PAPER

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 described[52] 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**. 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 metasta-

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.

[a] Data available only for the National Institutes of Health cohort (n = 216); data from Stanford University Hospital were not available.

[b] Thirty-nine patients with MEN1 with functional pNETs also had nonfunctional pNETs identified.

[c] Other functional syndromes include ectopic Cushing syndrome (n = 5), carcinoid syndrome (n = 2), and parathyroid hormone–related peptide-secreting tumor (n = 1).

[d] Other functional pNET symptoms include Zollinger-Ellison syndrome (eg, gastrointestinal reflux disease or diarrhea), insulinoma hypoglycemic symptoms, carcinoid syndrome, or ectopic Cushing syndrome.

[e] Fasting hormone level elevation over normal preoperatively in patients with functional pNETs.

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.
[a] Limited liver metastases refers to patients without diffuse liver metastases and liver metastatic disease thought to be completely resectable.
[b] Nine patients with multiple endocrine neoplasia 1 had multiple pancreatic neuroendocrine tumors identified preoperatively.
[c] Imaging studies frequently could not clearly differentiate between the pancreatic head or duodenum.
[d] Other tumor locations include primary pancreatic neuroendocrine tumor localized in the heart, lung, liver, ovary, common bile duct, and mesentery.
[e] Data are available only for the National Institutes of Health cohort (n = 216); data from Stanford University Hospital were not available.
[f] Refers to positive hormonal gradient with portal venous sampling or intra-arterial secretin injection (gastrinoma) or calcium (insulinoma) with hepatic venous sampling.

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.
[a] The number of patients undergoing surgery was used as 100% in this table.
[b] Other refers to primary pNETs located in the ovary, liver, mesentery, heart, lymph node, and lung.
[c] More than 1 primary pNET primarily occurred in patients with multiple endocrine neoplasia 1 (n = 45) or with multiple functional pNETs (n = 9).
[d] Data are available only for the Stanford University Hospital cohort (n = 110); the National Institutes of Health data were not available.
[e] Patients from the National Institutes of Health cohort with gastrinoma involving lymph nodes and no identifiable primary as previously described.[61]

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 patients 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 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 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.

[a] Percentage based on 326 patients who underwent surgical exploration. Eight patients had either unresectable disease or negative laparotomy (with gastrinomas).

[b] Thirty-one patients with liver metastases also had lymph node metastases.

[c] Twenty-nine patients had both enucleation of pancreatic tumors and resections of other pNETs.

[d] Includes trisegmentectomy (n = 2), hepatic lobe resection (n = 19), and segmentectomy (n = 6).

[e] There 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).

[f] Patients treated with interferon alfa (n = 14) or peptide receptor radionuclide therapy (n = 2).

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

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.
[a] Data are available only for the National Institutes of Health cohort (n = 216); data from Stanford University Hospital were not available.
[b] Statistically 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 approximately 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 al[20] 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 studies[12-20] 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.

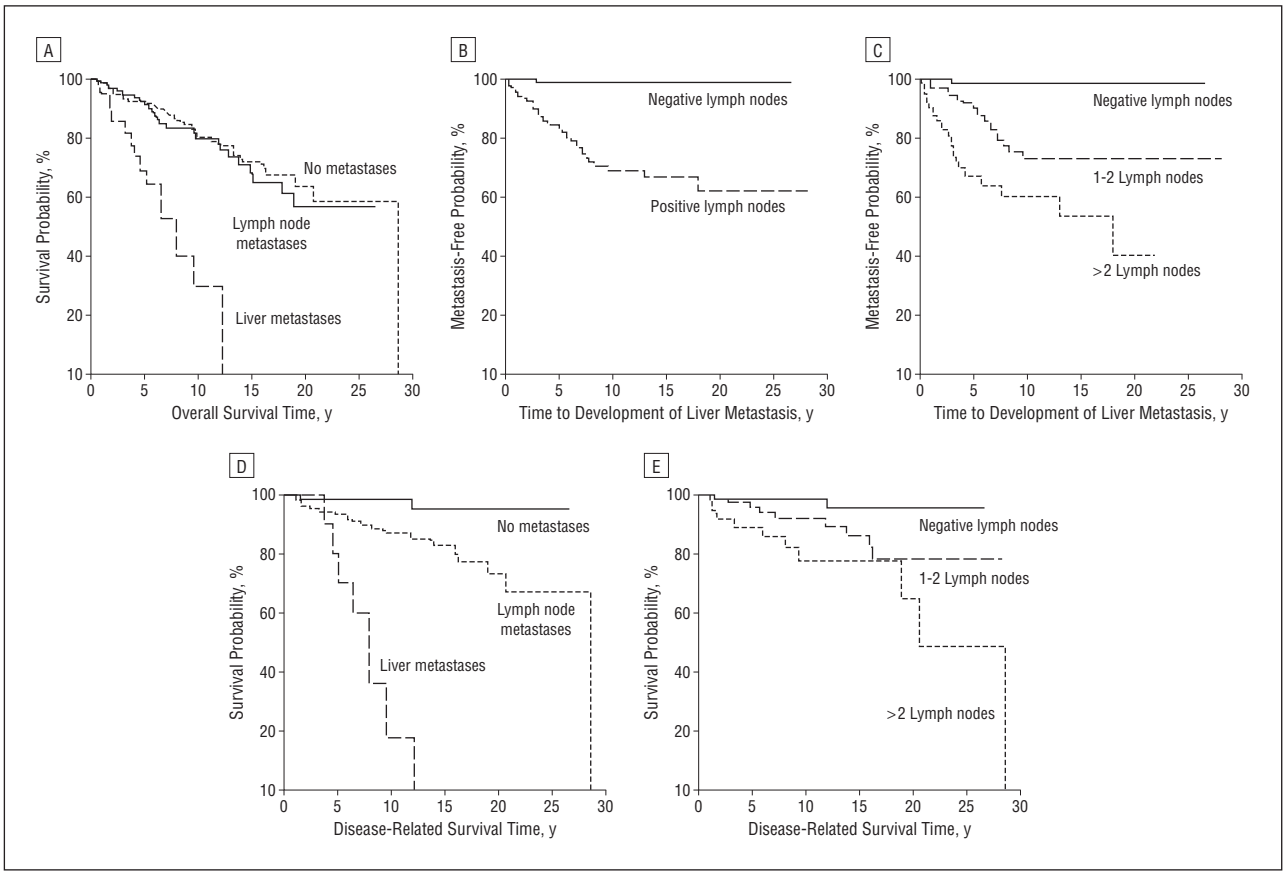

Figure. Kaplan-Meier plots. A, Overall survival; B and C, time to development of liver metastases; and D and E, disease-related survival. For National Institutes of Health (NIH) and Stanford University Hospital patients (N=326), overall survival was not significantly different between patients with lymph 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 al[19] demonstrated that lymph node metastases alone had no significant effect on survival. Similarly, a multicenter study by Cadiot et al[66] 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 study[45] 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 al[47] reported that lymph node metastases decreased survival, and in 2008, Bettini et al[48] 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 al[49] 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, noninsulinoma), 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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REFERENCES

1. Vortmeyer AO, Huang S, Lubensky I, Zhuang Z. Non-islet origin of pancreatic islet cell tumors. *J Clin Endocrinol Metab*. 2004;89(4):1934-1938.
2. Rindi G, Wiedenmann B. Neuroendocrine neoplasms of the gut and pancreas: new insights. *Nat Rev Endocrinol*. 2011;8(1):54-64.
3. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. *Gastroenterology*. 2008;135(5):1469-1492.
4. Yao JC, Shah MH, Ito T, et al; RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364(6):514-523.
5. Jensen RT, Delle Fave G. Promising advances in the treatment of malignant pancreatic endocrine tumors. *N Engl J Med*. 2011;364(6):564-565.
6. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364(6):501-513.
7. Ehehalt F, Saeger HD, Schmidt CM, Grützmann R. Neuroendocrine tumors of the pancreas. *Oncologist*. 2009;14(5):456-467.
8. Norton JA, Doherty GM, Fraker DL, et al. Surgical treatment of localized gastrinoma within the liver: a prospective study. *Surgery*. 1998;124(6):1145-1152.
9. Thompson GB, van Heerden JA, Grant CS, Carney JA, Ilstrup DM. Islet cell carcinomas of the pancreas: a twenty-year experience. *Surgery*. 1988;104(6):1011-1017.
10. Halfdanarson TR, Rabe KG, Rubin J, Petersen GM. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. *Ann Oncol*. 2008;19(10):1727-1733.
11. Norton JA, Fraker DL, Alexander HR, et al. Surgery to cure the Zollinger-Ellison syndrome. *N Engl J Med*. 1999;341(9):635-644.
12. Frilling A, Sotiropoulos GC, Li J, Kornasiewicz O, Plöckinger U. Multimodal management of neuroendocrine liver metastases. *HPB (Oxford)*. 2010;12(6):361-379.
13. Mayo SC, de Jong MC, Bloomston M, et al. Surgery versus intra-arterial therapy for neuroendocrine liver metastasis: a multicenter international analysis. *Ann Surg Oncol*. 2011;18(13):3657-3665.
14. Madoff DC, Gupta S, Ahrar K, Murthy R, Yao JC. Update on the management of neuroendocrine hepatic metastases. *J Vasc Interv Radiol*. 2006;17(8):1235-1250.
15. Norton JA, Warren RS, Kelly MG, Zuraek MB, Jensen RT. Aggressive surgery for metastatic liver neuroendocrine tumors. *Surgery*. 2003;134(6):1057-1063.
16. Saxena A, Chua TC, Sarkar A, et al. Progression and survival results after radical hepatic metastasectomy of indolent advanced neuroendocrine neoplasms (NENs) supports an aggressive surgical approach. *Surgery*. 2011;149(2):209-220.
17. Norton JA. Endocrine tumours of the gastrointestinal tract: surgical treatment of neuroendocrine metastases. *Best Pract Res Clin Gastroenterol*. 2005;19(4):577-583.
18. Norton JA, Kivlen M, Li M, Schneider D, Chuter T, Jensen RT. Morbidity and mortality of aggressive resection in patients with advanced neuroendocrine tumors. *Arch Surg*. 2003;138(8):859-866.
19. Weber HC, Venzon DJ, Lin JT, et al. Determinants of metastatic rate and survival in patients with Zollinger-Ellison syndrome: a prospective long-term study. *Gastroenterology*. 1995;108(6):1637-1649.

20. Yu F, Venzon DJ, Serrano J, et al. Prospective study of the clinical course, prognostic factors, causes of death, and survival in patients with long-standing Zollinger-Ellison syndrome. *J Clin Oncol*. 1999;17(2):615-630.
21. Norton JA, Jensen RT. Resolved and unresolved controversies in the surgical management of patients with Zollinger-Ellison syndrome. *Ann Surg*. 2004; 240(5):757-773.
22. Norton JA, Fraker DL, Alexander HR, et al. Surgery increases survival in patients with gastrinoma. *Ann Surg*. 2006;244(3):410-419.
23. Gu Y, Swisher SG, Ajani JA, et al. The number of lymph nodes with metastasis predicts survival in patients with esophageal or esophagogastric junction adenocarcinoma who receive preoperative chemoradiation. *Cancer*. 2006;106 (5):1017-1025.
24. House MG, Gönen M, Jarnagin WR, et al. Prognostic significance of pathologic nodal status in patients with resected pancreatic cancer. *J Gastrointest Surg*. 2007; 11(11):1549-1555.
25. Smith DD, Schwarz RR, Schwarz RE. Impact of total lymph node count on staging and survival after gastrectomy for gastric cancer: data from a large US-population database. *J Clin Oncol*. 2005;23(28):7114-7124.
26. Ceelen W, Van Nieuwenhove Y, Pattyn P. Prognostic value of the lymph node ratio in stage III colorectal cancer: a systematic review. *Ann Surg Oncol*. 2010; 17(11):2847-2855.
27. Loh KC, Greenspan FS, Gee L, Miller TR, Yeo PP. Pathological tumor-node-metastasis (pTNM) staging for papillary and follicular thyroid carcinomas: a retrospective analysis of 700 patients. *J Clin Endocrinol Metab*. 1997;82(11): 3553-3562.
28. Machens A, Gimm O, Ukkat J, Hinze R, Schneyer U, Dralle H. Improved prediction of calcitonin normalization in medullary thyroid carcinoma patients by quantitative lymph node analysis. *Cancer*. 2000;88(8):1909-1915.
29. Fischer L, Kleeff J, Esposito I, et al. Clinical outcome and long-term survival in 118 consecutive patients with neuroendocrine tumours of the pancreas. *Br J Surg*. 2008;95(5):627-635.
30. Schurr PG, Strate T, Rese K, et al. Aggressive surgery improves long-term survival in neuroendocrine pancreatic tumors: an institutional experience. *Ann Surg*. 2007;245(2):273-281.
31. Jensen RT, Niederle B, Mitry E, et al; Frascati Consensus Conference; European Neuroendocrine Tumor Society. Gastrinoma (duodenal and pancreatic). *Neuroendocrinology*. 2006;84(3):173-182.
32. Chu QD, Hill HC, Douglass HO Jr, et al. Predictive factors associated with long-term survival in patients with neuroendocrine tumors of the pancreas. *Ann Surg Oncol*. 2002;9(9):855-862.
33. Bilimoria KY, Talamonti MS, Tomlinson JS, et al. Prognostic score predicting survival after resection of pancreatic neuroendocrine tumors: analysis of 3851 patients. *Ann Surg*. 2008;247(3):490-500.
34. DiNorcia J, Lee MK, Reavey PL, et al. One hundred thirty resections for pancreatic neuroendocrine tumor: evaluating the impact of minimally invasive and parenchyma-sparing techniques. *J Gastrointest Surg*. 2010;14(10):1536-1546.
35. Ekeblad S, Skogseid B, Dunder K, Oberg K, Eriksson B. Prognostic factors and survival in 324 patients with pancreatic endocrine tumor treated at a single institution. *Clin Cancer Res*. 2008;14(23):7798-7803.
36. Ellison EC, Sparks J, Verducci JS, et al. 50-Year appraisal of gastrinoma: recommendations for staging and treatment. *J Am Coll Surg*. 2006;202(6):897-905.
37. Fendrich V, Langer P, Celik I, et al. An aggressive surgical approach leads to long-term survival in patients with pancreatic endocrine tumors. *Ann Surg*. 2006; 244(6):845-852.
38. Hochwald SN, Zee S, Conlon KC, et al. Prognostic factors in pancreatic endocrine neoplasms: an analysis of 136 cases with a proposal for low-grade and intermediate-grade groups. *J Clin Oncol*. 2002;20(11):2633-2642.
39. Kazanjian KK, Reber HA, Hines OJ. Resection of pancreatic neuroendocrine tumors: results of 70 cases. *Arch Surg*. 2006;141(8):765-770.
40. Nikfarjam M, Warshaw AL, Axelrod L, et al. Improved contemporary surgical management of insulinomas: a 25-year experience at the Massachusetts General Hospital. *Ann Surg*. 2008;247(1):165-172.
41. Pape UF, Jann H, Müller-Nordhorn J, et al. Prognostic relevance of a novel TNM classification system for upper gastroenteropancreatic neuroendocrine tumors. *Cancer*. 2008;113(2):256-265.
42. Roland CL, Bian A, Mansour JC, et al. Survival impact of malignant pancreatic neuroendocrine and islet cell neoplasm phenotypes. *J Surg Oncol*. 2012;105 (6):595-600.
43. Stabile BE, Passaro E Jr. Benign and malignant gastrinoma. *Am J Surg*. 1985;149 (1):144-150.
44. Bonney GK, Gomez D, Rahman SH, et al. Results following surgical resection for malignant pancreatic neuroendocrine tumours. A single institutional experience. *JOP*. 2008;9(1):19-25.
45. Casadei R, Ricci C, Pezzilli R, et al. Are there prognostic factors related to recurrence in pancreatic endocrine tumors? *Pancreatology*. 2010;10(1):33-38.
46. Panzuto F, Boninsegna L, Fazio N, et al. Metastatic and locally advanced pancreatic endocrine carcinomas: analysis of factors associated with disease progression. *J Clin Oncol*. 2011;29(17):2372-2377.
47. Tomassetti P, Campana D, Piscitelli L, et al. Endocrine pancreatic tumors: factors correlated with survival. *Ann Oncol*. 2005;16(11):1806-1810.
48. Bettini R, Boninsegna L, Mantovani W, et al. Prognostic factors at diagnosis and value of WHO classification in a mono-institutional series of 180 non-functioning pancreatic endocrine tumours. *Ann Oncol*. 2008;19(5):903-908.
49. Boninsegna L, Panzuto F, Partelli S, et al. Malignant pancreatic neuroendocrine tumour: lymph node ratio and Ki67 are predictors of recurrence after curative resections [published online November 28, 2011]. *Eur J Cancer*. 2011. doi:10 .1016/j.ejca.2011.10.030.
50. You DD, Lee HG, Paik KY, Heo JS, Choi SH, Choi DW. The outcomes after surgical resection in pancreatic endocrine tumors: an institutional experience. *Eur J Surg Oncol*. 2009;35(7):728-733.
51. Haynes AB, Deshpande V, Ingkakul T, et al. Implications of incidentally discovered, nonfunctioning pancreatic endocrine tumors: short-term and long-term patient outcomes. *Arch Surg*. 2011;146(5):534-538.
52. Norton JA, Alexander HR, Fraker DL, Venzon DJ, Gibril F, Jensen RT. Does the use of routine duodenotomy (DUODX) affect rate of cure, development of liver metastases, or survival in patients with Zollinger-Ellison syndrome? *Ann Surg*. 2004;239(5):617-626.
53. Roy PK, Venzon DJ, Shojamanesh H, et al. Zollinger-Ellison syndrome: clinical presentation in 261 patients. *Medicine (Baltimore)*. 2000;79(6):379-411.
54. Berna MJ, Hoffmann KM, Long SH, Serrano J, Gibril F, Jensen RT. Serum gastrin in Zollinger-Ellison syndrome: II. Prospective study of gastrin provocative testing in 293 patients from the National Institutes of Health and comparison with 537 cases from the literature: evaluation of diagnostic criteria, proposal of new criteria, and correlations with clinical and tumoral features. *Medicine (Baltimore)*. 2006;85(6):331-364.
55. Norton JA, Harris EJ, Chen Y, et al. Pancreatic endocrine tumors with major vascular abutment, involvement, or encasement and indication for resection. *Arch Surg*. 2011;146(6):724-732.
56. Krudy AG, Doppman JL, Jensen RT, et al. Localization of islet cell tumors by dynamic CT: comparison with plain CT, arteriography, sonography, and venous sampling. *AJR Am J Roentgenol*. 1984;143(3):585-589.
57. Doppman JL, Miller DL, Chang R, et al. Gastrinomas: localization by means of selective intraarterial injection of secretin. *Radiology*. 1990;174(1):25-29.
58. Strader D, Dopmann D, Orbuch M. Functional localization of enteropancreatic neuroendocrine tumors. In: Mignon M, Jensen RT, eds. *Endocrine Tumors of the Pancreas: Recent Advances*. Vol 23. Basel, Switzerland: Karger Publishing; 1996.
59. Gibril F, Schumann M, Pace A, Jensen RT. Multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome: a prospective study of 107 cases and comparison with 1009 cases from the literature. *Medicine (Baltimore)*. 2004;83(1): 43-83.
60. Benya RV, Metz DC, Venzon DJ, et al. Zollinger-Ellison syndrome can be the initial endocrine manifestation in patients with multiple endocrine neoplasia-type I. *Am J Med*. 1994;97(5):436-444.
61. Norton JA, Alexander HR, Fraker DL, Venzon DJ, Gibril F, Jensen RT. Possible primary lymph node gastrinoma: occurrence, natural history, and predictive factors: a prospective study. *Ann Surg*. 2003;237(5):650-659.
62. von Schrenck T, Howard JM, Doppman JL, et al. Prospective study of chemotherapy in patients with metastatic gastrinoma. *Gastroenterology*. 1988;94 (6):1326-1334.
63. Mignon M. Natural history of neuroendocrine enteropancreatic tumors. *Digestion*. 2000;62(suppl 1):51-58.
64. Jensen R. Natural history of digestive endocrine tumors. In: Mignon MCJ, ed. *Recent Advances in Pathophysiology and Management of Inflammatory Bowel Diseases and Digestive Endocrine Tumors*. Paris, France: John Libbey Eurotext Publishing Co; 1999:192-219.
65. Fraker DL, Norton JA, Alexander HR, Venzon DJ, Jensen RT. Surgery in Zollinger-Ellison syndrome alters the natural history of gastrinoma. *Ann Surg*. 1994; 220(3):320-330.
66. Cadiot G, Vuagnat A, Doukhan I, et al; Groupe d'Etude des Néoplasies Endocriniennes Multiples (GENEM and groupe de Recherche et d'Etude du Syndrome de Zollinger-Ellison (GRESZE). Prognostic factors in patients with Zollinger-Ellison syndrome and multiple endocrine neoplasia type 1. *Gastroenterology*. 1999; 116(2):286-293.
67. Vilar E, Salazar R, Pérez-García J, Cortes J, Oberg K, Tabernero J. Chemotherapy and role of the proliferation marker Ki-67 in digestive neuroendocrine tumors. *Endocr Relat Cancer*. 2007;14(2):221-232.
68. Rougier P, Mitry E. Chemotherapy in the treatment of neuroendocrine malignant tumors. *Digestion*. 2000;62(suppl 1):73-78.
69. Kaltsas GA, Besser GM, Grossman AB. The diagnosis and medical management of advanced neuroendocrine tumors. *Endocr Rev*. 2004;25(3):458-511.