Number and Localization of Positive Lymph Nodes Correlate with Recurrence in Nonfunctioning Pancreatic Neuroendocrine Neoplasms: Implications for Surgery, Staging and Surveillance

Stefano Partelli[1], Francesca Muffatti[1], Valentina Andreasi[1], Gianpaolo Balzano[1], Giuseppe Zamboni[2], Claudio Doglioni, [1,] Massimo Falconi[1]

[1]Pancreas Surgery Unit and Pathology Department (CD), IRCCS San Raffaele Hospital, "Vita-Salute" University, Milan, Italy
[2]Pathology Department, "Sacro Cuore-Don Calabria" Hospital, Negrar, Italy

Background: Lymph Nodes involvement is one of the most powerful predictor of failure after surgery for nonfunctioning pancreatic neuroendocrine neoplasms (NF-PNEN). The prognostic value of the number and localization of positive lymph-nodes (PLN) is unknown.

Methods: Among 370 patients with PNEN who underwent resection, those who underwent radical (R0 or R1) pancreaticoduodenectomy (PD) between January 2000 and December 2014 were identified. Patients with functioning neoplasms, inherited syndrome and distant metastases (M1) were excluded. Univariate and multivariate analysis of disease free survival (DFS) were performed.

Results: Overall, 53 patients were included in the study. Of those, 31 patients (58.5%) had nodal metastases (N1) at final histology. The median number of examined lymph nodes (ELN) and positive lymph nodes (PLN) were 20 (IQR 14-33) and 1 (IQR 0-2), respectively. Patients with N1 NF-PNEN were more likely to be male compared with N0 NF-PNEN (71% versus 41%, *P*=0.029) and had a higher frequency of perineural invasion (95.5% versus 74%, *P*=0.042). The median number of ELN was significantly higher among patients with N1 tumors (23 versus 17.5, *P*=0.048). At a median follow-up of 46 months (IR 28-68 months), 14 patients (26%) had disease recurrence and 4 (7.5%) eventually deceased. The 1-, 3-, and 5-years DFS were 92%, 79%, and 71%, respectively. Patients with N1 NF-PNEN had a significantly worse 3-year DFS compared with N0 NF-PNEN patients (69% versus 94%, *P*=0.013). Similarly, patients with PLN>1 had a worse DFS compared with those patients who had 0 or 1 PLN (62% versus 90%, *P*=0.005). On multivariate analysis, age>60 years (HR 4.25, *P*=0.024), G3 NF-PNEN versus G2-G1 NF-PNEN (HR 3.46, *P*=0.002), and PLN>1 (HR 8.42, *P*=0.002) were independent predictors of recurrence. No differences were found in terms of DFS among patients with N0 NF-PNEN according to different cut-offs of ELN. In all 31 patients with N1, PLN were localized in posterior and anterior pancreaticoduodenal stations (station 13 and 17). Superior mesenteric artery nodes (station 15) and hepatoduodenal ligament nodes (station 12) were involved in 5 and 3 cases, respectively. On multivariate analysis. Involvement of station 12 was associated with a significant poorer DFS compared with station 13, 15, and 17 (HR 2.5, *P*=0.005).

Conclusion: The number of PLN and their localization are associated with the risk of recurrence after radical PD for NF-PNEN. An adequate lymphadenectomy including station 12 and station 15 should be routinely performed whereas no data support an extended lymphadenectomy. This study suggests preliminary findings to support a revision of the current TNM-based staging systems for PNEN.

Figure 1

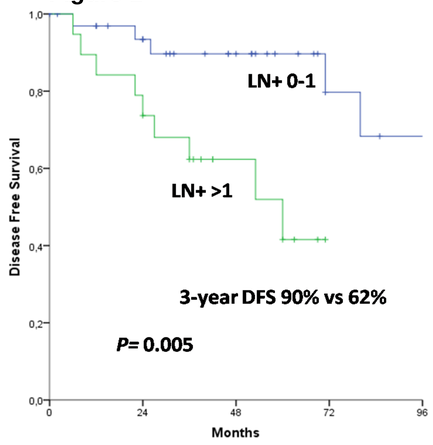
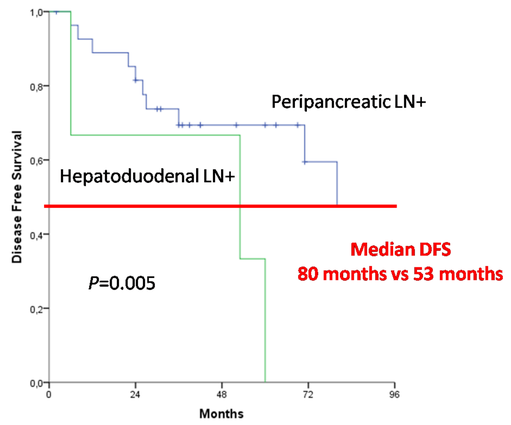


Figure 2



Variable	Hazard Ratio	95% CI	P
Age			
≤60	1	-	-
>60	4.248	1.211-14.901	0.024
Tumor Grading			
G1-G2	1	-	-
G3	3.457	1.547-7.726	0.002
N			
N0	1	-	-
N1	3.791	0.373-38.556	0.260
N+			
0-1	1	-	-
>1	8.418	2.191-32.344	0.002
LNR			
LNR<0.040	1	-	-
LNR>0.040	1.661	0.198-13.918	0.640

Table 1

Variable	Hazard Ratio	95% CI	*P*
Tumor Grading			
G1-G2	1	-	-
G3	4.473	1.584-12.630	0.005
N station			
Peripancreatic	1	-	-
Hepatoduodenal	2.555	1.584-12.630	0.005
N+			
0-1	1	-	-
>1<3	2.940	0.572-15.110	0.197
>3	2.541	0.287-22.516	0.402
LNR			
LNR<0.040	1	-	-
LNR>0.040	1.434	0.160-12.867	0.747

Table 2

Figure 1. Comparison of disease free survival after surgery in patients without Positive LN or with one positive LN (blu) and patients with more than one node positive (green).

Figure 2. Comparison of disease free survival for patients with positive lymph nodes according to localization: green line for peripancreatic (stations 13, 14,17), blu line Hepatoduodenal ligament (station 12).

Table 1. Multivariable analysis of factors associated with disease free survival in patients with PNEN after radical pancreaticoduodenectomy.

Table 2. Multivariable analysis of factors associated with disease free survival in patients with positive lymph nodes at hystological examination.