primary only	145 (44.5) ^b
With lymph node metastases	171 (52.5)
With liver metastases	41 (12.6)
Type of primary surgery, No. (%)	
Enucleation	40 (12.3) ^c
Resection	305 (93.6)
Duodenal tumor excision	178 (54.6)
Partial pancreatectomy	117 (35.9)
Whipple pancreaticoduodenectomy	30 (9.2)
Liver resection, No. (%)	
Wedge resection	21 (6.4)
Lobectomy	20 (6.1) ^d
Surgical complications, No. (%)	
Surgical death	1 (0.003)
Complications	66 (20.2) ^e
Status at last follow-up, No. (%)	
Alive	249 (76.4)
Dead	77 (23.6)
Disease-related death	51 (15.6)
Time from surgery to disease-related death, mean (SEM) [range], y	6.2 (3.4) [0.5-28.6]
Duration of follow-up, y	
Time from surgery to last follow-up, mean (SEM) [range], y	8.1 (4.5) [0.1-28.6]
Time from diagnosis to last follow-up, mean (SEM) [range], y	13.0 (0.5) [0.9-44.4] ^g
Liver metastases during follow-up	
No. developing liver metastases	68 (20.9)
Time to development, mean (SEM) [range], y	4.1 (2.1) [0.2-18]
No. developing new lesions during follow-up	114 (35.0)
Other antitumor treatment after initial surgery, No. (%)	
Chemotherapy	21 (9.7) ^g
Somatostatin analogues	20 (9.3) ^g
Other ^f	16 (7.4) ^g

Abbreviation: pNET, pancreatic neuroendocrine tumor.

^aPercentage based on 326 patients who underwent surgical exploration. Eight patients had either unresectable disease or negative laparotomy (with gastrinomas).

^bThirty-one patients with liver metastases also had lymph node metastases.

^cTwenty-nine patients had both enucleation of pancreatic tumors and resections of other pNETs.

^dIncludes trisegmentectomy (n = 2), hepatic lobe resection (n = 19), and segmentectomy (n = 6).

^eThere was 1 postoperative death secondary to a pulmonary embolus. Complications include postoperative pancreatitis (n = 9), abscess (n = 5), bleeding (n = 2), wound infection (n = 12), bile duct injury (n = 1), pulmonary embolus or deep venous thrombosis (n = 7), leak at pancreaticojejunostomy (n = 8) and ischemic bowel (n = 2), pancreatic fistula (n = 12), bile leak (n = 3), prolonged ileus (n = 4), and pseudomembranous colitis (n = 1).

^fPatients treated with interferon alfa (n = 14) or peptide receptor radionuclide therapy (n = 2).

^gData are available only for the National Institutes of Health cohort (n = 216); data from the Stanford University Hospital were not available.

node metastases (71.2% vs 76.4%, $P = .26$); however, they differed markedly in the percentage that had liver metastases at any time (initially or during follow-up) (17.1%

Table 5. Comparison of Results in Surgical Patients With Primary pNET Only, Primary Plus Lymph Nodes Only, or Liver Metastases

Characteristic	Primary Only (n = 145)	Primary and Lymph Node Only (n = 140)	Primary and Liver Metastases (n = 41)
Time of postoperative follow-up, mean (SEM) [range], y	7.5 (4.9) [0.3-26.5]	10.1 (4.4) [0.3-28.6]	5.0 (2.9) [0.6-12.2]
Current status, No. (%)			
Alive, last follow-up	130 (89.7)	107 (76.4)	12 (29.3)
Dead from any cause	15 (10.3)	33 (23.6)	29 (70.7)
Disease-related death	0 ^b	27 (19.3) ^b	29 (70.7) ^b
Developed new lesions, No. (%)			
Developed any new lesions	12 (8.3) ^b	61 (43.6) ^b	41 (100.0) ^b
Developed new liver metastases	3 (2.1) ^b	37 (26.4) ^b	28 (68.3) ^b
Probability of developing liver metastases at 10 y	1 ^b	30 ^b	100 ^b
1-2 Lymph nodes involved	...	25 ^b	...
>2 Lymph nodes involved	...	35 ^b	...
Probability of overall survival at 10 y	80	80	30 ^b
Age at surgery, mean (SEM), y	51.9 (9.9)	47.5 (9.8)	48.3 (6.3)
Male sex	85 (58.6)	68 (55.3)	26 (63.4)
Time from diagnosis to surgery, mean (SEM), y ^a	12.6 (0.7)	13.8 (0.7)	8.6 (1.3)
Primary pNET size, cm	2.0 (0.2)	2.1 (1.5)	3.2 (1.2)
Preoperative characteristics, No. (%) ^a			
Hormonal marker increased >x-fold, functional pNET	17 (11.7)	50 (40.7)	5 (12.2)
MEN1 present	18 (12.4)	41 (33.3)	5 (12.2)
pNET characteristic			
Nonfunctional	48 (33.1)	42 (34.1)	9 (22.0)
Largest pNET in pancreatic tail ^a	9/25 (36.0)	21/45 (46.7)	6/11 (54.5)

Abbreviations: MEN1, multiple endocrine neoplasia 1; pNET, pancreatic neuroendocrine tumor.

^aData are available only for the National Institutes of Health cohort (n = 216); data from Stanford University Hospital were not available.

^bStatistically significant difference from other 2 groups by the Fisher exact test ($P < .01$).

vs 45.3%, $P < .001$), the percentage that had liver metastases initially (1.8% vs 17.0%, $P < .001$), and the percentage that developed liver metastases during follow-up (16.4% vs 28.1%, $P = .001$). Furthermore, they differed in the percentage of patients with a duodenal or pancreatic gastrinoma who had a disease-related death (9.2% vs 27.4%, $P = .004$).

We analyzed the time to development of liver metastases for all patients with pNETs with and without lymph node metastases and found a significant difference ($P < .001$) between these 2 groups (Figure, B). This difference in time to development of liver metastases was related to the number of lymph nodes involved ($P < .001$) (Figure, C). Because of the longer mean follow-up time for the NIH cohort (11 years compared with 2.7 years for the SUH cohort), we performed an analysis of disease-related survival for the NIH subgroup (Figure, D) and found significant differences among patients with no metastases, lymph node metastases only, and liver metastases ($P < .001$). We then looked at the extent of lymph node involvement in the subgroup analysis (Figure, E) and found that disease-related survival decreases as a function of the number of lymph nodes involved with tumor ($P = .004$).

The 10-year overall survival probabilities for patients with primary-only tumors or positive lymph nodes were indistinguishable at 80%. However, patients with liver metastases had a 10-year survival probability of 30% ($P < .001$). Although few patients free of lymph node involvement developed liver metastases postoperatively, the 10-year probability of developing liver metastases for the lymph node–positive group was ap-

proximately 30%. The 10-year probability of developing liver metastases for patients with 1 to 2 positive lymph nodes was approximately 25%, whereas that for patients with greater than 2 positive lymph nodes was approximately 35%.

COMMENT

Yu et al²⁰ conducted the first large, prospective study describing the long-term natural history of gastrinomas and concluded that the 10-year survival rate for patients without liver metastases was 96%; single-lobe metastases, 78%; bilobar metastases, 80%; and diffuse metastases, 16%. In various studies,^{3,63,64} 50% to 80% of patients with advanced disease from malignant pNETs have died within 5 years of tumor progression. A number of ensuing studies¹²⁻²⁰ of patients with pNETs established that survival was primarily determined by the presence and/or development of liver metastases. As a result, subsequent studies^{22,65} demonstrated that early resection of potentially malignant pNETs decreased the development of liver metastases and increased survival. In addition, studies^{15,18,30} have found that aggressive surgical resection in the setting of advanced disease improved survival. The present study also found that localized, surgically resectable liver metastases decrease survival. Surgical resection of liver metastases from pNETs has been advocated; however, disease recurs and survival is adversely affected with long follow-up. Furthermore, in this group, all deaths were disease related.

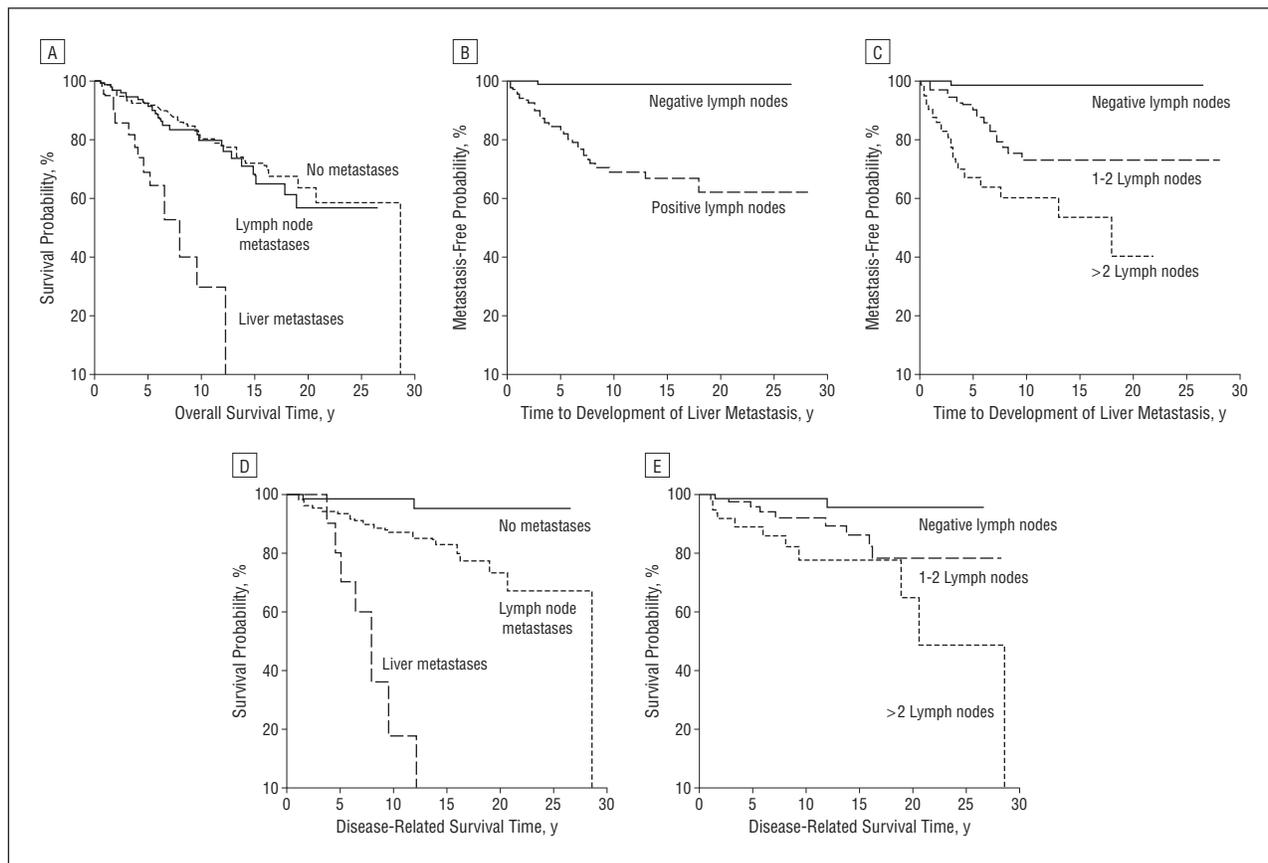


Figure. Kaplan-Meier plots. A, Overall survival; B and C, time to development of liver metastases; and D and E, disease-related survival. For National Institutes of Health (NIH) and Stanford University Hospital patients (N=326), overall survival was not significantly different between patients with lymph node involvement and those without metastases (A). As a result, we analyzed the time to development of liver metastases and found a significant difference ($P < .001$) between the 2 groups (B). This difference in time to development of liver metastases was related to the number of lymph nodes involved ($P < .001$) (C). Because of the longer follow-up time for the NIH cohort (n=216), we performed an analysis of disease-related survival on this subgroup (D) and found significant differences among patients with no metastases, lymph node metastases only, and liver metastases ($P < .001$). We then looked at the extent of lymph node involvement in the subgroup analysis (E) and found that disease-related survival decreases as a function of the number of lymph nodes involved with tumor ($P = .004$).

In contrast to the well-established effect of liver metastases on survival in patients with pNETs, the effect of lymph node metastases on patient survival is controversial and unclear. A single-institution, prospective study by Weber et al¹⁹ demonstrated that lymph node metastases alone had no significant effect on survival. Similarly, a multicenter study by Cadiot et al⁶⁶ concluded that the presence of lymph node metastases was not associated with increased risk of metachronous liver metastases or survival. In a recent analysis of the Surveillance, Epidemiology, and End Results database from 1980 to 2004 in 2350 patients with pNETs, the presence of lymph node involvement without liver metastases did not affect survival.⁴² A number of other studies^{19,20,29-41,43} also concluded that lymph node metastases do not significantly decrease survival in patients with pNETs. Furthermore, a recent study⁴⁵ suggests that lymph node metastases in patients with pNETs do not increase recurrence rates after surgical resection.

Conversely, some studies have reported that lymph node involvement can be an important prognostic factor in pNETs; however, in some of these studies, it is not apparent whether the analysis included only lymph node metastases or rather lymph node and liver metastases. In 2005, Tomassetti et al⁴⁷ reported that lymph node me-

tastases decreased survival, and in 2008, Bettini et al⁴⁸ reported that nodal metastases were significantly associated with mortality with a prognostic significance similar to liver metastases and Ki-67 expression. In 2011, Boninsegna et al⁴⁹ found that a lymph node ratio of 0 to 0.2 did not have a significant prognostic effect on recurrence; however, a higher lymph node ratio (ie, >0.2) was a significant predictor of recurrence, whereas the simple data of lymph node involvement and number of positive nodes were not significant in predicting recurrence. Because of these disparate results from different studies in the literature and the potential importance to patients with pNETs of clarifying this issue to their surgical management and to their subsequent follow-up and prognosis, we undertook the present study.

In the present study, when results from both surgical series were combined, the overall survival was not significantly different between patients with and those without lymph node metastases. However, the patients with lymph node metastases had a shorter time to development of metachronous liver metastases than those without metastases ($P < .001$), and this difference was related to the number of lymph nodes involved ($P < .001$). This finding has important potential implications for overall survival because either the develop-

ment or presence of liver metastases has been shown in numerous studies^{3,19,20,63,64,66} to be the most important predictor of survival. However, the development or presence of liver metastases may not be apparent on short-term follow-up but may become manifested later with longer follow-up.^{22,65} To examine this possibility, we performed a subset analysis on the NIH patients because they had a follow-up 4 times longer than the SUH group (ie, 11 vs 2.7 years). This subgroup analysis demonstrated that with this longer follow-up significant differences occurred in disease-related survival among patients with no metastases, lymph node metastases only, and liver metastases ($P < .001$). Furthermore, the decrease in disease-related survival was related to the number of lymph nodes involved with tumor ($P = .004$).

In terms of surgical management, our results support the conclusion that all patients with potential malignant pNETs at surgical exploration should undergo routine removal of lymph nodes in the peritumoral area and that each should be carefully examined histologically for metastatic disease. Our study does not define the exact number of nodes that should be removed routinely, although we found the number of positive lymph nodes had additional prognostic significance. This finding suggests that this may be an important area of future study to attempt to define the optimum lymph node number that should be excised. In contrast to the surgical approach now widely used in many other malignant tumors, the inclusion of routine lymph node removal with pNETs would be a marked change from the standard surgical approach that is used in patients without gastrinoma. In patients with Zollinger-Ellison syndrome, lymph node primary gastrinomas have also been described, although their existence is controversial.⁶¹ This finding has led to the suggestion that lymph nodes be routinely removed in patients with gastrinoma.⁶¹ However, in the other pNETs that are potentially malignant (ie, nonin-sulinoma), the tumor is frequently enucleated or removed by a limited resection without lymph node harvest, and therefore our study suggests that important prognostic information is lost.

Our study has important implications for the follow-up of patients with pNETs after surgery. Currently, the tumor markers commonly used have not been clearly established (eg, serum chromogranin A or serum pancreatic polypeptide), and subsequent imaging studies are expensive. Our results provide an additional prognostic marker that allows better stratification of patients for follow-up. Furthermore, chemotherapy and new biological treatments may be applicable to patients with advanced nodal disease after radical resection.⁶⁷⁻⁶⁹ These results, as well as those from previous studies, suggest that lymph node metastases from pNETs place patients at high risk for the development of recurrence with subsequent metachronous liver metastases and consequently decreased disease-related survival. These patients may benefit from more aggressive treatment.

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