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A High Lymph Node Ratio is Associated with Distant Recurrence After Surgical Resection of Ampullary Carcinoma

Christina L. Roland, MD¹, Matthew H. G. Katz, MD¹, Graciela M. N. Gonzalez, MPH², Peter W. T. Pisters, MD¹, Jean-Nicolas Vauthey, MD¹, Robert A. Wolff, MD³, Christopher H. Crane, MD⁴, Jeffrey E. Lee, MD¹, and Jason B. Fleming, MD¹

¹Department of Surgical Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas

²Department of Biostatistics, University of Texas MD Anderson Cancer Center, Houston, Texas

³Department of Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas

⁴Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas

Abstract

Background—For ampullary carcinoma (AC), the lymph node ratio (LNR) has been associated with overall survival. However, the use of the LNR to predict distant recurrence risk remains unknown. The purpose of this study was to determine if the LNR is associated with distant recurrence risk.

Methods—One hundred forty three patients with AC who underwent pancreaticoduodenectomy between 1995–2011 were identified from a single-institution prospective database. Data on clinicopathologic factors and recurrence were analyzed.

Results—At a median follow-up of 43 months (62 months for survivors), 55 patients (38%) had developed recurrent disease, with a median time to recurrence of 13 months. Patients with a LNR 0.15 were more likely to have T3/4 tumors, advanced AJCC stage, lymphovascular (LVI) or perineural invasion (PNI) and develop recurrent disease. Univariate analysis demonstrated that T-stage, lymph node status, AJCC stage, LVI, PNI, and LNR were significantly associated with decreased time to distant recurrence (TTDR). In multivariate stepwise regression, only LNR and LVI were significantly associated with decreased TTDR.

Conclusions—A high LNR is associated with distant recurrence after surgical resection of AC. Given the high risk of disease recurrence, consideration for adjuvant therapy is warranted in patients with a LNR 0.15.

Corresponding author and reprint requests: Jason B. Fleming, MD, Department of Surgical Oncology, Division of Surgery, University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, Phone: 713-745-0890, Fax: 713-745-4426, jbflemin@mdanderson.org.

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Keywords

ampullary carcinoma; lymph node ratio; recurrence

INTRODUCTION

Although patients with ampullary carcinoma (AC) have improved survival compared to patients with pancreatic adenocarcinoma, up to 40% of patients develop recurrent disease, highlighting the importance of adjuvant therapy [1]. Several factors have been associated with outcomes for patients with AC, including advanced T stage, tumor grade, pancreatobiliary histologic subtype, tumor budding, lymphovascular (LVI) or perineural invasion (PNI) and node-positive disease [2–15].

Recently, the lymph node ratio (LNR), defined as the number of nodes with metastatic disease among the total number of retrieved nodes, has demonstrated prognostic utility for overall survival in many types of malignancies including pancreatic, colon, breast, gastric, and esophageal carcinoma [16–22]. For AC, using the LNR as a categorical variable, previous studies have shown a cutoff point between 0.1 and 0.2 as having prognostic significance for overall survival [7, 11, 23]. However, the use of the LNR to predict distant recurrence risk remains unknown. The current study was conducted to identify factors associated with distant recurrence for patients with surgically resected AC with specific focus on pathologic data available to the health care team after pancreaticoduodenectomy (PD).

METHODS

This retrospective study was approved by the Institutional Review Board at The University of Texas MD Anderson Cancer Center. We retrieved clinical data on all patients who underwent PD for AC between 1989–2011 from our prospectively maintained, institutional AC database [24]. We excluded from analysis patients with a final diagnosis of invasive adenocarcinoma arising from the pancreas or duodenum.

Treatment Sequencing and Therapy

Our multidisciplinary team coordinated the treatment algorithm for each patient. PD was performed using standardized technique [25]. For those patients who underwent preoperative chemoradiation, diagnosis was established with endoscopic ultrasound and biopsy. Significant complications were defined as those requiring inpatient hospitalization. The decision to administer adjuvant therapy was influenced by the prevalence of high-risk factors, the perceived benefit of adjuvant therapy, the bias of the surgeon, and the referral pattern. Biliary decompression was accomplished with a plastic or metal stent before preoperative chemoradiation [26]. Patients were staged according to the AJCC Cancer Staging guidelines [27].

Follow-up and Definitions of Recurrence

Following resection, patients were evaluated every 3–4 months using a standard surveillance protocol, including physical examination, chest radiography and abdominal CT. Intervals were extended to 6 months after 2 years. The development of a new low-density mass or abdominal lymphadenopathy in the region of the resected pancreas or mesenteric root was considered locoregional recurrence in this area. Radiographic evidence of a low-density mass in the liver or lungs or new-onset ascites was considered evidence for distant recurrence. Biopsy of recurrence was rarely performed. Only the first site(s) of recurrent disease was documented for this study. Time to distant recurrence (TTDR) is defined as from the time of surgery to the time of first distant recurrence or to the time of last contact.

Statistics

For categorical variables, descriptive statistics were compared using χ^2 or Fisher's exact test; Wilcoxon's rank sum test (t-test) and the Kruskal-Wallis test (ANOVA) were used to compare the distributions of continuous variable among different groups. TTDR was defined as the interval between the date of resection and first evidence of distant recurrence or last follow-up if recurrence was not observed. The Kaplan-Meier product limit method was used to estimate the median survival time and median time to distant recurrence. The Cox proportional hazards regression model, in which a backward elimination process was used for variable selection with an entry and removal limit of $P < 0.1$ and $P < 0.05$, respectively, was applied to identify independent factors associated with TTDR. Statistical analysis was performed using STATA/SE version 12.0 statistical software (Stata Corp. LP, College Station, TX).

RESULTS

Clinicopathologic Characteristics Associated with Distant Recurrence

The clinicopathologic and treatment characteristics of 143 consecutive patients with histologically confirmed AC who underwent PD between 1989 and 2011 are reported in Table 1. Median clinical follow-up time was 43 months (range, 1–222), 62 months for survivors. 33 patients (23%) received preoperative chemoradiation. Median tumor size was 1.8 cm and 98% of patients underwent a margin-negative resection. Among the 143 patients, 72 (50%) had N1 disease. Twenty-five patients (17%) developed a perioperative complication with one perioperative mortality.

Fifty-five patients (38%) developed recurrent disease, with a median time to recurrence of 13 months (Fig. 1; Table 1). These two groups were compared and several factors were identified as significantly different between patients that developed a recurrence and those who did not. Patients with recurrent disease were more likely to have advanced T-stage ($p=0.007$), lymph node positive (N1) disease ($p=0.001$), higher LNR ($p<0.001$), advanced AJCC stage ($p=0.002$), LVI ($p=0.003$) or PNI ($p=0.002$). There was no difference in the number of lymph nodes harvested between the groups. The median number of lymph nodes involved was 1 (0–14) with a LNR of 0.02 (range: 0–0.82; Table 1). The median LNR for N1 patients was 0.13 (range: 0.01–0.82).

Lymph Node Ratio and Time to Distant Recurrence

Given the identification of LNR as a factor highly associated with distant recurrence, we sought to understand the relative impact of subgroups based upon LNR. LNR was stratified into the following groups: 0, 0.1–0.14, 0.15 (Table 2). These cutoff points were chosen for two reasons: (1) they included the range of LNRs found to have a significant relation with survival in previous studies [7, 11, 23], and (2) they were centered around the median LNR for N1 patients in our dataset. Although there was no difference in the rate of preoperative chemoradiation between the groups, patients with N1 disease (LNR = 0.01) were more likely to receive postoperative chemotherapy and/or chemoradiation. Patients with a high LNR (> 0.15) were more likely to have T3/4 tumors, advanced AJCC stage, LVI or PNI. At last follow-up, 22 patients (73%) with a high LNR developed recurrent disease, of which the majority had a component of distant failure (Table 2). Sixteen patients developed a local recurrence and there was no difference in the local recurrence rate based on LNR. 8 patients developed simultaneous local and distant recurrences. The pattern of recurrence is listed in Table 2.

The univariate analysis shown in Table 3 demonstrates that T-stage ($p=0.014$), lymph node status ($p=0.001$), AJCC stage ($p=0.012$), LVI ($p=0.005$), PNI ($p=0.02$) and LNR > 0.15 ($p<0.001$, Figure 1) were significantly associated with decreased time to distant recurrence (TTDR). Patients with a LNR > 0.15 had the shortest time to distant recurrence with a median of 13 months (Table 3 and Fig. 1B). Interestingly, patients with N0 disease and a low LNR (LNR = 0.01–0.14) had similar 3-yr distant recurrence rates (21.2% vs 24.6%; $p=0.499$; Table 3). All further examined parameters including the number of examined lymph nodes, tumor size, CA 19-9 level, preoperative chemoradiation, and degree of differentiation did not influence TTDR (data not shown). In the multivariate Cox stepwise regression model, only LNR and LVI were significantly associated with decreased TTDR (Table 4).

DISCUSSION

Patients with AC have improved outcomes compared to patients with pancreatic adenocarcinoma. However, local and distant failure remains a long-term problem [2, 28–30]. Metastatic disease to regional lymph nodes has consistently represented a strong predictor of survival and recurrence risk [1, 9, 12]. Our study is the first to report the use of the LNR as a predictor of distant recurrence risk in patients who underwent resection for AC. Similar to previous studies, 38% of patients in this study developed recurrent disease, with the majority having some component of distant failure (Table 2) [1, 9]. In this study, patients with a LNR > 0.15 had significantly decreased TTDR than patients with node-negative or low LNR (LNR = 0.01–0.14; Table 4, Figure 1B). Patients with a high LNR were more likely to have advanced T stage, LVI, and PNI. 98% of patients had a microscopically negative resection, highlighting the importance of tumor biology on recurrence risk. Interestingly, we found no difference in the risk of distant recurrence between patients with node-negative disease or a low-LNR. Patients with a low LNR were more likely than patients with node-negative disease to receive postoperative chemotherapy or chemoradiation, which could account for this finding. Within the study population, 21% of patients fell within this high-risk

population (LNR = 0.15) with a risk of recurrence of 73%. However, 37% of patients within this group did not receive potentially beneficial postoperative therapy. The use of the LNR may serve as an easy tool to identify high-risk patients who could benefit from adjuvant therapy.

Several studies have evaluated factors associated with the development of recurrent disease [2, 4, 5, 8–11, 15, 23, 31]. Advanced T-stage, LVI and PNI have repeatedly been shown to be important predictors of recurrence risk. The use of ancillary pathologic tests, such as tumor budding, loss of β -catenin and osteopontin staining has demonstrated prognostic value for recurrence risk [10, 13, 14]. However, these tests require additional evaluation outside of routine TNM staging, making them more expensive and labor intensive. In this study, multivariate analysis demonstrated the lymph node ratio and the presence of lymphovascular invasion as the only clinicopathologic factors associated with an increased risk of distant recurrence (Figure 1, Table 4).

25% of patients in this study received preoperative chemoradiation. The utility of the LNR for patients that have undergone preoperative therapy has not been validated. However, in this study, patients that received preoperative therapy had equivalent survival and LNR distribution as those that did not have preoperative therapy (data not shown). Interestingly, patients that received preoperative therapy were less likely to have LVI on final pathologic analysis compared to patients that had postoperative therapy or surgery alone (25% versus 56% versus 52%, respectively; $p < 0.001$). Thus the data suggests that the delivery of preoperative therapy may reduce LVI in patients with AC. As the sample size for the preoperative therapy group is small (33 patients), it is difficult to draw any firm conclusions regarding this data, but presents an interesting finding that warrants further investigation.

The current study has several limitations: the retrospective nature of the analysis, the small number of patients treated over a long time period, and the variability in the use of preoperative and postoperative adjuvant therapy. We believe, however, that these limitations did not greatly affect the results of the study as the differences between the groups were too marked to have resulted from bias. The benefit of adjuvant chemotherapy and chemoradiation has been demonstrated in several recent studies. A large cooperative analysis from Johns Hopkins and the Mayo Clinic demonstrated a significant survival benefit for patients who received adjuvant chemoradiation [1]. A recent retrospective study of 137 patients demonstrated that 3-year local control was improved in patients receiving chemoradiation therapy (88% vs 55%, $P = .001$). In this context, patients with node-positive ampullary carcinoma, especially those with a LNR = 0.15, appear to be good candidates for adjuvant therapy.

CONCLUSION

A high lymph node ratio is associated with distant recurrence after surgical resection of ampullary carcinoma. Given the high risk of disease recurrence, consideration for adjuvant therapy is warranted in patients with a LNR = 0.15.

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Figure 1. Time to Distance Recurrence

Kaplan-Meier estimate of time to distant recurrence for ampullary carcinoma patients after pancreaticoduodenectomy for (A) entire cohort (B) by LNR

Table 1
Clinicopathologic Characteristics of Patients with Resected Ampullary Carcinoma by Recurrence Status.

		All patients N=143	Recurrence N=55	No Recurrence N=88	p-value
Age, median (range), y		65 (28–87)	64 (38–87)	66 (28–84)	0.357
Gender, n (%)	Male	85 (59)	29 (53)	56 (63)	0.196
	Female	58 (41)	26 (47)	32 (37)	
Race, n (%)	Caucasian	101 (71)	43 (78)	58 (66)	0.407
	African-American	8 (5)	2 (4)	6 (7)	
	Hispanic	17 (12)	6 (11)	11 (12)	
	Other	17 (12)	4 (7)	13 (15)	
Preop Chemoradiation, n (%)		33 (23)	15 (27)	18 (20)	0.437
Postop Chemotherapy, n (%)		28 (20)	13 (24)	15 (17)	0.251
Postop Chemoradiation, n (%)		34 (24)	14 (25)	20 (23)	0.594
T Stage, n (%)	T0–T2	80 (56)	23 (42)	57 (65)	0.007
	T3–T4	63 (44)	32 (58)	31 (35)	
Tumor Size, median (range), cm		1.8 (0–7.8)	2 (0–7.8)	1.6 (0–5.5)	0.282
N Stage, n (%)	N0	71 (50)	18 (33)	53 (60)	0.001
	N1	72 (50)	37 (67)	35 (40)	
# LN examined, median (range)		19 (4–54)	18 (4–38)	20 (4–54)	0.204
# positive LN, median (range)		1 (0–14)	1 (0–14)	0 (0–9)	<0.001
Lymph Node Ratio, median (range)		0.02 (0–0.82)	0.08 (0–0.82)	0 (0–0.27)	<0.001
Lymph Node Ratio Group	0	71 (50)	18 (33)	53 (60)	<0.001
	0.01–0.14	42 (29)	15 (27)	27 (31)	
	0.15	30 (21)	22 (40)	8 (9)	

		All patients N=143	Recurrence N=55	No Recurrence N=88	p-value
AJCC Stage, n (%)	0-2A	66 (46)	16 (29)	50 (57)	0.002
	2B-3	77 (54)	39 (71)	38 (43)	
Lymphovascular invasion, n (%)	Negative	61 (43)	16 (29)	45 (51)	0.003
	Positive	54 (38)	29 (53)	25 (28)	
	Missing	28 (20)	10 (18)	18 (21)	
Perineural invasion, n (%)	Negative	49 (34)	12 (22)	37 (42)	0.002
	Positive	33 (23)	19 (35)	14 (16)	
	Missing	61 (43)	24 (44)	37 (42)	
CA 19-9, median (range), u/mL		43 (1-13,764)	71 (1-13,764)	30 (1-977)	0.088
Grade, n (%)	Well	13 (9)	2 (4)	11 (13)	0.155
	Moderate	96 (66)	40 (73)	56 (64)	
	Poor	29 (20)	13 (24)	16 (18)	
	Missing	5 (4)	0	5 (6)	
Resection Status, n (%)	R0	140 (98)	54 (98)	86 (98)	0.854
	R1	3 (2)	1 (2)	2 (2)	
Perioperative Complications, n (%)		25 (17)	6 (11)	19 (22)	0.102

Clinicopathologic Characteristics of Patients with Resected Ampullary Carcinoma by LNR group

Table 2

		LNR:0 N=71	LNR: 0.01-0.14 N=42	LNR 0.15 N=30	p-value
Age, median (range), y		67 (28-84)	64 (40-78)	64 (37-87)	0.312
Gender, n (%)	Male	44 (62)	24 (57)	17 (57)	0.828
	Female	27 (38)	18 (43)	13 (43)	
Race, n (%)	Caucasian	46 (64)	32 (76)	23 (76)	0.322
	African-American	7 (10)	1 (2)	0	
	Hispanic	9 (13)	3 (7)	5 (17)	
	Other	9 (13)	6 (15)	2 (7)	
Preop Chemoradiation, n (%)		20 (28)	7 (17)	6 (20)	0.523
Postop Chemotherapy, n (%)		4 (6)	13 (31)	11 (37)	<0.001
Postop Chemoradiation, n (%)		8 (11)	21 (49)	19 (63)	<0.001
T Stage, n (%)	T0-T2	50 (70)	23 (55)	7 (23)	<0.001
	T3-T4	21 (30)	19 (45)	23 (77)	
Tumor Size, median (range), cm		1.8 (0-7.8)	1.5 (0-7)	2 (0-5.5)	0.264
# LN examined, median (range)		18 (4-45)	22 (8-54)	19 (4-37)	0.019
# positive LN, median (range)		0	1 (1-6)	5 (1-14)	<0.001
Number of Positive LN group	0	71 (100)	0	0	<0.001
	1-3	0	40 (93)	12 (40)	
	4-6	0	3 (7)	10 (33)	
	7	0	0	8 (27)	
AJCC Stage, n (%)	0-2A	65 (92)	1 (2)	0	<0.001
	2B-3	6 (8)	41 (98)	30 (100)	

		LNR:0 N=71	LNR: 0.01-0.14 N=42	LNR 0.15 N=30	p-value
Lymphovascular invasion, n (%)	Negative	40 (56)	15 (36)	6 (20)	<0.001
	Positive	16 (23)	18 (43)	20 (67)	
	Missing	15 (21)	9 (21)	4 (13)	
Perineural invasion, n (%)	Negative	29 (41)	15 (36)	5 (17)	0.001
	Positive	10 (14)	8 (19)	15 (50)	
	Missing	32 (45)	19 (45)	10 (33)	
CA 19-9, median (range), u/mL		42 (3-13764)	26 (1-689)	59 (1-5184)	0.159
Grade, n (%)	Well	9 (13)	3 (7)	2 (3)	0.781
	Moderate	46 (65)	29 (69)	21 (70)	
	Poor	11 (15)	10 (24)	8 (27)	
	Missing	5 (7)	0	0	
Resection Status, n (%)	R0	69 (99)	42 (98)	29 (97)	0.781
	R1	1 (1)	1 (2)	1 (3)	
Perioperative Complications, n (%)		14 (20)	7 (17)	4 (13)	0.741
First Recurrence		18 (25)	15 (36)	22 (73)	<0.001
	Local recurrence	5 (7)	5 (12)	6 (20)	0.154
	Distant recurrence	16 (23)	12 (29)	19 (63)	0.001
	<i>Peritoneal</i>	3 (21)	2 (18)	2 (13)	
	<i>Liver</i>	6 (43)	4 (36)	8 (53)	
	<i>Lung</i>	4 (29)	5 (46)	4 (27)	
	<i>Other</i>	1 (7)	0	1 (7)	

Table 3

Univariate Analysis of Risk Factors for Time to Distant Recurrence in Resected Ampullary Carcinoma.

		3-yr Distant Recurrence (%)	Univariate Analysis	
			Hazard Ratio (95% CI)	p-value
T stage	T0–T2	22.5	Ref.	0.014
	T3–T4	39.5	2.11 (1.16–3.82)	
N Stage	N0	20.9	Ref.	0.014
	N1	38.6	2.15 (1.16–3.96)	
AJCC Stage	0–2A	19.5	Ref.	0.012
	2B–3	38.4	2.25 (1.19–4.23)	
LNR	0	20.9	Ref.	
	0.01–0.14	23.9	1.3 (0.61–2.74)	0.499
	0.15	60.9	4.11 (2.06–8.2)	<0.001
Lymphovascular Invasion	Negative	20.4	Ref.	0.005
	Positive	37.3	2.71 (1.34–5.46)	
Perineural Invasion	Negative	23.5	Ref.	0.02
	Positive	51.2	2.54 (1.16–5.56)	

Table 4

Multivariate Analysis of Risk Factors for Time to Distant Recurrence in Resected Ampullary Carcinoma.

		Recurrence	
		Hazard Ratio (95% CI)	p-value
T stage	T0–T2	Ref.	0.741
	T3–T4	1.21 (0.38–3.85)	
LNR	0	Ref.	0.771
	0–0.14	1.18 (0.39–3.52)	
	0.15	3.49 (1.14–10.68)	
Lymphovascular Invasion	Negative	Ref.	0.031
	Positive	3.27 (1.12–9.6)	
Perineural Invasion	Negative	Ref.	0.549
	Positive	0.68 (0.19–3.52)	