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ORIGINAL ARTICLE

Lymph node ratio and preoperative CA 19-9 levels predict overall survival and recurrence-free survival in patients with resected pancreatic adenocarcinoma

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Abstract

AIM: Clinicopathologic factors predicting overall survival (OS) would help identify a subset to benefit from adjuvant therapy.

METHODS: One hundred and sixty-nine patients patients from 1984 to 2009 with curative resections for pancreatic adenocarcinoma were included. Tumors were staged by American Joint Committee on Cancer 7th edition criteria. Univariate and multivariable analyses were performed using Kaplan-Meier methodology or Cox proportional hazard models. Log-rank tests were performed. Statistical inferences were assessed by two-sided 5% significance level.

RESULTS: Median age was 67.1 (57.2-73.0) years with equal gender distribution. Tumors were in the head (89.3%) or body/tail (10.7%). On univariate analysis, adjuvant therapy, lymph node (LN) ratio, histologic grade, negative margin status, absence of peripancreatic extension, and T stage were associated with improved OS. Adjuvant therapy, LN ratio, histologic grade, number of nodes examined, negative LN status, and absence of peripancreatic extension were associated with improved recurrence-free survival (RFS). On multivariable analysis, LN ratio and carbohydrate antigen (CA) 19-9 levels were associated with OS. LN ratio was associated with RFS.

CONCLUSION: The LN ratio and CA 19-9 levels are independent prognostic factors following curative resections of pancreatic cancer.

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Key words: Pancreatic adenocarcinoma; Lymph node ratio; Carbohydrate antigen 19-9; Recurrence-free survival; Overall survival

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INTRODUCTION

Pancreatic adenocarcinoma is the fourth leading cause of cancer deaths in the United States, and its incidence is steadily rising[1]. The 5-year overall survival (OS) rate is less than 4%[2]. The only potential curative option is surgical resection. Unfortunately, less than 20% of patients are eligible for surgical resection. Even in this select population, the 5-year OS ranges from 18%-24%[3-7]. Given the poor survival with surgery alone, multiple attempts have been made to improve this outcome with the addition of adjuvant therapy. In multiple retrospective studies, chemoradiation therapy has been shown to confer a survival advantage compared with surgical resection alone[3,8,9]. A prospective randomized trial conducted by the Gastrointestinal Tumor Study Group also found that median survival was improved in patients receiving adjuvant chemoradiation therapy as compared with patients treated with surgery alone[10,11]. Contrary to these findings, more recent randomized trials have shown a benefit to adjuvant chemotherapy but not to adjuvant chemoradiation therapy[12-14]. The role of adjuvant therapy in the management of localized pancreatic cancer remains controversial as many of the randomized clinical trials were statistically underpowered and used outdated radiation fractionation schema/techniques. In a recent phase Ⅲ study (radiation therapy oncology group 9704) that utilized newer chemotherapeutic agents as well as radiation techniques, there was a slight improvement in survival when compared to 5-fluorouracil-based chemoradiation[15]. Recently Charité Onkologie-01 trial which was a phase Ⅲ study that compared adjuvant gemcitabine to surgery alone also found that the median disease free survival was improved with the use of adjuvant chemotherapy[16]. Thus, the use of adjuvant therapy and the ideal treatment strategy remain controversial. It is clear, however, that pretreatment clinicopathologic factors that could predict survival would be helpful to clinicians to determine which patient subset is most likely to benefit from additional therapy.

Traditional pathologic predictors of outcome with consistent prognostic value include small tumor diameter as defined by T stage in the current International Union Against Cancer/American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) classification. Although the presence or absence of lymph node (LN) involvement is taken into account in the current N-staging, neither the total number of nodes positive nor the fraction of nodes involved are taken into account[17]. In other tumors of the gastrointestinal tract, both the nodal status (positive or negative) and the total number of nodes involved/total number of nodes removed or the LN ratio have been shown to be of prognostic importance[18-21]. The number of nodes involved can be affected by the actual number of nodes involved, the aggressiveness of the lymphadenectomy performed by the surgeon as well as the diligence of the pathologist examining the nodes. In other tumor sites where nodal ratio has been shown to have prognostic significance, a minimum number of nodes must be resected to evaluate nodal status[22]. Inadequate nodal assessment can result in inadequate staging using the current pN classification. The nodal ratio (total number of nodes that are positive/number of nodes retrieved) reflects the probability of nodal involvement while controlling for the extent of nodal dissection. LN ratio has been shown to be of prognostic value in a variety of other gastrointestinal tumors including cancers of the stomach, esophagus, colon and rectum, and biliary tract[19-20,23-25]. It has been suggested that LN ratio may also be an important prognostic factor in pancreatic cancer[26-29]. In a large retrospective analysis, LN ratio was categorized into 4 groups based on sensitivity analyses that identified these cutoff values as potentially being discriminating. These groups included (1) node negative; (2) LN ratio > 0 to 0.2; (3) > 0.2 to 0.4; and (4) > 0.4[27,28]. We therefore, chose these cutoffs in our analysis.

Another potential prognostic marker includes carbohydrate antigen (CA) 19-9 which is a sialylated Lewis antigen of the type I transmembrane protein protein. Serial measurements of CA 19-9 have been shown to be useful to monitor treatment response[30,31]. There are a handful of studies that have evaluated as a pretreatment prognostic marker[32-36]. Although there is no established cut-off value for prognostic evaluation, 370 U/mL has been found to divide patients into two groups with a significant difference in survival[37]. We, therefore, used this as the cut-off to test the role of CA 19-9 as a prognostic factor in patients with resected pancreatic cancer. The objective of this study was to assess the association between the pretreatment clinicopathologic factors and the patient post-surgery survival, and thus identify factors that predict OS.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board. One hundred and sixty-nine patients patients from 1984 to 2009 with pancreatic adenocarcinoma who underwent curative resection were identified for whom both clinical data and research tissue were available. Only patients with histologically confirmed adenocarcinomas were included. All tumors were restaged by a single pathologist (XXX, blinded) according to AJCC 7th edition criteria[17]. Data collected included patient demographics, operative details, treatment details and survival. Pathologic data obtained included tumor location, total number of nodes involved, total number of nodes resected, tumor size, differentiation and margin status. A positive margin was defined as tumor within 1 mm of the inked resection margin on microscopic examination. Tumor differentiation was recorded according to the guidelines outlined by the College of American Pathologists[38]. The

Table 1 Patient demographics *n* (%)

Gender	
Female	78 (46.2)
Male	91 (53.8)
Ethnicity	
African American	8 (4.7)
Caucasian	146 (86.4)
Unknown	15 (8.9)
Tumor location	
Head	151 (89.3)
Body/tail	18 (10.7)
Operation type	
Whipple	150 (88.8)
Distal pancreatectomy	12 (7.1)
Total pancreatectomy	5 (2.9)
En bloc resection	2 (1.2)
Adjuvant therapy	
Chemoradiation	72 (42.6)
Chemotherapy	33 (19.5)
Radiation	3 (1.8)
None	50 (29.6)
Unknown	11 (6.5)
Age at surgery (yr) (*n* = 169)	67.1 (57.2-73.0)[1]
Followup range (m) (*n* = 169)	0.13-156.6

The total number of patients is 169. [1]Median (interquartile range).

LN ratio was defined as the number of positive LNs as a fraction of the total number of LNs examined/resected. Details regarding adjuvant treatment both chemotherapy and radiation therapy were recorded. CA 19-9 levels prior to surgery were recorded. Postoperative CA 19-9 levels were not evaluated as the frequency of serum draws was highly variable and was often used only as a marker of recurrence. The CA 19-9 reference range at our institution has not changed since the assay's first use over 25 years ago.

Statistical analysis

The primary objective of this study was to determine the association between patients' post surgery survival and the clinicopathologic risk factors. The primary endpoint was defined as the time from surgery to the date of all-cause death (OS) or last follow-up. The secondary endpoint was defined as the time from surgery to the date of disease recurrence (recurrence-free survival, RFS) or last follow-up. Continuous variables were summarized using median with 25th and 75th percentiles (interquartile range). For categorical variables, frequency and percentages were shown. Data reduction techniques were applied. Kaplan-Meier method, Log-rank test, likelihood ratio test, and Cox proportional hazard models were used in univariate and multivariable analysis when appropriate to investigate the associations between the endpoints and the risk factors. CA 19-9 and LN ratio were analyzed as continuous variables and were presented graphically using cutoff found in the literature. All statistical inferences were assessed at a two-sided 5% significant level and all summary statistics, graphics, and survival models were generated using R version 2.13 statistical software[39].

RESULTS

Patient characteristics

From 1984 to 2009, 169 patients were identified who had undergone curative resections for pancreatic adenocarcinoma for whom tissue samples were also available for study. Table 1 summarizes the demographic and adjuvant therapy details. The median age at surgery was 67.1 (57.2-73.0) years. Follow-up times ranged from 0.13-156.6 mo. The patient population was equally distributed between the two genders. African-Americans comprised less than 5% of the total study population. Tumors were located in the pancreatic head (89.3%) or body/tail (10.7%). Most patients (88.8%) underwent a pancreaticoduodenectomy with gastrojejunostomy [Whipple procedure, pylorus-sparing (65.3%, 98/150) or non-pylorus-sparing (34.7%, 52/150)] and lymphadenectomy (all lymphatic tissue along the anterior and posterior pancreaticoduodenal arteries, pylorus and gastric antrum, lower hepatoduodenal ligament, superior and inferior pancreatic head, and right lateral aspect of the superior mesenteric vessels). Other curative procedures included distal pancreatectomy (7.1%), total pancreatectomy (2.9%), or *en bloc* resection of multiply involved adjacent organs (colon and spleen, 1.2%).

Almost 60% of patients received some form of adjuvant therapy, either chemoradiation (42.6%) or chemotherapy alone (19.5%). Less than 2% of patients received radiation alone. Of the patients who did not receive adjuvant therapy, 88% were due to personal choice or postoperative debilitation.

Clinicopathologic findings

Of the 169 patients undergoing surgical resection, 72.2% had microscopically negative surgical margins. 75.1% of tumors showed perineural invasion, and peripancreatic extension was found in 83.4%. Median tumor size was 3.0 (2.1-3.6) cm. Most tumors were classified as T3 and showed N1 involvement. The stage distribution was as follows: Stage Ⅰ (9.5%), ⅡA (23.1%), ⅡB (58.0%), Ⅲ (5.9%), and stage Ⅳ (3.0%). 14.2% of tumors were classified as low histologic grade (grade 1), 55.6% as intermediate grade (grade 2), and 28.4% as high-grade (grade 3). A median of 11.0 (7.5-18) LNs were examined/resected for all procedures, with a median of 1.0 (0.0-4.0) involved by carcinoma. For Whipple procedures, the median LN count was 12.0 (8.0-18.0), with a median of 1.0 (0-4.0) LNs involved by carcinoma. The median LN ratio for all procedures was 0.09 (0.0-0.286). Of the 124 patients who had pretreatment serum CA 19-9, the median level was 146.0 U/mL (47.5-378.2) (Table 2).

Patient outcomes

The median OS for all patients was 15.1 (8.0-33.5) mo and the median recurrence-free interval was 9.8 (5.1-21.1) mo. Nearly three-fourths (73.3%) of patients had a documented recurrence of disease (53.2% with distant recurrence, 16.9% with local recurrence, and 5.6% with both local and distant recurrence) (Table 3).

Table 2 Clinicopathologic characteristics *n* (%)

Resection margin	
Negative	122 (72.2)
Positive	47 (27.8)
Perineural invasion	
Negative	41 (24.2)
Positive	127 (75.1)
Unknown	1 (0.6)
Peripancreatic extension	
Negative	28 (16.6)
Positive	141 (83.4)
Unknown	1 (0.6)
TNM stage	
Ⅰ	16 (9.5)
ⅡA	39 (23.1)
ⅡB	98 (58.0)
Ⅲ	10 (5.9)
Ⅳ	5 (3.0)
Unknown	1 (0.6)
Tumor grade	
1	24 (14.2)
2	94 (55.6)
3	48 (28.4)
Unknown	4 (2.4)
LN examined (n = 167)[2]	11.0 (7.5-18)[1]
LN positive (n = 167)[2]	1.0 (0.0-4.0)[1]
LN examined (n = 150)[3]	12.0 (8.0-18.0)[1]
LN positive (n = 150)[3]	1.0 (0.0-4.0)[1]
LN ratio (n = 167)	0.09 (0.0-0.29)[1]
Tumor size (cm) (n = 167)	3.0 (2.1-3.6)[1]
CA 19-9 (U/mL) (n = 124)	146.0 (47.5-378.2)[1]

The total number of patients is 169. [1]Median (interquartile range); [2]All procedures; [3]Whipple procedures. TNM: Tumor-node-metastasis; LN: Lymph node; CA: Carbohydrate antigen.

Univariate analysis

OS was significantly improved with the use of chemoradiation as compared with no treatment (P = 0.002), and a similar effect was found for RFS (P = 0.041) (Table 4). Kaplan-Meier curves show a significant association between treatment and OS (P = 0.012) but no association with RFS (P = 0.227) (Figure 1A and B). Low LN ratios were associated with improved OS (P = 0.001) and RFS (P < 0.001) (Table 4). Stratifying the LN ratio revealed a significant association with improved OS (P = 0.002) and RFS (P = 0.001) (Figure 1C and D). Low pretreatment serum CA 19-9 levels showed a trend toward improved OS (P = 0.075) but did not show an association with improved RFS (P > 0.05) (Table 4). A cut-off value for CA 19-9 of 370 U/mL showed nonsignificant trends in improved OS (P = 0.137) and RFS (P = 0.086) (Figure 1F and G).

Other well-established clinicopathologic factors including the absence of peripancreatic extension (P = 0.005), negative resection margins (P < 0.001), lower T stage (P = 0.001), negative LN status (P < 0.001) and low histologic grade (P = 0.004) were all associated with improved OS (Table 4). Gender, race, age, tumor location, type of surgical resection, tumor size, perineural invasion, and total number of LNs examined/resected were not found to be associated with OS (Table 4).

Table 3 Patient outcomes *n* (%)

Recurrence status (n = 169)	
Recurred	124 (73.3)
No recurrence	45 (26.6)
Recurrence location (n = 124)	
Local	21 (16.9)
Distant	66 (53.2)
Local and distant	7 (5.6)
Unknown	30 (24.2)
Overall survival time (mo)	15.1 (8.0-33.5)[1]
Time to recurrence (mo)	9.8 (5.1-21.1)[1]
Disease-related survival status (n = 169)	
Death from disease	104 (62.5)
Death from other causes	19 (11.2)
Alive with disease	21 (12.4)
Alive with no disease	25 (14.8)

[1]Median (interquartile range).

Improved RFS correlated with the absence of peripancreatic extension (P = 0.01), negative LN status (P < 0.001), low histologic grade (P = 0.005), total number of LNs examined/resected (P = 0.01), and lower LN ratio (P < 0.001) (Table 4). Gender, race, age, tumor location, type of surgical resection, tumor size, margin status, perineural invasion, and T stage, were not found to be associated with RFS (Table 4).

Multivariable analysis

When adjusting for known covariates such as age, gender, perineural invasion, tumor grade, adjuvant therapy status only LN ratio [P < 0.001, hazards ratio (HR) = 1.66] and CA 19-9 levels (P = 0.049, HR = 1.27) remained as independent predictors of OS (Table 5, Figure 2A). LN ratio was associated with improved RFS (P = 0.008, HR = 1.50) while low CA 19-9 levels were associated with a trend towards improvement in RFS (P = 0.086, HR = 1.24) (Table 5, Figure 2B).

DISCUSSION

Despite improvements in surgical outcome, the OS for patients with adenocarcinomas of the pancreas remains poor and the large majority of patients die of recurrent disease. Therefore, prognostic markers that can be used to predict survival would be of great benefit to clinicians to determine which patient is most likely to benefit from what type of adjuvant therapy.

This is a large retrospective study done from a single institution spanning 25 years and including 169 patients with resectable pancreatic adenocarcinoma. Being a tertiary referral center, not all patients received their therapy at our institution. Therefore it would be impossible for us to fully know the subset of unresectable patients were in our group. For uniformity across time, all patients were re-staged using the American Joint Committee on cancer pancreatic exocrine carcinoma staging guidelines (7th edition)[17]. The current staging system takes into account whether nodes are positive or negative but does

Table 4 Hazard ratios of clinicopathologic variables analyzed on univariate analysis for overall survival and recurrence-free survival

	Overall survival			Recurrence-free survival		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age at surgery (73 yr *vs* 57.2 yr)	1.43	1.05-1.94	0.021	1.22	0.91-1.64	0.188
Gender						
Female	1			1		
Male	1.06	0.74-1.51	0.76	1.02	0.71-1.45	0.934
Tumor location						
Head	1			1		
Body/tail	1.26	0.73-2.16	0.406	1.66	0.96-2.86	0.07
Operation type						
Whipple	1			1		
Distal pancreatectomy	0.88	0.44-1.73	0.704	1.56	0.81-2.99	0.184
Total pancreatectomy	0.56	0.14-2.27	0.417	0.88	0.28-2.79	0.832
En bloc resection	1.73	0.54-5.46	0.354	1.92	0.61-6.08	0.267
Adjuvant therapy						
Chemoradiation	1			1		
Chemotherapy	1.09	0.67-1.79	0.722	1.14	0.71-1.83	0.587
Radiation	0.73	0.1-5.32	0.758	0.98	0.24-4.04	0.98
None	1.89	1.26-2.84	0.002	1.55	1.02-2.37	0.041
Resection margin						
Negative	1			1		
Positive	1.99	1.35-2.94	0.001	1.38	0.93-2.06	0.114
Perineural invasion						
Negative	1			1		
Positive	1.22	0.79-1.88	0.372	0.93	0.62-1.41	0.736
Peripancreatic extension						
Negative	1			1		
Positive	2.23	1.27-3.91	0.005	2	1.16-3.45	0.013
TNM stage						
Ⅰ-ⅡA	1			1		
ⅡB-Ⅳ	2	1.33-3.02	0.001	1.87	1.25-2.8	0.002
Tumor grade						
Ⅰ	1			1		
Ⅱ-Ⅲ	2.43	1.34-4.42	0.004	2.24	1.28-3.92	0.005
LN examined (18 *vs* 7.5)	1.21	0.95-1.55	0.132	1.4	1.09-1.81	0.012
LN positive (4 *vs* 0)	1.52	1.26-1.83	0	1.57	1.3-1.9	< 0.001
LN ratio (0.29 *vs* 0)	1.44	1.18-1.76	0.001	1.57	1.27-1.95	< 0.001
Tumor size (3.5 *vs* 2.1)	1.08	0.95-1.23	0.279	1.2	1.07-1.34	0.007
CA 19-9 (378.25 *vs* 47.5)	1.04	1-1.07	0.075	1.02	0.99-1.06	0.238

HR: Hazards ratio; TNM: Tumor-node-metastasis; LN: Lymph node; CA: Carbohydrate antigen.

Table 5 Hazard ratios of variables analyzed on multivariable analysis for overall survival and recurrence-free survival

	Overall survival			Recurrence-free survival		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Lymph node ratio (0.29 *vs* 0)	1.66	1.226-2.225	< 0.001	1.50	1.109-2.028	0.008
Preoperative CA 19-9 (378.25 *vs* 47.5)	1.27	1.001-1.619	0.049	1.24	0.97-1.584	0.086
Tumor grade (Ⅰ *vs* Ⅱ-Ⅲ)	0.91	0.539-1.532	0.720	1.38	0.813-2.344	0.232
Perineural invasion (Neg *vs* Pos)	0.54	0.256-1.145	0.108	0.45	0.204-1.002	0.050
Adjuvant chemotherapy (no *vs* yes)	1.48	0.876-2.505	0.142	1.32	0.744-2.357	0.339

HR: Hazards ratio; CA: Carbohydrate antigen; Neg: Negative; Pos: Positive.

not take into account either the total number of nodes involved or the ratio of nodes involved/total number removed. This study suggests that both of these parameters would help to improve on the current staging system. Node positive patients are not a homogenous group and can be subdivided further based on both total number of positive LNs as well as LN ratio. LN ratio decreases the possibility of stage migration and "normalizes" the aggressiveness of the surgery. In other cancer of the gastrointestinal tract, nodal ratio has been shown to be superior to simply summating the total number of involved LNs[20-21].

In this study, adjuvant therapy (chemotherapy with or without radiation) was associated with improved OS but

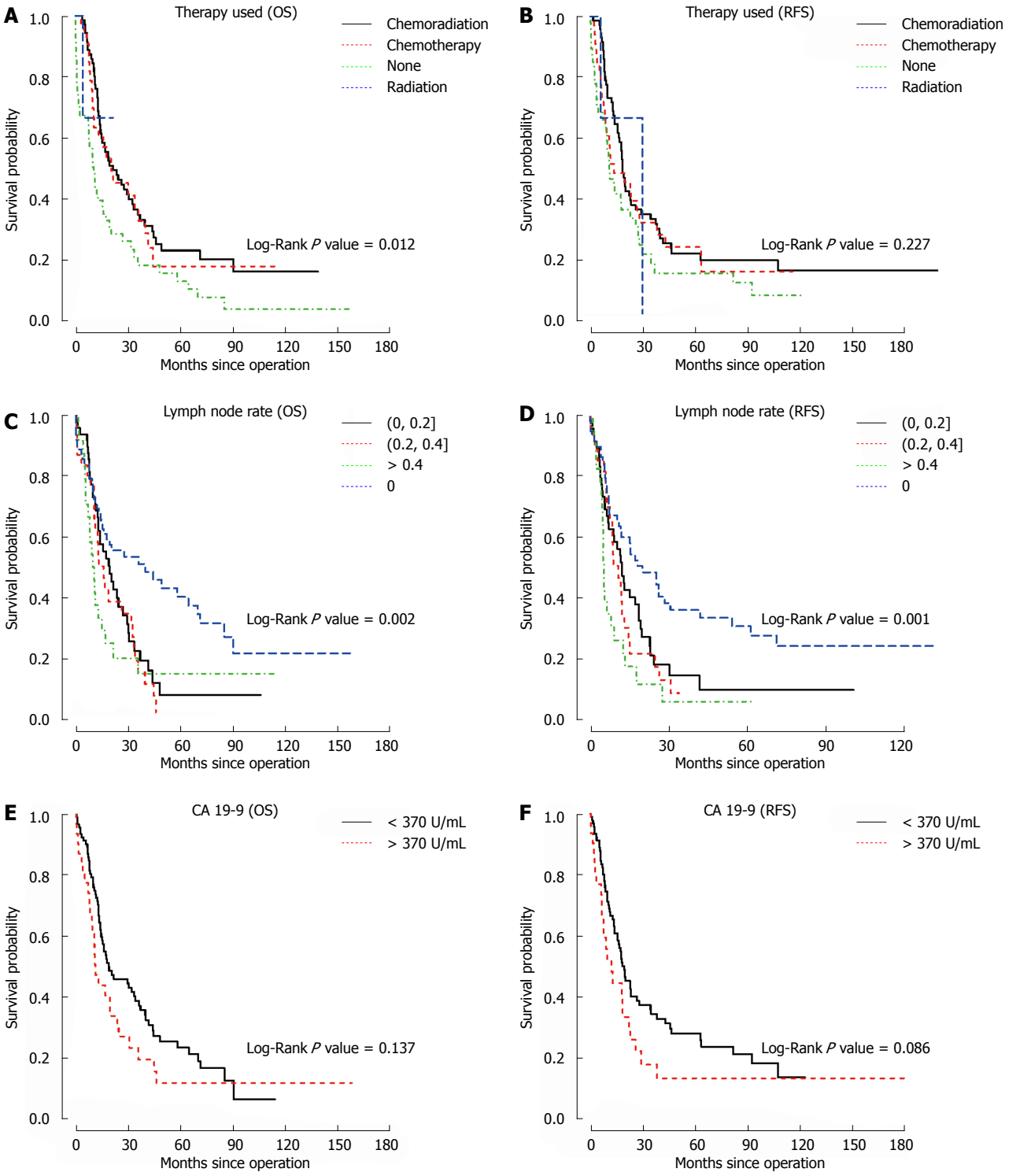

Figure 1 Kaplan-Meier curves. A, B: Univariate analysis Kaplan-Meier curve of adjuvant therapy demonstrates improvements in overall survival (OS) (P = 0.012), but not recurrence-free survival (RFS). The protective effect of adjuvant therapy was lost on multivariate analysis (n = 169); C, D: Univariate analysis Kaplan-Meier curves of lymph node ratio using an arbitrary stratification (0, < 0.2, 0.2-0.4 and > 0.4) shows significant improvements in OS (P = 0.002) and RFS (P = 0.001) (n = 169); E, F: Multivariate analysis Kaplan-Meier curves of peroperative carbohydrate antigen (CA) 19-9 levels using an arbitrary cutoff of 370 U/mL demonstrate no correlation with OS (P = 0.137) and marginal improvement in RFS (P = 0.086) (n = 124).

not RFS. This effect was lost on multivariate analysis. Several large retrospective studies have shown a benefit to the use of adjuvant therapy[21]. The retrospective nature of this study has several drawbacks, including the variety of chemotherapeutic agents that were utilized over the 25 year period. Some of the agents used on patients in this study include gemcitabine, 5-fluoruracil, paclitaxel, cisplatin, cetuximab, mitomycin C, irinotecan, vascular endothelial growth factor inhibitors, and 5-fluorouracil with leucovorin and oxaliplatin. The loss of beneficial effect of adjuvant therapy on OS and RFS on multivariate analysis may be due to the heterogeneity

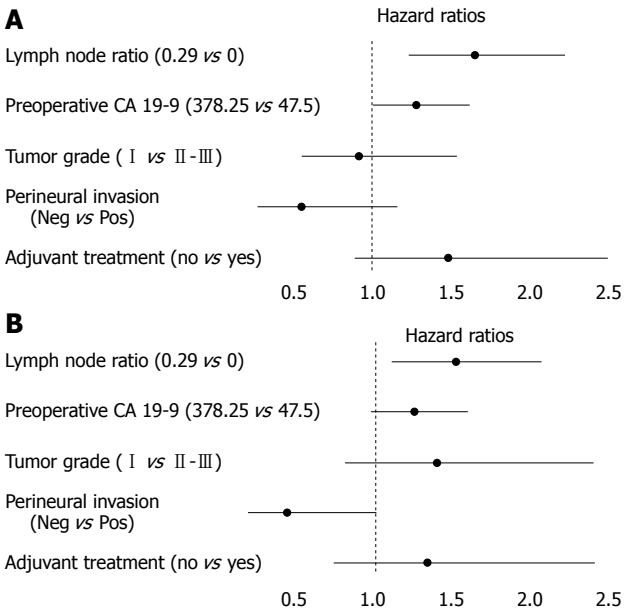

Figure 2 Hazard ratios of variables analyzed on multivariable analysis for overall survival (A) and recurrence-free survival (B). CA: Carbohydrate antigen; Neg: Negative; Pos: Positive.

of chemotherapeutic regimens employed in this study population. Furthermore, as this was not a randomized study, patients who were given adjuvant therapy likely had a worse prognosis with increased number of nodes involved, positive margins, and peripancreatic extension.

LN ratio and preoperative CA 19-9 levels were consistently the only clinicopathologic variables associated with improved OS on both univariate and multivariate analysis. Significant associations with OS were also seen when these variables were analyzed using cutoffs previously described in the literature. The current staging system uses tumor size, peripancreatic extension, and vascular involvement (celiac axis or superior mesenteric artery) to determine T stage and the presence or absence of LN involvement to determine N stage. Tumor size, however, did not demonstrate consistently significant improvements in OS and RFS and may not be the most accurate reflection of tumor burden. We propose that in addition to peripancreatic extension, CA 19-9 level may better characterize tumor burden as opposed to tumor size. Furthermore, we propose that the N stage (positive or negative) may be better delineated as total number of positive LNs divided by the total number of LNs that underwent histologic examination. The LN ratio normalizes the technical variations of the operative procedure and pathologic examination and thus provides a more accurate picture of extent of disease than simply the presence or absence of positive LNs. The serum CA 19-9 value of 370 U/mL was chosen as this value has been used in recent literature. Thus, it is current, relevant, and allows for interstudy comparison.

In addition to the well-established clinicopathologic factors that are currently accounted for in the AJCC TNM classification including peripancreatic extension, margins, T and N staging, we propose that LN ratio and CA 19-9 levels can be used as prognostic markers to predict OS following curative resections of pancreatic cancer.

COMMENTS

Background

Pancreatic cancer is a deadly disease with mortality nearly equal to incidence. Despite advances in surgical technique and chemotherapeutic agents, the prognosis remains grim. Determining clinico-histopathologic factors which influence prognosis may provide insight into the tumor biology and allow for proper patient selection for adjuvant treatment.

Research frontiers

Multiple recent clinical trials have yielded conflicting results regarding the benefit of adjuvant therapy. Multiple retrospective studies have shown the benefit of chemoradiation therapy compared with surgical resection alone. A prospective randomized trial conducted by the Gastrointestinal Tumor Study Group demonstrated improved median survival in patients receiving adjuvant chemoradiation therapy as compared with patients treated with surgery alone. More recent randomized trials have shown a benefit to adjuvant chemotherapy but not to adjuvant chemoradiation therapy. In a recent phase Ⅲ study (radiation therapy oncology group 9704) that utilized newer chemotherapeutic agents as well as radiation techniques, there was a slight improvement in survival compared to 5-fluorouracil-based chemoradiation. The Charité Onkologie-01 Phase Ⅲ study comparing adjuvant gemcitabine to surgery alone also found that the median disease free survival was improved with the use of adjuvant chemotherapy. Furthermore, the issue of lymph node (LN) status has come under review as other methods of assessing nodal tumor burden have been identified. The nodal ratio (total number of nodes that are positive/number of nodes retrieved) reflects the probability of nodal involvement while controlling for the extent of nodal dissection. LN ratio has been shown to be of prognostic value in a variety of other gastrointestinal tumors including cancers of the stomach, esophagus, colon and rectum, and biliary tract. It has been suggested that LN ratio may also be an important prognostic factor in pancreatic cancer.

Innovations and breakthroughs

In this study, adjuvant therapy (chemotherapy with or without radiation) was associated with improved overall survival (OS) but not recurrence-free survival (RFS). This effect was lost on multivariate analysis. LN ratio and preoperative carbohydrate antigen (CA) 19-9 levels were consistently the only clinicopathologic variables associated with improved OS on both univariate and multivariate analysis. Significant associations with OS were also seen when these variables were analyzed using cutoffs previously described in the literature. Tumor size, however, did not demonstrate consistently significant improvements in OS and RFS and may not be the most accurate reflection of tumor burden.

Applications

The authors propose that in addition to peripancreatic extension, CA 19-9 level may better characterize tumor burden as opposed to tumor size. Furthermore, the authors propose that the N stage (positive or negative) may be better delineated as total number of positive LNs divided by the total number of LNs that underwent histologic examination. The LN ratio normalizes the technical variations of the operative procedure and pathologic examination and thus provides a more accurate picture of extent of disease than simply the presence or absence of positive LNs. In addition to the well-established clinicopathologic factors that are currently accounted for in the American Joint Committee on Cancer TNM classification including peripancreatic extension, margins, T and N staging, the authors propose that LN ratio and CA 19-9 levels can be used as prognostic markers to predict OS following curative resections of pancreatic cancer.

Peer review

This is a moderately powered retrospective study assessing clinic-histopathologic predictors of outcomes in resected pancreatic ductal adenocarcinoma. LN ratio and CA 19-9 are important clinicopathologic factors in OS and RFS. The beneficial effect of adjuvant therapy (chemoradiation) was lost on multivariate analysis, which may reflect the heterogeneity of chemotherapeutic agents used over the 25-year span of the study, which was not randomized. The results are interesting and support recent prior studies which assess the LN ratio.

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