Hepatic Artery Lymph Node in Pancreatic Cancer: A Retrospective Analysis of Survival Outcomes

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Abstract

Background

After optimal management, 5 years survival of pancreatic cancer is 12 - 15%. Factors associated with poor prognosis are tumoral histology, harvested regional lymph nodes, and recently, hepatic artery lymph node HLA(8a) involvement. In fact, evidence has shown negative impact of node 8a involvement on overall survival and disease free-survival. Therefore, we aimed to describe the prognostic significance of the HLA(8a) lymph node metastasis in terms of disease-free survival (DFS) and overall survival (OS) on a specific cohort of patients.

Methods

A retrospective study was conducted based on a prospective database from the HPB department of patients who underwent a pancreaticoduodenectomy (PD) due to pancreatic cancer during 2014 - 2021. Overall survival (OS) and disease-free survival (DFS) were estimated to be associated with positive HLA(8a) using Kaplan-Meier analysis. Log Rank test and Cox proportional hazards regression analysis were used.

Results

111 patients were included, 55,4% female. The most frequent pathology was ductal adenocarcinoma (60.3%). Positive rate of the HLA(8a) node was 21.62%. Median OS time was 25.5 months, and median DFS time was 13,8 months. Positive HLA(8a) node, the cutoff of lymph node ratio (LNR) resection, and vascular invasion showed a strong association with OS. (CoxRegression $p = 0.03$ HR 0.5, $p = 0.003$ HR = 1.8, $p = 0.02$ HR 0.4 CI 95%). In terms of DFS, lymph node ratio cutoff, tumoral size, and vascular invasion showed a statistically significant association with the outcome ($p = 0.008$, HR = 1.5; $p = 0.04$ HR=2.1; $p=0.02$ HR=0.4 CI 95%).

Conclusion

In this series of pancreaticoduodenectomies, OS and DFS are significantly reduced in patients with HLA(8a) node compromise in patients with pancreatic cancer. In multivariate analysis, lymph node status remains an independent predictor of OS and DFS. Further studies are needed.

Introduction

Pancreatic cancer is the third cause of cancer-related death in the United States and the seventh worldwide [1]. The survival rate after diagnosis is 24% for the first year and 9% for the fifth [1]. Treatment is built on several options, but currently, these options cannot improve the poor survival rate [2]. The surgical management followed by adjuvant chemotherapy is still the gold standard for these patients [3]; However, even with optimal treatment, just 12–18% of the population achieve a maximal survival at 5 years [3].

Several prognostic factors are associated with disease-free survival (DFS) and overall survival (OS). Besides well-defined prognostic factors as resection margins, tumoral biology, and vascular invasion; lymph node status is one of the most relevant factors, because the prognosis worsens significantly with the lymph node metastasis [2–5]. Particular interest is the compromise of the hepatic artery lymph node (HLA), also called station 8a, a second-echelon node according to the Japan Pancreas Society classification [6]. Some evidence shows the reduction of OS in almost 8 months when HLA(8a) node is positive [10]. Furthermore, some case series report that the prognosis of HLA(8a) node metastases can be compared with peritoneal carcinomatosis or liver metastases [9]. Contrarily, Perlmutter et al[7], found no difference in survival outcomes regardless of HLA(8a) status, compared to patients with stage IV disease, increasing uncertainty regarding the prognostic value of HLA(8a) nodes [7].

During pancreatoduodenectomy, resection of the hepatic artery node is performed routinely, to dissect and visualize the emergency of the gastroduodenal artery, but is not mandatory in lymph node dissection [2, 7–9].

Given the different perspectives of the relation of HLA positive and poor prognosis, this retrospective study is proposed to assess the oncologic impact of HLA(8a) in our series of pancreaticoduodenectomies.

Materials And Methods

Patients

After institutional review board and Ethical Committee approval, a retrospective cross – sectional review of patients of the single institution of hepato-pancreato-biliary database was performed. Patients who underwent pancreatoduodenectomy for pancreatic cancer during 2014–2021 were included in this study (Fig. 1). Pathologic reports were reviewed to identify hepatic node resection, oncological margins and lymph nodes harvested.

Cases with incomplete data, positive macroscopic margins (R2), not reported hepatic nodes in pathologic specimens and non – pancreatic cancer confirmed by pathology were excluded from the analysis. A descriptive analysis was made calculating proportions and frequencies of qualitative variables and central tendency measures for quantitative variables.

Variables were analyzed according to factors that have been shown relevance in previous studies for pancreatic cancer: tumor size, histologic grade, vascular invasion, and completeness of resection.

Statistical analysis

Overall Survival and Disease-free survival

OS was defined from the date of the surgery until June 2021. Disease-free survival was defined as the time since the postoperative period, to the first documentation of tumoral relapse such as clinical

(ascites), biomarkers analysis (Ca 19 – 9 antigen elevation), or imagenologic findings (tomographic evidence of local or distance relapse) until June 2021. Survival analysis was performed using Kaplan-Meier method for OS and DFS. LogRank tests were used to examine the association of clinical and pathological variables with the OS and DFS. A differential analysis was performed: patients that receive adjuvant therapy versus HLA(8a) node compromise or not. Significant characteristics (p value < 0.20) in LogRank tests were included in a multivariate cox proportional hazard regression model. Data with p < 0.05 were considered statistically significant. Statistical analysis for the comparison of mean values will be performed using t tests or Wilcoxon-Mann-Whitney tests as appropriate. Assumptions regarding normal distribution will be checked by graphic representation, Shapiro-Wilk-Tests, and Q-Plots, respectively. The Chi squared and Fisher's exact tests were used to compare categorical variables, as appropriate. Statistical analysis will be carried out using the Statistical Package of STATA Version 17.0 BE-Basic Edition (StataCorp LLC StataCorp 4905 Lakeway Drive College Station, Texas 77845 USA). A two-tailed P-value of < 0.05 will be considered as statistically significant.

Lymph Node Ratio Resection (LNRR)

A lymph node ratio resection (LNRR) was established as a main variable. LNRR is defined as the ratio between the total lymph node resected and the positive ones in the pathology report. A cutoff value was generated for this variable with logarithmic regression after Kaplan-Meier estimates, and a ROC value of 0.6 was estimated for the LNRR cutoff for the study population.

Follow up

By institutional protocol, follow up was performed 6, 12, 18, 24, 30, 36 months to determine the time of tumoral relapse, using tumoral biomarkers, clinical assessment, and tomographic studies. Mortality was determined by the time of deaths reported in the national database.

Results

Patients and tumor characteristics

A total of 136 patients underwent PD resection for pancreatic cancer during 2014–2020. Twenty-five patients were excluded from the study because of incomplete data. A total of 111 patients were included. The overall positive rate of lymph node resection, HLA(8a) positive rate, and the LNRR were analyzed for each patient.

Females constituted 54,05% (n = 60) of cases. The mean age at the time of resection was 63.11y (SD 10.7), Other patient's characteristics are summarized in Table 1. All patients underwent standard PD without pylorus preservation. The pathology in most of the patients was ductal adenocarcinoma 60.36% (n = 67) followed by 22.52% for tumors of the ampulla of Vater. Moderate grade of differentiation of the tumor was found in 57% (n = 64) of the patients and a well-differentiated pathology (31.5%, n = 35).

Table 1
Patient demographics

<i>VARIABLE</i>	<i>VALUE</i>
Demographic Characteristics	
Sex. N (%)	Male 51 (45,95)
	Female 60 (54,05)
Age (Mean)	Male 63,2y
	Female 56,5y
Body Mass Index median (SD)	23,6(4,29)
Diabetes Mellitus N (%)	19 (17,12)
Smoker N (%)	13 (11,71)

R0 resections were achieved in 95,05% of the patients (n = 106); The majority of the patients have a vascular and perineural invasion in the pathology report (60,36% and 68,47% respectively). (See Table 2). The mean number of harvested lymph nodes was 14.53 (SD 5.8). The positive rate of the HLA(8a) node was 21.62% (n = 24). The overall positive nodes harvested was 9,01% (179 nodes of 1613). The LNRR mean was 0.45 (SD 0.05). In the postoperative period, 42.34 % (n = 47) do not receive adjuvant therapy due to both health insurance issues and personal decisions. During the analysis, the maximum time that patients receive chemotherapy after surgery was 24 months. 62,5% (n = 15) of the patients with positive HLA(8a) receive postoperative chemotherapy. Tumoral relapse was documented in 53.15% of the patients at 5 years of follow-up.

Table 2
Pathologic characteristics.

VARIABLE		VALUE
Tumor Characteristics		
Tumoral size N (%)	< 2 cm	19(17,12)
	> 2cm	92(82,88)
Type of Tumor N(%)	Ductal Adenocarcinoma	67(60,36)
	Ampullary tumors	25(22,5)
	Cystadenocarcinoma	5(4,50)
	Other	14(12,64)
Differentiation grade N (%)	Well differentiated	35(31,53)
	Moderate grade	64(57,66)
	Poorly differentiated	10(9,01)
	Undifferentiated	2(1,80)
Adjuvant therapy N(%)	Received	64 (57,66)
Pathology report		
	Vascular invasion N(%)	67 (60,36)
	Perineural Invasion N(%)	76 (68,47)
	R0 Margins N(%)	106 (95,05)
	Positive rate of HLA node N(%)	24(21,62)
Tumoral relapse at 5 years %		55,8

Survival Analysis

The median follow-up for all the patients was 19.98 months. The median OS time was 25,5 months (IQR 12,5–84), the median DFS time was 13.58 months (IQR 7,5–57). For patients that received adjuvant chemotherapy (57,66% n = 64/111), the median OS time was 16,3 months (IQR 5,5–84,6) the median DFS time was similar with 16 months (IQR 7,5–57), with a maximum of 57 months.

Overall Survival

The OS was analyzed taking into consideration the HLA(8a) positive rate and its relation to most relevant prognostic factors (vascular, perineural invasion, and margin of resection). For HLA(8a) positive cases (21,62% n = 24/111) the OS time was 12.5 months, versus 20.4 in the negative node group (CI 95% 9–26). Figure 2. OS was significantly different in the chemotherapy group analysis: for patients that did not receive adjuvant chemotherapy with positive HLA(8a) (62,5% n = 15/24), the median OS time was 12,5 months compared with 20,5 months in those who did received adjuvant chemotherapy (36,5% n = 9/24). (Cox regression P = 0.02, HR 0.3, CI 95%) Kaplan Meier curves are displayed in **Fig. 3**.

Regarding other prognostic variables, logRank test showed, for positive vascular invasion an OS time of 15.5 months, compared to 27.5 months (CI 95% 12–36) in the negative group. For perineural invasion, the positive group had an OS time of 15.9 months versus the negative one 30,7 months (CI 95% 15–61).

In the Cox regression model including relevant variables (HLN +/-, Vascular invasion +/-, perineural invasion +/-, resection margins +/-, and our new cutoff value for LNRR) statistical association was present between the positive HLA(8a), the cutoff of lymph node ratio resection, and vascular invasion (CoxRegression p = 0.05 HR 0.5; 0.003 HR1.8; p = 0.02 HR 0.4 CI 95%, respectively). LogRank tests and cox regression results are displayed in Table 3

Table 3
Log rank and Cox regression analysis for OS.

<i>VARIABLE</i>	<i>LOGRANK 95% CI</i>	<i>COX PROPORTIONAL 95% CI</i>	<i>CHI SQUARE (HR)</i>
HLN +	P 0.05	P 0.05	3.1 (0.5)*
TUMORAL SIZE > 2 CM	P 0.09	P 0.09	3.1(1.8)
PERINEURAL INVASION	P 0.05	P 0.06	3.8(0.5)
VASCULAR INVASION	P 0.02	P 0.02	5.2(0.4)*
RESECTION MARGINS	0.92	0.92	0.01(0.9)
LNRR	P 0.001	P 0.003	9.67 (1.8)
ADJUVANT THERAPY / HLA Node (+)	P 0.05	P 0.02	4.5(0.3)*
*Statistically significant value.			

Disease Free Survival Time

The disease-free survival time also had significant differences between the analysis groups. The positive HLA(8a) group patients have a DFS time of 13 months, compared with 20 months (CI 95% 12–22) in the negative HLA(8a) group, with a statistically significant value as an independent factor to DFS (p = 0.09),

but failed to be significative in the Cox proportional regression model. DFS was significantly different in the chemotherapy group analysis: HLA(8a) positive and adjuvant chemotherapy + patients (36,5% n = 9/24) have had a prolonged DFS time: (29 months), compared with the non-chemotherapy (62,5% n = 15/24) group: (13 months). In the Cox proportional regression model, DFS in HLA(8a) negative patients and adjuvant chemotherapy + did not differ significantly compared to HLA(8a) negative and non-chemotherapy group (18 months CI 95%17–20 vs 19 months CI 95% 6–21, respectively).

Regarding other relevant prognostic factors, positive vascular invasion presented a DFS of 14 months versus 53 months in the negative group (CI 95% 14–60). In the positive perineural invasion group, the DFS was 18 months, and in the negative one, the DFS was 53 months (CI 95% 15–55). Kaplan Meier estimates curves for OS and DFS are displayed in **Fig. 3**.

Cox proportional regression showed as relevant variables the lymph node ratio cutoff (p = 0.008, HR = 1.5 CI 95%), tumoral size > 2 cm (p = 0.04 HR = 2.1 CI 95%), and vascular invasion (p = 0.02 HR = 0.4, CI 95%). In this analysis, HLA(8a) + does not show a significant relationship with DFS. LogRank tests and cox regression results are displayed in Table 4.

Table 4
Log rank and Cox regression analysis for DFS

<i>VARIABLE</i>	<i>LOGRANK</i>		<i>CHI</i>
	95% CI	COX PROPORTIONAL 95 % CI	SQUARE (HR)
HLN +	P 0.09	P 0.1	—
TUMORAL SIZE > 2 CM	P 0.03	P 0.04	4.63(2.1)*
PERINEURAL INVASION	P 0.1	P 0.1	—
VASCULAR INVASION	P 0.001	P 0.02	5.71(0.4)*
RESECTION MARGINS	0.6	—	—
LNRR	P 0.01	P 0.008	6.01 (1.5)*
ADJUVANT THERAPY / HLA Node (+)	P 0.2	P 1.0	
*Statistically significant value			

Discussion

Given the ominous prognosis in pancreatic cancer, survival is still a matter of concern. There are several factors to predict survival [10–23], and lymph node 8(a) involvement seems to be an important new poor prognosis factor [11]. In the last few years, there has been an increasing interest in hepatic artery lymph node evaluation as a potential intraoperative prognostic marker. However, the data on HLA(8a) node prognosis strength is limited and differs substantially across studies [12].

This study evidenced a reduction in OS in patients with positive HLA(8a) nodes. OS was 20.4 months in negative HLA(8a) compromise versus 12.5 months in the positive group with a positive statistical difference ($p = 0.05$). These results are similar to those reported by Cordera et al. who described in 175 patients a median overall survival time of 14.7 months in a positive HLA(8a) node compared with 16.1 months in peripancreatic node involvement and 22.9 months in all negative nodes [20]. LaFemina et al described in 147 patients with HLA(8a) node analyzed with OS of 26 months in the Peripancreatic lymph node (PPLN)-/HALN- group, 17 months in the PPLN+/HALN-, and 13 months in the setting of HALN+; ($p = 0.017$) [13]. therefore, similar to some studies, we identify the worst overall survival of patients with a positive HLA(8a) node. [10–13]

When analyzing the results in Maithel's study, who described 94 cases of PD there was no difference regarding the survival of patients with HLA(8a) positive and patients with metastatic disease [11]. However, the population analyzed in the latter embraces a great variety of malignant diseases (ampullary adenocarcinoma, duodenal adenocarcinoma, neuroendocrine tumor) and does not limit itself to pancreatic cancer [13–15]. We also describe some different histologic cancer types; pancreatic cancer was the most frequent. These results show the variation of the evidence among the HLA node and the relationship with oncologic outcomes.

Regarding OS, perineural invasion, tumoral size, and vascular invasion showed a significant association in the logRank test analysis; but only vascular invasion showed a strong and independent correlation with poor prognosis. In the primary evaluation of DFS significant variables were LNRR + (cutoff $p = 0.01$ χ^2 6.01), HLN + ($p = 0.09$ χ^2 3.32), tumoral size > 2 cm ($p = 0.03$ χ^2 4.6), vascular invasion ($p = 0.002$ χ^2 5.71), perineural invasion ($p = 0.1$ χ^2 3.36), and resection margins (p -value 0.6 χ^2 0.01). The multivariate analysis found a strong association of the lymph node ratio cutoff with a significant statistical value ($p = 0.008$, CI 95%), tumoral size > 2 cm ($p = 0.02$ CI 95%), and vascular invasion ($p = 0.02$ CI 95%). HLA(8a) compromise failed to confirm relevance in DFS Cox proportional hazard model.

In LaFemina's work, poor differentiation and positive peripancreatic lymph nodes were both associated with a significant reduction in survival (2.17 and 1.41-folds for OS and 2.19 and 1.84-folds for DFS). HLA(8a) + has a 2.94-fold reduction in OS and 2.66-fold reduction in DFS [12]. These results are similar to those observed in our population. (In HLA node-positive a 2.0-fold reduction of OS and 1.77-fold of DFS).

Phillips et al documented that patients with lymphatic involvement (peripancreatic) had an OS of 19,5 months. However, patients without lymph node involvement had a median of 40,2 months ($p < 0,001$) [3] They didn't find a difference between OS and DFS of patients with positive HLA(8a) (mean 18,4 months and 10,6 months) and negative patients (mean 19,7 months and 11,6 months) [3]. One of the limitations of this study is the lack of evidence in pathology reports of HLA nodes, and this could impact the final results.

Taking into consideration that patients with positive HLA(8a) have a significantly greater tumoral load and worse tumoral biology, some authors have compared the prognosis with peritoneal carcinomatosis [10]. Connor et al, found that the OS for patients with positive HLA(8a) was poor when compared to those

with negative HLA(8a) (mean of 197 vs 470 days, $p = 0,003$), which is why it could be compared with patients with unresectable metastatic disease (mean of 98 days, $p = 0,072$), thus considering the compromise of HLA(8a) an important predictor of occult metastatic disease and general outcomes. Nonetheless, current data does not support the involvement of HAL(8a) as a non-resectability criterion [9, 23]

As is known, multimodal treatment including surgery and chemotherapy is a cornerstone in the management of pancreatic cancer, Liu et al [27] described the well-known impact in the prognosis of patients that receive chemotherapy after an R0 surgery, with an OS of 20 months compared with the non-chemotherapy group with 11.6 months. A large proportion of patients from this study did not receive adjuvant chemotherapy 42.34 % ($n = 47$) because of health insurance issues or personal decisions, that might cause negative impact in the results. Therefore, a differential analysis of patients was performed in separate groups of patients who receive or do not adjuvant chemotherapy. Patients with HLA(8a) node compromised plus chemotherapy have an OS of 20.5 months versus non-chemotherapy with 12.5 months [27–29].

To the best of our knowledge, this is the first report in Colombia evaluating survival analysis in the context of pancreatic cancer, reports in Latin American countries are limited to some systematic reviews. [24, 25]

In conclusion, this retrospective study with prospective data from an HPB center shows significant relevance of positive node 8(a) in pancreatic cancer with poor OS. Data, and statistical analysis, suggest that HLA(8a) compromise must be considered as an impact factor in the overall survival. The data suggest that there are multiple factors involved in the overall prognosis but given its limitations, we cannot recommend stopping surgery in patients with positive HLA(8a). However, it could suggest aggressive biology of the tumor based on the reduced OS. HLA(8a) metastases and an LNRR bigger than 0.6 are relevant prognostic factors in pancreatic cancer to predict reduced OS and DFS respectively. Limitations in our study include the retrospective nature of the study as well some patients do not receive chemotherapy. Further prospective studies are needed to confirm these results.

Declarations

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Figures

Figure 1. Methodology

Methods used in the study.

Figure 1

See image above for figure legend.

Figure 2. Kaplan Meier curve estimates for OS and DFS (HLN +/-)

Figure 2

See image above for figure legend.

Figure 3. Kaplan Meier curve estimates for OS (HLN +/- vs Chemo/Non chemotherapy groups).

Figure 3

See image above for figure legend.