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Superior Prognostic Importance of Perineural Invasion vs. Lymph Node Involvement After Curative Resection of Duodenal Adenocarcinoma

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Abstract
Background Unlike other gastrointestinal tumors, lymph node involvement has not consistently been a negative prognostic factor for survival in patients with duodenal adenocarcinoma. Our aim is to examine prognostic factors in patients who underwent a curative resection of their duodenal adenocarcinoma.
Methods A retrospective review of 169 patients diagnosed with primary duodenal lesions between 1982 and 2010 was performed, of whom 103 were treated with curative intent. Clinico-pathologic factors were evaluated.
Results A potentially curative resection was performed in 103 patients with a median age of 67 years (range, 22–91). Perineural and lympho-vascular invasion were identified in 30 (29.1%) and 39 patients (37.9%), respectively. Median follow-up was 26.5 months. The 5-year overall survival was 62% vs. 25% for patients with or without nodal metastases ($p<0.001$) and 56% vs. 19% for patients with or without perineural invasion ($p<0.001$), respectively. Lymph node ratio, type of resection, and size of tumor failed to stratify prognosis. By multivariate analysis, perineural invasion was the most powerful independent predictor of survival (HR, 2.520; CI, 1.361–4.664).
Conclusions Perineural invasion is a stronger predictor for recurrence and survival than tumor size, depth of infiltration, lymph node involvement, and type of resection in patients with duodenal adenocarcinoma.

Keywords Duodenal adenocarcinoma · Duodenal cancer · Nodal metastases · Perineural invasion · Prognosis · Survival · Predictor · Lymph node

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Introduction

Adenocarcinoma of the duodenum is an uncommon disease with a poorly defined natural history.[1] Surgical resection is the only potentially curative treatment, but not all patients in whom the tumor is removed will survive long term. Due to the low incidence of this neoplasm, it has been difficult to determine which factors influence overall survival. Therefore, several controversial issues remain to be studied including the significance of the depth of invasion and degree of differentiation,[2] the prognostic value of nodal involvement,[3–6] the type of surgical resection performed for tumors located in the third and fourth portion of the duodenum,[1,2,7] and indications and type of adjuvant treatments.[3,8] Moreover, because of the predominant prevalence in the second portion of the duodenum, duodenal adenocarcinoma has often been grouped with other periampullary cancers (pancreatic, biliary, ampullary), thereby leading to controversial definitions and inconsistent conclusions.[5,9–11]

One of the most debated topics is the prognostic significance of nodal involvement. The lack of a unified association between nodal metastases and poor prognosis may be due to inaccurate lymph node dissections and pathological examinations[5,10] or a biological behavior which is different from other gastrointestinal malignancies.[3] Many single-center studies attempt to resolve this issue without arriving at a consensus.

Similar to lymph node metastases, perineural invasion is an important prognostic factor in many other types of cancer.[11–18] While perineural invasion has been evaluated as a prognostic factor in patients with periampullary malignancies including pancreatic adenocarcinoma, distal cholangiocarcinoma, and ampulla of Vater carcinoma,[8,11,19] we know of no studies which have addressed the significance of perineural invasion in a large series of patients with duodenal adenocarcinoma.

The aim of the present study is to investigate the prognostic relevance of a panel of clinico-pathological features in patients with duodenal adenocarcinoma, focusing on nodal involvement, lymph node ratio, and perineural invasion.

Materials and Methods

Study Protocol and Data Collection

The medical records of patients with the diagnosis of a primary duodenal lesion treated at the Massachusetts General Hospital (MGH) between 1982 and 2010 were retrospectively reviewed. Patients were identified by reviewing data from the MGH Research Patient Data Registry of our institution. A database of patients with a histological diagnosis of primary duodenal adenocarcinoma was created. Non-adenocarcinoma diagnosis was an exclusion criteria. Follow-up data were obtained from the MGH Tumor Registry and the patient clinical charts. This study was approved by the Institutional Review Board.

Demographic and clinical data (age, gender, ethnicity, history of cancer, history of colonic polyposis, family history of cancer, initial symptom, subsequent symptoms), surgical data (resectability, type of operation, perioperative morbidity and mortality), pathological data (tumor location; tumor size; grade; tumor, node, and metastasis (TNM) staging according to the American Joint Committee on Cancer (AJCC) (7th Edition); number of lymph nodes examined; number of lymph nodes positive; lymph nodes ratio; presence of perineural invasion; presence of lympho-vascular invasion; origin from a villous adenoma), and adjuvant chemotherapy and radiotherapy were collected.

Patients undergoing a non-curative resection were deemed unresectable at the time of surgery. Lymph node ratio (LNR) was calculated by dividing the total number of lymph nodes harboring metastases by the total number of examined nodes. Perineural invasion was defined as tumor cells within any layer of the nerve sheath or perineural space.

Mortality was defined as death within 90 days of the operation. Pancreatic fistula was defined as drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content greater than three times the serum amylase activity, according to the International Study Group on Pancreatic Fistula.[20] Delayed gastric emptying was defined as the need for maintenance of a nasogastric tube (NGT) for three or more days, need for reinsertion of the NGT for recurrent vomiting after postoperative day 3, or inability to tolerate a solid diet by postoperative day 7 in accord with the International Study Group on Pancreatic Surgery recommendation.[21]

Statistical Analysis

Data were analyzed using the SPSS software (version 14.0; SPSS, Inc., Chicago, IL, USA). Survival analysis was performed utilizing the Kaplan–Meyer method. Possible prognostic factors influencing survival were first evaluated by univariate analysis (log–rank test). Only parameters which showed significance by univariate analysis were further analyzed by multivariate analysis (Cox proportional hazards test, method forward-conditional). Statistical significance was defined as a p value of less than 0.05.

Results

Demographics

The records of 256 patients with primary duodenal lesions were reviewed, of whom 169 were adenocarcinomas (66%), 31 were neuroendocrine tumors (12.1%), 29 were GISTs (11.3%), 17 were lymphomas (6.6%), 8 had other cancers (3.1%), and 2 had a missing pathological diagnosis (0.8%) (Table 1).

The median age at the time of diagnosis for patients with adenocarcinoma was 67 years (range, 22–91); 93 were male (55%) and 149 were Caucasian (88.2%). Sixteen patients were considered to have a high-risk genetic syndrome including seven patients with familial adenomatous polyposis (FAP), five with Lynch syndrome, two with juvenile polyposis (JP) associated with Osler–Rendu–Weber syndrome, one with Gardner's syndrome (GS), and one patient with a history of multiple bowel cancers. The majority of cancers (66%) arose in the descending part of the

Table 1 Prevalance of histotypes of primary duodenal cancer

	Number	Percentage
Adenocarcinoma	169	66
Neuroendocrine	31	21.1
Carcinoid	26	
Gastrinoma	3	
Somatostatinoma	2	
GIST	29	11.3
Lymphoma	17	6.6
Others	8	31
Leiomyosarcoma	3	
Leiomyoma	2	
Sarcomatoid carcinoma	1	
Malignant peripheral nerve sheath tumor	1	
Missing	3	1.2

duodenum (D2); in 16, 21, and 14 cases, the cancer arose in the bulb (D1), transverse (D3), and ascending parts (D4), respectively.

Clinical Presentation of Duodenal Adenocarcinoma

The most frequent symptoms at presentation were abdominal pain (59%), weight loss (34%), and gastrointestinal bleeding (31%). In 16 patients (9.5%), the diagnosis was incidental during a diagnostic procedure performed for other reasons, including routine screening in patients with FAP or JP. Not surprisingly, 40% of patients with a genetic risk factor had lesions identified incidentally, compared to 6% of patients without risk factors ($p<0.001$). In patients diagnosed with unresectable adenocarcinoma, the most frequent initial symptoms were abdominal pain (39%) and emesis (26%), compared to abdominal pain (34%) and gastrointestinal bleeding (31%) in patients with resectable disease.

Operative Treatment

Of the 169 patients with duodenal adenocarcinoma, 103 were treated with curative intent, 41 were bypassed, and 25 received non-surgical palliative treatments, resulting in an overall resectability rate of 61%. Palliative non-surgical treatment consisted of chemotherapy alone and supportive therapy. Resectability was not influenced by location of the adenocarcinoma in the duodenum, although D3 cancers had the lowest resectability rate (D1, 63%; D2, 64%; D3, 48%; and D4, 79%; $p=0.312$).

Of the 103 patients treated with curative intent, 87 underwent a pancreaticoduodenectomy (PD), whereas 14 underwent a duodenal segmentectomy (DS). The median length of stay was 9.5 days (range, 5–66) for PD and 10 days (range, 5–23) for DS ($p=0.928$). Two patients underwent an endoscopic mucosal resection for adenocarcinoma in situ arising in a duodenal adenoma, which was a same-day procedure. Overall postoperative morbidity was 48%, with a rate of 53% after PD and 29% after DS ($p=0.136$). The most common complications after PD were pancreatic fistula (12.5%), intra-abdominal collection requiring drainage (10.3%), and delayed gastric emptying (8%). After DS there were two hemodynamic complications but no other procedure-related complications. Perioperative mortality after PD was 3.4% (3 of 87) versus 0% (0 of 14) after DS.

Pathological Findings of Resected Patients

Patients most frequently presented with stage III disease (stage I, 25%; stage II, 26%; stage III, 45%; stage IV, 4%). The TNM staging and pathological data are summarized in Table 2. The median tumor size was 36 mm (range, 2–130 mm), with larger tumors developing in the distal duodenal segments (D1, 31 mm; D2, 40 mm; D3, 48 mm; D4, 51 mm). An R0 resection was achieved in 91 patients (88%). The majority of patients had well to moderately differentiated tumors (54%). Adenocarcinoma arose within a tubulo-villous adenoma in 36 cases, 27 of which were located in the D2 portion separate from the ampulla (75%). Adenocarcinoma arising in a tubulo-villous adenoma was unrelated to all other clinico-pathological features, in particular to a history of FAP (Fisher $p=0.090$) or other heredo-familial syndromes (Fisher $p=1.00$). A mucinous component was reported in 17 cases, with the majority located in D2 (65%), which was also unrelated to other clinico-pathological features. Patients with heredo-familial syndromes, in particular patients with a history of FAP, were more often diagnosed with an adenocarcinoma in situ or stage I cancer when compared to sporadic cases (stage < II, 44% vs. 20%; $p=0.041$).

Perineural invasion and lympho-vascular invasion were evaluated in 74 of 103 and 79 of 103 patients, respectively, and were present in 30 of 74 (41%) and 42 of 79 (53%) cases, respectively. Of the 16 patients with an associated genetic syndrome, slides were available for nine patients. None of the nine patients had perineural invasion, and only two patients out of ten presented with lympho-vascular invasion. In 26 patients (35%), there was no concordance between perineural invasion and nodal involvement, and in 22 patients (30%), there was no concordance between perineural and vascular invasion.

Adjuvant Treatment

Adjuvant treatment was administered to 46 patients, whereas 48 were treated with surgery alone and 9 patients were lost to follow-up. Overall, 13 patients were treated with

Table 2 TNM staging of patients with resected adenocarcinoma of the duodenum and pathological features

		All (n=103)	D1 (n=10)	D2 (n=72)	D3 (n=10)	D4 (n=11)
Median tumor size (mm)		40	31	40	48	51
Grading (poorly differentiated, %)		40 (37/93)	60 (6/8)	41 (26/64)	40 (4/9)	10 (1/10)
LN examined (median)		10	9	10	12	9
pN+		49	7	31	6	5
Lymph node ratio	=0	43	2	34	2	5
	>0 and ≤0.2	20	0	14	3	3
	>0.2	29	7	17	3	2
AJCC stage (n)	I	24	0	21	2	1
	II	27	3	17	2	5
	III	46	7	30	5	4
	IV	4	0	2	1	1
Perineural invasion (%)		29 (30/74)	3	31	3	4
Lympho-vascular invasion (%)		41 (42/79)	5	34	8	6
Cancer arisen from villous adenoma		35 (36/78)	4	35	5	3

chemotherapy alone, 29 patients received chemo-radiation, and 4 received neoadjuvant plus adjuvant chemo-radiation. The most common chemotherapeutic regimen administered was 5-fluorouracil with leucovorin. Radiation therapy alone was performed in one patient with a D3, stage I adenocarcinoma who underwent an R1 duodenal segmentectomy. Adjuvant therapy was administered to 13 patients diagnosed with stage II duodenal adenocarcinoma. Due to patient preference, 12 patients diagnosed with advanced disease (stage III–IV) were treated with surgery alone. There was no significant improvement in overall survival for patients treated with adjuvant and/or neoadjuvant therapy when compared with patients who were not treated. When comparing sites of recurrence and time to recurrence, there was no difference based on adjuvant treatment, for the overall cohort and on a stage-by-stage analysis.

Survival Analysis and Prognostic Factors

Mean and median follow-up were 30 and 26.5 months, respectively. Overall median survival was 44 vs. 9 months for patients who were resected and unresectable, respectively. The overall actuarial survival at 3 and 5 years was 57% and 42% for resected patients and 2% and 0% for unresectable patients (p<0.001). Four patients had an intraoperative diagnosis of resectable distant metastases (two solitary hepatic metastases and two retroperitoneal nodules) which were treated with curative intent concomitantly with the resection of the primary duodenal site. The 3- and 5-year disease-specific survivals for those four patients were 68% and 57%.

Univariate analysis demonstrated that nodal involvement, LNR, advanced tumor stage, and perineural invasion were each associated with a significant decrease in overall survival (Table 3) (Figs. 1 and 2).

The 5-year overall survival was 55% vs. 27% for stage I–II and stage III–IV patients. The 5-year overall survival for patients without and with nodal metastases was 62% vs. 25%, respectively, compared with 56% vs. 19% for the absence and presence of perineural invasion, respectively. The effect of perineural invasion and nodal metastases on overall survival is demonstrated in Fig. 3.

Multivariate analysis identified perineural invasion as the most powerful independent predictor of survival (HR, 2.520; p=0.003; CI, 1.361–4.664) (Table 3).

Tumor Recurrence

Oncologic follow-up was available for 83 patients. A recurrence was documented in 37 patients (45%). The first site of recurrence was loco-regional in 16 patients (19%), distant in 17 patients (21%), and both in 4 (5%) patients. The most common site of distant failure was the liver (nine patients, 24%). Median time to tumor recurrence was 14.5 months, and median survival of patients after the diagnosis of recurrent disease was 9.5 months. Univariate analysis demonstrated that pT, nodal involvement, presence of distant metastasis, advanced AJCC stage, margin involvement, and perineural invasion were predictors of recurrence. A logistic regression model identified perineural invasion as the strongest independent predictor of recurrence (OR, 3.770; CI, 1.034–13.744; p=0.044).

Discussion

Relative to other gastrointestinal malignancies, small-bowel cancers are uncommon. NCI's SEER Cancer Statistics reports an age-adjusted incidence of 1.9 cases per 100,000

Table 3 Variable influencing survival in patients undergoing resection for duodenal adenocarcinoma

	Univariate analysis	Multivariate analysis
Age	0.109 (0.996–1.037)	
Gender	0.757 (0.654–1.792)	
Ethnicity	0.233 (0.170–1.020)	
FPH of cancer	0.339 (0.709–2.670)	
PMH of cancer	0.435 (0.467–1.391)	
PMH of FAP	0.452 (0.612–2.983)	
Initial symptom	0.145 (0.974–1.227)	
Type of operation	0.492 (0.332–1.372)	
PO morbidity	0.201 (0.429–1.200)	
Tumor location	0.051 (0. 522–1.089)	
Tumor size	0.307 (0.978–1.007)	
Grade	0.672 (0.779–1.775)	
AJCC stage (I–II vs. III–IV)	0.026 (1.301–3.834)*	0.279 (0.890–5.701)
R1	0.870 (0.424–2.068)	
nLN collected	0.793 (0.970–1.041)	
Nodal metastases	0.001 (1.447–4.304)*	0.193 (0.276–15.882)
LNR	0.019 (2.109–17.903)*	
=0	.	0.404
>0 and ≤0.2	.	0.642 (0.250–15.516)
>0.2	.	0.329 (0.284–17.464)
Perineural invasion	0.002 (1.361–4.664)*	0.003 (1.361–4.664)*
Lympho-vascular invasion	0.069 (0.946–3.187)	
Origin from a villous adenoma	0.442 (0.436–1.442)	

*p value<0.05

population per year. Duodenal adenocarcinoma is even more rare, representing only 40% of all small-bowel cancers.[22] Due to its low incidence, most studies lump duodenal adenocarcinoma with other small intestinal tumors or periampullary tumors. Few retrospective series have been able to evaluate the prognostic impact of specific clinico-

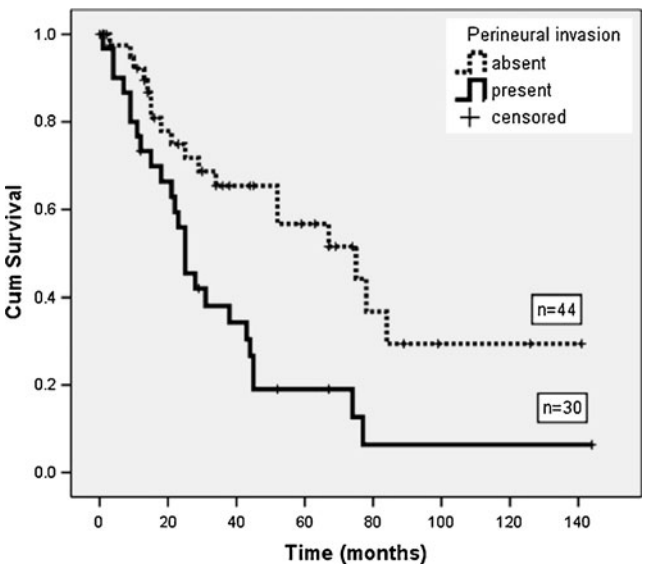

Fig. 1 Kaplan–Meyer survival curves comparing patients within the curative resection group by perineural invasion. Five-year overall survival 56% vs. 19% for absence and presence of perineural invasion, respectively

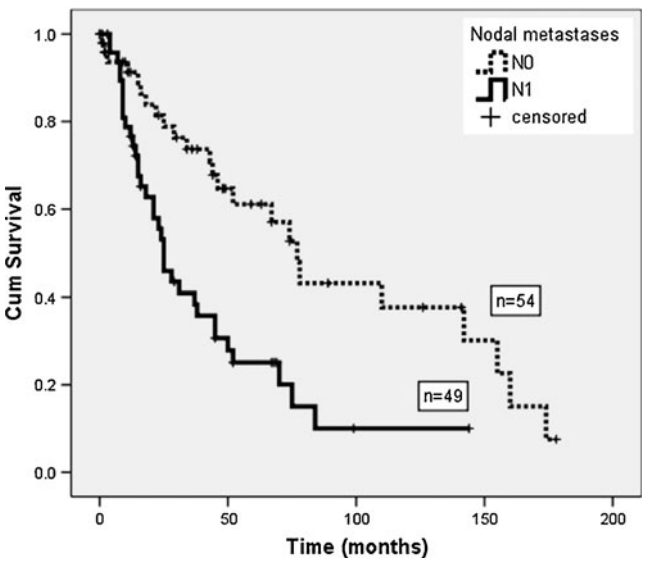

Fig. 2 Kaplan–Meyer survival curves comparing patients within the curative resection group by nodal status. Five-year overall survival 65% vs. 25% for absence and presence of nodal metastases, respectively

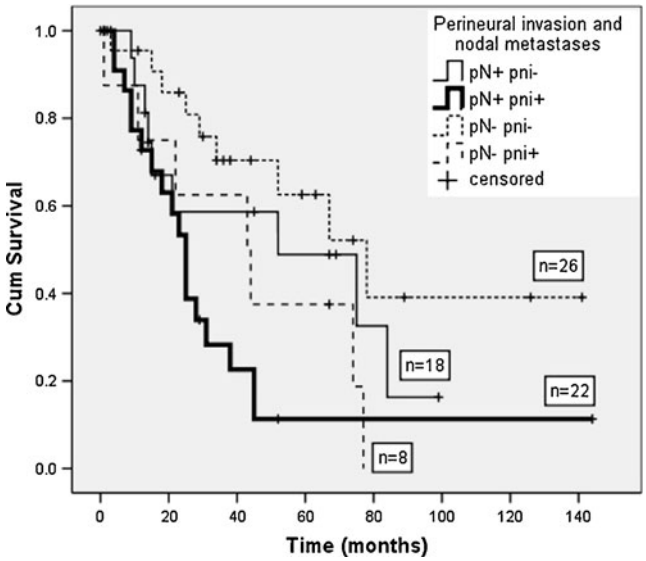

Fig. 3 Kaplan–Meyer survival curves comparing patients within the curative resection group by combination of nodal status (*pN−* absence of nodal metastases, *pN+* presence of nodal metastases) and perineural invasion (*pni−* absence of perineural invasion, *pni+* presence of perineural invasion)

pathologic factors for duodenal adenocarcinoma[1–3,5,8,23,24] (Tables 4). The aim of the present study was to investigate the prognostic relevance of a panel of clinico-pathological features in patients with duodenal adenocarcinoma, focusing on nodal involvement, lymph node ratio, and perineural invasion, through a retrospective analysis of our institutional experience over the past 28 years. This study is the first to demonstrate perineural invasion as the strongest prognostic factor for recurrence and overall survival in patients with adenocarcinoma of the duodenum.

Similar to other series, we demonstrated no difference in survival based on the location of the cancer in different portions of the duodenum.[2,4] In our series, the primary lesion in the distal part of the duodenum was larger, but there was no association with a more advanced stage of disease.

Most small-bowel adenocarcinomas arise from adenomas, and the available data suggest an adenoma-carcinoma sequence driven by a multistep process of specific genetic changes similar to that described for colorectal cancers.[25] We failed to identify any association with other clinico-pathological features, heredo-familial syndromes, and overall survival.

Many aspects of adjuvant therapy for duodenal adenocarcinoma remain unclear. Other small series have reported an improved median survival for patients with adjuvant therapy.[8] Our series was unable to demonstrate a benefit. Only a phase III randomized clinical trial for duodenal adenocarcinoma will be able to clarify the role of adjuvant therapy.

The inconsistency in the prognostic value of nodal involvement in prior studies has been attributed to several factors, including the intrinsic limitations and biases of retrospective studies.[1] In our series, nodal metastases significantly decreased actuarial survival, but it lost its significance as a prognostic factor on multivariate analysis. Sarela et al. hypothesized that patients with duodenal adenocarcinoma in whom less than 15 lymph nodes are examined could be under-staged.[5] In the present study, there was no obvious difference in the survival of patients with or without positive lymph nodes if fewer than 15 nodes were examined.

Perineural invasion has been described as a distinct clinico-pathological entity that can be identified in the

Table 4 Overview of literature with analysis of prognostic factor for survival in patients with duodenal adenocarcinoma

Author [ref] (year)	Number of cases	% 5-year OS	Predictors
Rose [4] (1996)	42	60	pN
Sohn [3] (1998)	48	53	Margin involvement location D1–2
Yeo [9] (1998)	17	59	pN
Ryder [1] (2000)	27	43	pT
			Grading
Bakaeen [2] (2000)	68	54	pT
			pN
			Margin involvement
			Weight loss
Tocchi [7] (2003)	47	23	pN
Sarela [5] (2004)	72	71[a]	pN
			Age
Lee [23] (2008)	28	44	pT
			pN
Zhang [24] (2010)	55	33	pN
			Margin involvement

[a]Disease-specific survival

pN pathological node states

pT pathological tumor states

absence of lymphatic or vascular invasion, and in some tumors can be the sole route of metastatic spread.[26] However, perineural invasion is a complex interaction between tumor cells, nerve cells, and stromal cells via autocrine and paracrine mechanisms involving neurotrophic growth factors and axonal guidance molecules.[27,28] Why carcinomas exhibit a predilection for perineural invasion and others do not remains unknown. Perineural invasion is emerging as an important feature in many malignancies, including oropharyngeal,[12] prostate,[13] colorectal,[14] biliary,[15] gastric,[16] lung,[17] breast,[18] and ampullary cancers.[11] The highest rate of perineural invasion is documented in pancreatic cancer, head and neck squamous cell carcinomas, and prostate cancer, while lower rates are documented in gastrointestinal cancers. Perineural invasion appears to signify more advanced disease.[26] To date, the prognostic relevance of perineural invasion in duodenal adenocarcinoma has not been demonstrated. Several studies have analyzed perineural invasion in periampullary cancers, finding it associated with poor survival.[8,11,19,29,30] However, perineural invasion had never been analyzed in the duodenal adenocarcinoma subgroup separately from the other periampullary histotypes, most likely due to an inadequate sample size. In our series of duodenal adenocarcinomas, perineural invasion was present in 40% of cases. The absence of concordance between perineural invasion and nodal involvement in more than one third of patients and between perineural invasion and vascular invasion in 30% of cases leads us to hypothesize that perineural invasion may be due to a different pathogenic pathway. Additionally, none of the nine patients with heredo-familial syndromes presented with tumors with perineural invasion. Nonetheless, given the limitation of a retrospective study, validation of these observations in a prospective study would be prudent.

There is a significant association between perineural invasion, overall survival, and recurrence. Interestingly, perineural invasion is the strongest independent predictor of overall survival and recurrence. On multivariate analysis, nodal metastases showed no additional predictive value when analyzed in a model along with perineural invasion.

The present study establishes perineural invasion as the most important single prognostic factor in duodenal adenocarcinoma and may indicate a future target for directed adjuvant treatment.

References

1. Ryder NM, Ko CY, Hines OJ, Gloor B, Reber HA. Primary duodenal adenocarcinoma: a 40-year experience. Arch Surg. 2000 Sep;135(9):1070–4; discussion 1074–5.
2. Bakaeen FG, Murr MM, Sarr MG, Thompson GB, Farnell MB, Nagorney DM, Farley DR, van Heerden JA, Wiersema LM, Schleck CD, Donohue JH. What prognostic factors are important in duodenal adenocarcinoma? Arch Surg. 2000 Jun;135(6):635–41; discussion 641–2.
3. Sohn TA, Lillemoe KD, Cameron JL, et al. Adenocarcinoma of the duodenum: factors influencing long-term survival. J Gastrointest Surg. 1998;2:79–87.
4. Rose DM, Hochwald SN, Klimstra DS, Brennan MF. Primary duodenal adenocarcinoma: a ten-year experience with 79 patients. J Am Coll Surg. 1996;183: 89–96.
5. Sarela AI, Brennan MF, Karpeh MS, Klimstra D, Conlon KC. Adenocarcinoma of the duodenum: importance of accurate lymph node staging and similarity in outcome to gastric cancer. Ann Surg Oncol. 2004 Apr;11(4):380–6.
6. Pickleman J, Koelsch M, Chejfec G. Node-positive duodenal carcinoma is curable. Arch Surg. 1997 Mar;132(3):241–4.
7. Tocchi A, Mazzoni G, Puma F, Miccini M, Cassini D, Bettelli E, Tagliacozzo S. Adenocarcinoma of the third and fourth portions of the duodenum: results of surgical treatment. Arch Surg. 2003 Jan;138(1):80–5.
8. Swartz MJ, Hughes MA, Frassica DA, Herman J, Yeo CJ, Riall TS, Lillemoe KD, Cameron JL, Donehower RC, Laheru DA, Hruban RH, Abrams RA. Adjuvant concurrent chemoradiation for node-positive adenocarcinoma of the duodenum. Arch Surg. 2007 Mar;142(3):285–8.
9. Yeo CJ, Sohn TA, Cameron JL, Hruban RH, Lillemoe KD, Pitt HA. Periampullary adenocarcinoma: analysis of 5-year survivors. *Ann Surg* 1998;227:821–31.
10. Duffy JP, Hines OJ, Liu JH, Ko CY, Cortina G, Isacoff WH, Nguyen H, Leonardi M, Tompkins RK, Reber HA. Improved survival for adenocarcinoma of the ampulla of Vater: fifty-five consecutive resections. Arch Surg. 2003 Sep;138(9):941–8; discussion 948–50.
11. van Roest MH, Gouw AS, Peeters PM, Porte RJ, Slooff MJ, Fidler V, de Jong KP. Results of pancreaticoduodenectomy in patients with periampullary adenocarcinoma: perineural growth more important prognostic factor than tumor localization. Ann Surg. 2008 Jul;248(1):97–103.
12. Soo KC, Carter RL, O'Brien CJ, Barr L, Bliss JM, Shaw HJ. Prognostic implications of perineural spread in squamous carcinomas of the head and neck. Laryngoscope. 1986;96:1145–1148.
13. Ayala GE, Dai H, Ittmann M, Li R, Powell M, Frolov A, Wheeler TM, Thompson TC, Rowley D. Growth and survival mechanisms associated with perineural invasion in prostate cancer. Cancer Res. 2004;64:6082–6090.
14. Liebig C, Ayala G, Wilks J, Verstovsek G, Liu H, Agarwal N, Berger DH, Albo D. Perineural invasion is an independent predictor of outcome in colorectal cancer. J Clin Oncol. 2009 Nov 1;27(31):5131–7.
15. Nagakawa T, Mori K, Nakano T, Kadoya M, Kobayashi H, Akiyama T, Kayahara M, Ohta T, Ueno K, Higashino Y, et al. Perineural invasion of carcinoma of the pancreas and biliary tract. Br J Surg. 1993;80:619–621.
16. Scartozzi M, Galizia E, Verdecchia L, Berardi R, Graziano F, Catalano V, Giordani P, Mari D, Silva RR, Marmorale C, Zingaretti C, Cascinu S. Lymphatic, blood vessel and perineural invasion identifies early-stage high-risk radically resected gastric cancer patients. Br J Cancer. 2006;95:445–449.
17. Sayar et al. A, Turna A, Solak O, Kiliçgün A, Urer N, Gürses A. Nonanatomic prognostic factors in resected nonsmall cell lung carcinoma: the importance of perineural invasion as a new prognostic marker. Ann Thorac Surg. 2004;77:421–425.
18. McCready DR, Chapman JA, Hanna WM, Kahn HJ, Murray D, Fish EB, Trudeau ME, Andrulis IL, Lickley HL. Factors affecting distant disease-free survival for primary invasive breast cancer: use of a log-normal survival model. Ann Surg Oncol. 2000;7:416–426.
19. Bouvet M, Gamagami RA, Gilpin EA, Romeo O, Sasson A, Easter DW, Moossa AR. Factors influencing survival after resection for periampullary neoplasms. Am J Surg. 2000 Jul;180(1):13–7.

20. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Buchler M; International Study Group on Pancreatic Fistula Definition. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery. 2005;138:8–13.
21. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Traverso LW, Yeo CJ, Büchler MW. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 2007 Nov; 142 (5):761–8.
22. Bilimoria KY, Bentrem DJ, Wayne JD, Ko CY, Bennett CL, Talamonti MS. Small bowel cancer in the United States: changes in epidemiology, treatment, and survival over the last 20 years. Ann Surg. 2009;249:63–71.
23. Lee HG, You DD, Paik KY, Heo JS, Choi SH, Choi DW. Prognostic factors for primary duodenal adenocarcinoma. World J Surg. 2008;32(10):2246–52.
24. Zhang S, Cui Y, Zhong B, Xiao W, Gong X, Chao K, Chen M. Clinicopathological characteristics and survival analysis of primary duodenal cancers: a 14-year experience in a tertiary centre in South China. Int J Colorectal Dis. 2011 Feb; 26(2):219–26.
25. Wheeler JM, Warren BF, Mortensen NJ, Kim HC, Biddolph SC, Elia G, Beck NE, Williams GT, Shepherd NA, Bateman AC, Bodmer WF. An insight into the genetic pathway of adenocarcinoma of the small intestine. Gut 2002; 50:218.
26. Liebig C, Ayala G, Wilks JA, Berger DH, Albo D. (2009) Perineural invasion in cancer: a review of the literature. Cancer. 2009 Aug 1;115(15):3379–91. Review.
27. Chilton JK. Molecular mechanisms of axon guidance. Dev Biol. 2006;292:13–24.
28. Chedotal A, Kerjan G, Moreau-Fauvarque C. The brain within the tumor: new roles for axon guidance molecules in cancers. Cell Death Differ. 2005;12:1044–1056.
29. Lowe MC, Coban I, Adsay NV, Sarmiento JM, Chu CK, Staley CA, Galloway JR, Kooby DA. Important prognostic factors in adenocarcinoma of the ampulla of Vater. Am Surg. 2009 Sep;75(9):754–60.
30. Chan C, Herrera MF, de la Garza L, Quintanilla-Martinez L, Vargas-Vorackova F, Richaud-Patín Y, Llorente L, Uscanga L, Robles-Diaz G, Leon E, et al. Clinical behavior and prognostic factors of periampullary adenocarcinoma. Ann Surg. 1995 Nov;222(5):632–7.

Discussant

Dr. Jean Nicolas Vauthey (Houston, TX): I congratulate Dr. Ferrone and her collaborators for another excellent contribution analyzing the factors associated with outcome following resection of duodenal adenocarcinoma. In this study, the authors show that the only independent predictor of outcome is perineural invasion while lymph node status or lymph node ratio, type of resection, or size of tumor fails to stratify prognosis. This study is in contrast with previous studies on pancreatic or biliary malignancies, and it suggests biologic differences associated with duodenal adenocarcinoma are linked to outcome.

I have three questions for the authors:

1. The number of pathology blocks and the intensity of the review may affect the yield of a pathological study. How many blocks were reviewed per specimen? The authorship indicates that one pathologist reviewed the slides. What is the interobserver agreement of a pathological review of perineural invasion?

Rodriguez-Urrego PA, Cronin AM, Al-Ahmadie HA, Gopalan A, Tickoo SK, Reuter VE, Fine SW. Interobserver and intraobserver reproducibility in digital and routine microscopic assessment of prostate needle biopsies. Hum Pathol. 2011 Jan; 42(1):68–74. Epub 2010 Oct 20. PubMed PMID: 20970164.

2. The fact that lymph node status or tumor size failed to correlate with prognosis is somewhat unexpected. Do the authors feel that these findings are related to the biology of the tumor or the quality and extent of their surgical resection and lymph node dissection?

3. The authors have previously correlated the biology of ampullary carcinoma with telomerase and hTERT. Can the authors speculate and provide a basic science explanation for their interesting findings?

Liebig C, Ayala G, Wilks JA, Berger DH, Albo D. Perineural invasion in cancer: a review of the literature. *Cancer. 2009 Aug* 1; 115(15):3379–91. Review.

Closing Discussant

Dr. Cristina Ferrone: Thank you for your thoughtful questions.

We reviewed three blocks per specimen. Since all of the specimens were originally reviewed by a GI pathologist, we felt that re-review of the slides by a single senior GI pathologist was sufficient. According to a study performed in prostate cancer, the interobserver agreement for perineural invasion amongst four pathologists is good (k, 0.55).

Over the past decade, the prognostic value of tumor size and lymph node status in duodenal adenocarcinoma has been frequently debated. Neither factor consistently emerges as a significant prognostic factor in large retrospective series. In our series, LN status was significant on univariate analysis, but lost its significance on multivariate analysis because of the superior prognostic power of perineural invasion. It appears that the biology of the tumor, as yet incompletely known, once again is king.

Our search of the literature has turned up no correlation between telomerase and perineural invasion. We do know that perineural invasion is the result of a complex set of interactions between tumor cells, nerve cells, and stromal cells. These interactions are still incompletely understood. Perineural invasion has been most extensively studied in pancreatic, prostate, and colorectal cancers and is consistently associated with a decreased survival. Certain neurotrophic factors and metalloproteinases clearly play a role in perineural invasion. We assume that these factors may also contribute to perineural invasion in duodenal adenocarcinoma.