Lymph Node Ratio Is an Independent Prognostic Factor After Resection of Periampullary Malignancies

Data From a Tertiary Referral Center in the Middle East

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Objective: The prognostic impact of nodal involvement in resected pancreatic carcinoma and biliary malignancy has been relatively well established. It has been suggested that lymph node ratio (LNR) may be a more informative way of stratifying patients with node positive disease. Our retrospective review aimed to investigate the significance of such variables and test for independent prognostic factors for survival.

Methods: One hundred eighty-three pancreatic and periampullary malignancy cases were registered at the American University of Beirut Medical Center from 1990 to 2004. Of those, 80 had complete data on lymph node status. We analyzed the impact of the number of lymph nodes resected, the number of positive lymph nodes retrieved and LNR using Kaplan-Meier and Cox proportional hazard models. The measured outcome in the KM model was the survival probability at 1, 3, and 5 years while the Cox model was used to measure the hazard ratio (HR) of the previously identified predictors on survival.

Results: For the 80 patients included in this analysis, overall survival rates were 65% (54 to 78), 32% (18 to 47), and 21% (8 to 34) were alive at 1, 3, and 5 years, respectively. The median number of resected lymph nodes was 9. In the node positive patients, those who had >12 nodes examined were found to have a significantly better survival (HR = 0.24; $P = 0.013$). On multivariate analysis, our model showed the following factors to be significant: age 60 years or older (HR = 5.92; $P = 0.018$), poorly differentiated tumors (HR = 21.87; $P = 0.018$), number of lymph nodes examined <12 LN (HR = 6.77; $P = 0.022$), 3 or more metastatic LN (HR = 7.21; $P = 0.028$), and LNR $\geq$ 0.2 (HR = 7.12; $P = 0.007$).

Conclusions: After pancreaticodudonectomy for adenocarcinoma of the pancreas and biliary malignancies, ratio-based lymph node staging is an independent and powerful prognostic factor.

Key Words: pancreatic cancer, positive lymph nodes, lymph node ratio, survival

(*Am J Clin Oncol* 2014;37:13–18)

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The authors declare no conflicts of interest.

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ISSN: 0277-3732/14/3701-0013
DOI: 10.1097/COC.0b013e31826b9c74

Pancreatic cancer is the fourth most common cause of cancer-related mortality in the United States with an estimated 40,000 new cases and 37,000 deaths.[1] Patients usually present with locally advanced or metastatic disease, and even for patients who are candidates for potentially curative resection, 5-year survival has been reported to be in the range of 15% to 25%.[2–4] Advances in radiologic imaging, surgical technique, and adjuvant therapies have improved the outcomes for those patients, however progress has been slow. Accurate staging and establishing clinically useful prognostic factors is essential. Prognostic factors such as tumor size, degree of histologic differentiation and resection margin status have been clearly validated.[5,6] Lymph node involvement has been associated with poor survival after pancreatic cancer resection[3,4,7]; however, this has not been a consistent finding.[8,9] The use of nodal status (positive vs. negative) or the absolute number of positive lymph nodes for prognostic purposes may be subject to error. Patients may be under-staged due to inadequate surgical lymphadenectomy or inadequate histopathologic examination of the resected specimen. An alternative method of stratifying nodal involvement involves calculating the lymph node ratio (LNR) by dividing the number of positive nodes by the total number of examined nodes. Several studies have found this to be an independent prognostic factor in resected pancreatic carcinoma.[2,10–12]

The aim of this retrospective study was to describe the clinicopathologic, demographic, and surgical characteristics of the patients diagnosed with pancreaticobiliary malignancies at our institution. We also set out to determine the relevant prognostic factors affecting survival in the patients undergoing resection, and in particular, to determine whether LNR is an independent predictor of survival after pancreaticoduodenectomy for malignancy.

METHODS

One hundred eighty-three patients with pancreatic and/or periampullary malignancies were registered at the American University of Beirut Medical Center (AUBMC) from 1990 to 2004. After obtaining approval from the Institutional Review Board, clinicopathologic data were gathered from medical records. These data included medical and social history, staging of primary cancers, presenting signs and symptoms, pathologic diagnosis, and operative procedures.

Inclusion Criteria

Only 80 patients who underwent pancreaticoduodenectomy, total pancreatectomy, or partial pancreatectomy, and had data on LN status, were considered in the LNR analysis. Seventy-eight patients did not undergo any surgical resections, and 27 patients

had unknown LN status because of missing pathologic analysis. Therefore, a prospective database of 80 operative patients was studied and used in the survival analysis. LNR was determined by dividing the total number of positive lymph nodes by the total number of examined lymph nodes. The "impact of surgeon" was considered a prognostic factor. Impact of surgeon is defined as the impact of hepatobillliary specialty on the patient's survival. At AUBMC, a general surgeon was performing the pancreatic and periampullary surgeries before 1998, when a hepatobilliary specialist stepped in and solely started performing such surgeries.

Staging Criteria

Staging of patients was assessed following both the TNM classification system and American Joint Committee on Cancer (AJCC) staging system (6th edition).[13]

Statistical Analysis

Sample characteristics were summarized mainly using frequency and percentage with the exception of age where the mean and the median were calculated. Overall survival was determined using the date of diagnosis and the date of last follow-up which could be either date of death or date of last contact of the patient. In the latter case the patients were censored in the survival analysis. Cumulative survival rates at 1, 3, and 5 years were estimated using the Kaplan-Meier method, whereas differences in strata was determined using the log rank test. Hazard ratios and 95% confidence intervals at the univariate and multivariate level were estimated using the Cox proportionate hazard models. Data were analyzed using SPSS v 18, and α was set at 5%.

TABLE 1. Clinical Characteristics of Patients

Variables	N (%)
Age	
Median	63
Sex	
Female	30 (37.5)
Male	50 (62.5)
Type of resection	
Whipple procedure	71 (89)
Total pancreatectomy	2 (2)
Distal pancreatectomy	7 (9)
Pathology type	
Pancreatic carcinoma	61 (76)
Cholangiocarcinoma	10 (13)
Duodenal carcinoma	3 (4)
Papillary carcinoma	6 (7)
Tumor differentiation	
Well to moderate	53 (79)
Poor	14 (21)
Surgical margins	
Negative	53 (73)
Positive	20 (27)
Total number of lymph node resected	
N0 patients	
<12	22 (28)
≥ 12	21 (26)
N1 patients	
<12	21 (26)
≥ 12	16 (20)

RESULTS

Clinicopathologic Characteristics

Of the 80 patients, 50 were males (62.5%) and 30 were females (37.5%), median age was 63 (range, 17 to 81 y), and 49 patients were of age 60 and above. No 30-day postoperative death was encountered (Table 1). Tumors were located in the pancreatic head in 57 patients (86%), body or tail in 9 patients (14%), and 14 patients had undetermined tumor location. Final pathologic analysis revealed that the most common carcinomas were moderately differentiated (64%) whereas only 21% were poorly differentiated, and 10% were well differentiated.

These patients had different pathology types, declared according to the tumor location. Sixty-one patients had pancreatic adenocarcinoma (76%), located either in the head, body, or tail of the pancreas. Six patients had papillary carcinoma (7%), located in the ampulla of Vater. Ten had cholangiocarcinoma (13%), and 3 had duodenal carcinoma (4%), located in the bile duct and the duodenum, respectively.

Surgical resection was performed on these 80 patients, where only 2 (2%) underwent total pancreatectomy, 7 (9%) underwent distal pancreatectomy, 71 (89%) underwent standard pancreaticoduodenectomy (Whipple's procedure). The surgical procedures performed are listed in Table 1.

Staging

TNM staging followed was that of the American Joint Committee of Cancer (AJCC 6th edition).[13] Tumor classification revealed 11 patients as stage I (16%), 30 patients as stage II (43%), 17 patients as stage III (24%), and 12 patients as stage IV (17%) (Table 2).

It was shown that the most common metastatic site for patients presenting with stage IV disease was the liver followed by the lungs, lymph nodes, peritoneum, and omentum. Nineteen patients had missing staging information.

LN and LNR

The median number of total nodes evaluated was 9 (range, 1 to 45). However, of these 80 patients, 43 (51%) had no lymph node metastasis (N0), whereas 37 (49%) presented with at least 1 metastatic lymph node (N1). The median number of lymph nodes resected was calculated in the 2 groups, giving a median of 7 (interquartile range = 8) in the node negative (N0) group, compared with a median of 11 (interquartile range = 9) in the node positive (N1) group. The (N1) group was further divided into 3 subgroups according to the LNR; LNR = 0: n = 43 (54%), LNR $\leq$ 0.2: n = 19 (24%), LNR $\geq$ 0.2: n = 18 (22%) (Figs. 1 and 2).

Survival

Survival analysis of the whole population showed that 65% (54 to 78), 32% (18 to 47), and 21% (8 to 34) were alive at 1, 3, and 5 years, respectively. The estimated median survival for the whole population was 2.13 years (range, 0.92 to 3.35 y).

Prognostic Factors Associated With Survival

Clinicopathologic and other factors were tested for their prognostic significance (Tables 2 and 3). On univariate analysis, factors associated with worse overall survival included age >60 (hazard ratio [HR] = 2.38), a pathology of pancreatic carcinoma (HR = 7.16) or papillary carcinoma (HR = 9.91), poorly differentiated histology (HR = 4.24), positive margin (HR = 2.81), and impact of surgeon before 1998 (HR = 2.56) (all $P < 0.05$). The LNR itself was also a very significant prognostic factor; patients with a LNR $\geq$ 0.2 had a 2-fold

TABLE 2. Univariate Hazard Ratio Analysis of Prognostic Factors After Pancreatic Resection

Prognostic Factors	N	HR	95% CI	*P*
Sex				
Male	50	1	0.61-2.30	0.615
Female	30	1.19		
Age				
< 60	31	1	1.13-4.04	0.016
≥ 60	49	2.38		
Tumor size (cm)				
> 3	17	1	0.86-5.79	0.098
≥ 3	33	2.23		
Vascular invasion				
No	73	1	0.74-6.26	0.161
Yes	7	2.15		
Tumor differentiation				
Well to moderate	53	1	1.99-13.81	0.001
Poor	14	5.24		
Pathology				
Cholangiocarcinoma and duodenal carcinoma	13	1	1.40-24.99	0.016
Pancreatic carcinoma	61	5.91	1.28-40.27	0.025
Ampullary carcinoma	6	7.16		
Surgical margins				
Negative	53	1	1.29-6.12	0.01
Positive	20	2.81		
Impact of surgeon				
1998-2004	63	1	1.11-5.98	0.028
1990-1998	17	2.57		
Stage				
I-II	41	1	0.52-1.72	0.467
III	17	1.47	0.65-3.64	0.333
IV	12	1.53		
LN status				
N0	43	1	0.70-2.52	0.388
N1	37	1.32		
Total number of LN resected				
N0 patients				
< 12	22	1	0.74-5.73	0.164
≥ 12	21	2.06	0.08-0.74	0.013
N1 patients				
< 12	21	1		
≥ 12	16	0.24		
No. metastatic LN				
N0	43	1	0.46-2.33	0.936
1-2	21	1.03	0.80-3.55	0.169
3 or more	16	1.69		
LNR				
LNR = 0	43	1	0.25-1.60	0.327
LNR < 0.2	19	0.63	1.20-5.05	0.014
LNR ≥ 0.2	18	2.47		

CI indicates confidence interval; HR, hazard ratio; LN, lymph node; LNR, lymph node ratio.

increase in the disease-specific death risk (HR = 2.47) compared with patients who had a LNR = 0 ($P = 0.01$; Table 2).

As for the multivariate analysis, our model showed significant factors to be the following: age ≥ 60 (HR = 5.92; $P = 0.018$), poorly differentiated tumors (HR = 21.87; $P = 0.018$), number of lymph nodes examined <12 LN (HR = 6.77; $P = 0.022$), 3 or more metastatic LN (HR = 7.21; $P = 0.028$), and LNR ≥ 0.2 (HR = 6.77; $P = 0.007$) (Table 4).

DISCUSSION

To overcome some of the limitations associated with nodal staging, namely suboptimal surgical harvest or histopathologic examination, stratification according to LNR has been investigated as an independent prognostic factor after resection of a number of solid tumors. Data have been reported for lung,[14] colorectal,[15] gastric,[16] esophageal,[17] and breast cancer.[18] Despite the growing body of evidence that LNR is a valuable prognostic tool, it has yet to be adopted by any formal staging system.

In our series, there was no significant difference found between the survival of patients designated N0 postresection compared with those designated N1 on univariate analysis (Table 2), whereas LNR ≥ 0.2 was found to be highly statistically significant. These data may reflect small sample size, however, they support the hypothesis that LNR is a more sensitive way of stratifying patients with nodal involvement compared with the traditional method of using the total number

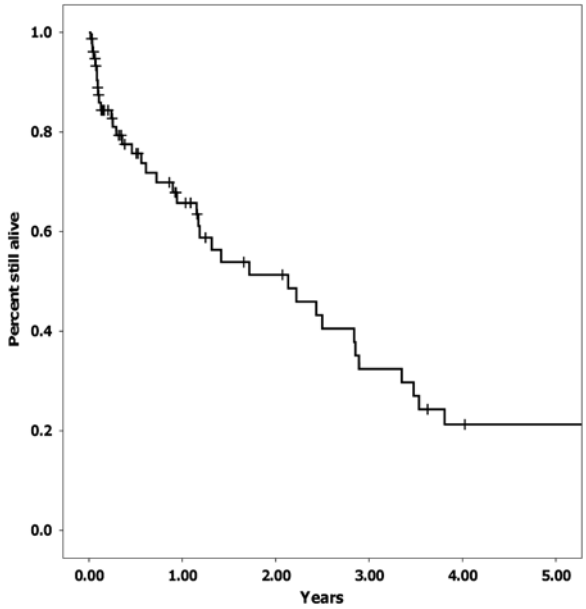

FIGURE 1. Overall survival curve with censored subjects.

of involved nodes. In a large series of 616 patients undergoing resection for adenocarcinoma of the pancreas from the Johns Hopkins group, nodal involvement was not found to be a significant prognostic factor on multivariate analysis.[8]

Lymph node harvest and accurate staging involves several factors; however, an important aspect is the quality of the surgery performed. Retrospective reports published in the 1980s suggested

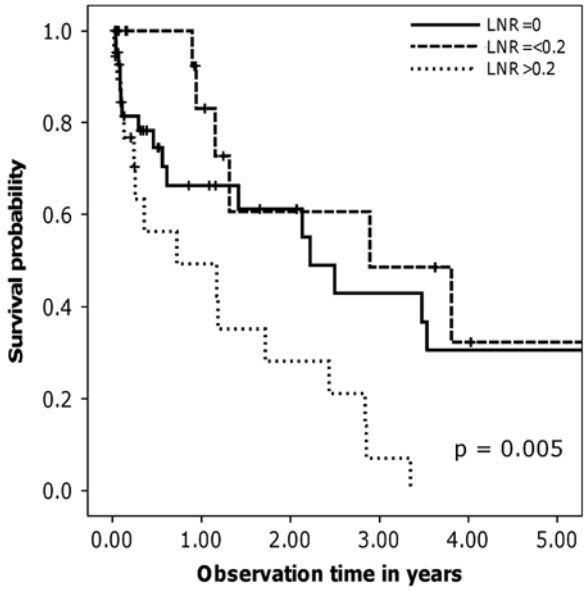

FIGURE 2. Postoperative survival of patients with LNR = 0 is compared with that of patients with $0.01 \leq LNR \leq 0.2$ and $LNR \geq 0.2$ ($P = 0.005$). Taken separately, the *P*-value calculated between LNR = 0 and $0.01 \leq LNR \leq 0.2$ is 0.114, and the *P*-value calculated between $0.01 \leq LNR \leq 0.2$ and LNR > 0.2 is 0.004, while the *P*-value calculated between LNR = 0 and LNR > 0.2 is 0.120. LNR = ratio of metastatic nodes/examined lymph nodes.

that there was a survival benefit associated with extended lymphadenectomy in pancreatic and periampullary malignancies,[19,20] however subsequent randomized studies failed to demonstrate this.[21,22] In the study reported by Yeo et al,[22] the mean number of lymph nodes resected in the standard lymphadenectomy group was 17 compared with 28.5 in the extended lymphadenectomy group. A large series of 696 patients undergoing resection for pancreatic adenocarcinoma at the Memorial Sloan-Kettering Cancer Center reported similar survival outcomes for patients designated N0 and N1 if <12 nodes were examined in total, this study also found LNR to be a strong predictor of survival for node positive patients.[2] In our series, we also found that patients who had >12 nodes examined had a better outcome which may be a reflection of superior surgical/pathologic technique. Our data show a dramatic improvement in outcomes for patients associated with the arrival of a specialist hepatobiliary surgeon in 1988 with a $33 \pm 16\%$ at 1 year and 0% at 3 and 5 years survival rate from 1990 to 1998, versus $59 \pm 8\%$, $24 \pm 7\%$, and $24 \pm 7\%$ from 1998 to 2004 ($P = 0.023$). Consistent with the view that lymph node harvest is partly a measure of surgical quality, we observed a subsequent rise in the mean number of nodes examined from 6 to 10.

Although stages III and IV have been shown to be significantly associated with poor prognosis and low survival rate for pancreatic tumors and biliary malignancies, these estimates did not show any significance in our study. Although this is unexpected, it may be related to the small number of cases recruited.

When comparing our paper to a similar study done by the John Hopkins team,[12] we notice a similarity in age of presentation, but differences exists in female to male ratio, tumor differentiation (our data show a prevalence of grade 1 and 2, whereas the pawli paper shows a prevalence for grade 2 and 3). Another difference is the median number of LN resected: in our institution, the median was 9 for all the LN dissected, 7 for the negative LN, and 11 for the positive, whereas in the pawli study, the median of the total LN dissected was 17, for negative LN was 15 and 18 for the positive LN. Regarding the LNR, we both took 0.2 as a cutoff point, and we proved that a higher ratio has a worse survival than a ratio of <0.2. Another similarity between our paper and the John Hopkins team, is the better survival of patients who had >12 LN resection and the better outcome of patients who had LN negative (or LN0) versus the patients who had LN positive (or LN 1) (Tables 2 and 3). We can say that regarding the prognostic variable of pancreatic and periampullary malignancies our paper confirms other studies in the literature with a bigger sample size.

We have faced some limitations in our study: The very small population and some missing data were the main factors. This has decreased the statistical power and widened the confidence intervals of the estimated ratios (survival and hazard ratio). Some medical charts were missing, and some provided case numbers were wrong. Furthermore, this study included patients since 1990, when the biotechnology was not as advanced as it is in our days, thus creating some diagnostic and history collecting drawbacks. For example, some patients had inadequate surgical lymphadenectomy or inadequate histopathologic examination of the resected specimen. Pathologic analysis on the lymph nodes resected during surgery.

The study was based in a tertiary health care center (AUBMC) which is also a referral center for pancreatic and periampullary related surgeries. Thus, referred cases are usually operable cases and patients with poor prognosis not referred as much to surgery as they are less likely to benefit from it. For that reason, our sample had a high percentage of

TABLE 3. Factors Predictive of Survival Following Pancreaticoduodenectomy—Univariate Analysis

Prognostic Factors	1-Y Survival (%)	3-Y Survival (%)	5-Y Survival (%)	*P*
Sex				
Male	56 ± 9	21 ± 6	21 ± 8	0.614
Female	52 ± 11	26 ± 12	26 ± 12	
Age				
< 60	70 ± 11	45 ± 13	45 ± 13	0.019
≥ 60	44 ± 9	12 ± 6	12 ± 6	
Tumor size				
> 3	72 ± 14	40 ± 16	40 ± 16	0.046
≤ 3	42 ± 11	27 ± 11	27 ± 11	
Vascular invasion				
Yes	17 ± 20	0	0	0.151
No	56 ± 7	24 ± 7	24 ± 7	
Tumor differentiation				
Well to moderate	54 ± 9	23 ± 9	23 ± 9	< 0.001
Poor	—	—	—	
Surgical margins				
Negative	65 ± 8	30 ± 9	30 ± 9	0.007
Positive	25 ± 14	—	—	
Impact of surgeon				
1990-1998	33 ± 16	—	—	0.023
1998-2004	59 ± 8	24 ± 7	24 ± 7	
Stage				
I-II	52 ± 9	26 ± 9	26 ± 9	0.544
III	41 ± 23	—	—	
IV	—	—	—	
LN status				
N0	64 ± 9	32 ± 11	32 ± 11	0.387
N1	46 ± 10	14 ± 8	14 ± 8	
No. examined LN				
N1				
< 12	69 ± 9	52 ± 13	44 ± 13	0.154
≥ 12	67 ± 44	—	—	0.008
N2				
< 12	28 ± 11	—	—	
≥ 12	67 ± 44	44 ± 19	44 ± 19	
No. metastatic LN				
N0	64 ± 9	36 ± 11	36 ± 11	0.206
1-2	41 ± 13	19 ± 13	19 ± 13	
3 or more	41 ± 13	8 ± 8	—	
LNR				
0	63 ± 9	32 ± 11	32 ± 11	0.005
< 0.2	65 ± 15	37 ± 17	37 ± 17	
≥ 0.2	29 ± 12	0	0	

LN indicates lymph node; LNR, lymph node ratio.

N0 patients, which might cause a selection bias that could not be controlled by the investigators. In that sense, patients with positive lymph nodes might gain a higher weight than those without and the hazard of death in the N1/2 sample might be more sensitive to changes than that in the N0 sample. Nonetheless, when comparing our pattern or survival with that of other studies,[3,12] we can see that out sample had a similar survival patterns, eliminating the effect of this bias on the integrity of the outcome.

TABLE 4. Factors Predictive of Survival After Pancreaticoduodenectomy—Multivariate Analyses

Prognostic Factors	HR	95% CI	*P*
Age			
< 60	1	1.35-25.58	0.018
≥ 60	5.92		
Tumor differentiation			
Well to moderate	1	1.58-105.10	0.018
Poor	21.87		
No. examined LN			
≥ 12	1	1.32-34.62	0.022
< 12	6.77		
LNR			
< 0.2	1	2.05-84.50	0.007
≥ 0.2	6.77		
No. metastatic LN			
1-2	1	1.23-41.22	0.028
3 or more	7.12		

CI indicates confidence interval; HR, hazard ratio; LN, lymph node; LNR, lymph node ratio.

In conclusion, this retrospective review is the first series to be published from a tertiary referral center in the Middle East. In analyzing prognostic factors post-pancreaticoduodenectomy we have established several important practice points; pancreaticoduodenectomy should be performed by a surgeon with appropriate specialist skills, adequate assessment of at least 12 regional lymph nodes is vital to correctly stage disease, and LNR is an independent prognostic factor that can be used to stratify node-positive patients.

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