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Short Report

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Prognostic significance of nodal micrometastases of non-functioning pancreatic neuroendocrine tumours

Valentina Andreasi[1,2], Stefano Partelli[1,2], Marco Schiavo Lena[3], Francesca Muffatti[2], Anna Battistella[1,2], Domenico Tamburrino[2], Nicolò Pecorelli[1,2], Stefano Crippa[1,2], Gianpaolo Balzano[2], Claudio Doglioni[1,3] and Massimo Falconi[1,2,*]

[1]School of Medicine, Vita-Salute San Raffaele University, Milan, Italy
[2]Pancreas Translational and Clinical Research Centre, Pancreatic Surgery Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy
[3]Pathology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

Correspondence to: Massimo Falconi, Pancreas Translational and Clinical Research Centre, Pancreatic Surgery Unit, IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20132, Milan, Italy (e-mail: falconi.massimo@hsr.it)

Introduction

Nodal metastases have been recognized as one of the most powerful prognostic factors after curative surgery for pancreatic neuroendocrine tumours (PanNETs)[1–5]. However, only a fraction of patients with node-positive PanNETs will develop disease relapse. Nowadays, the ability to identify very small nodal metastases that are not detected before surgery has significantly improved[6]. Nodal micrometastases have previously been described in the setting of neuroendocrine tumours, although their prevalence is unknown, and a universally accepted definition is lacking. A study considering gastrointestinal neuroendocrine tumours suggested that approximately one-third of lymph nodes (LNs) could be classified as histologically positive due to the presence of nodal micrometastases[7]. The significance of nodal micrometastases has been extensively studied for other cancers[8], but its prognostic role in PanNETs has never been investigated.

The aim of this study was to assess the role of nodal micrometastases as a predictor of disease recurrence after surgery for non-functioning PanNETs (NF-PanNETs).

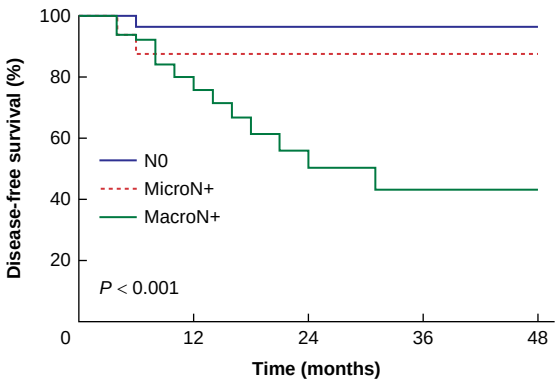
Methods

All of the patients previously enrolled in the DETECTYON trial (NCT03918759), a prospective observational study investigating the accuracy of preoperative imaging in the assessment of nodal metastases of NF-PanNETs, were included[6]. Only consecutive patients undergoing formal pancreatic resection for sporadic NF-PanNETs (San Raffaele Hospital, October 2018 to December 2021) were considered (*Fig. S1*).

Disease-free survival (DFS) and its predictors represented the main outcomes. DFS was defined as the time from surgery to any kind of disease recurrence and it was censored at the last follow-up if no events had occurred.

Nodal status was defined according to the European Neuroendocrine Tumor Society classification[9]. The size of LN metastases was prospectively recorded and nodal metastases were defined as nodal micrometastases or as nodal macrometastases, when their maximum diameter was less than 5 mm or greater than or equal to 5 mm, respectively. The nodal sampling protocol is reported in the *Supplementary Methods*.

The type of pancreatic resection was chosen based on the lesion site. As all patients underwent formal resections, standard



No. at risk					
N0	58	52	36	26	13
MicroN+	16	14	12	9	4
MacroN+	26	18	9	5	4

Fig. 1 Comparison of disease-free survival between patients without nodal metastases, patients with nodal micrometastases, and patients with nodal macrometastases of non-functioning pancreatic neuroendocrine tumours

N0, patients without nodal metastases; MicroN+, patients with nodal micrometastases; MacroN+, patients with nodal macrometastases.

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Table 1 Univariable and multivariable Cox regression analyses to identify determinants of disease recurrence after curative surgical resection performed for non-functioning pancreatic neuroendocrine tumours

Variable	*n*	Univariable		Multivariable	
		HR (95% c.i.)	*P*	HR (95% c.i.)	*P*
Sex			0.470		
Male	60	1			
Female	40	1.435 (0.539,3.825)			
Age (years)			0.304		
<70	77	1			
≥70	23	1.742 (0.605,5.019)			
Histological site			0.947		
Pancreatic head	36	1			
Pancreatic body/tail	64	0.966 (0.351,2.661)			
Tumour grade[11]			0.007*		
Pancreatic neuroendocrine tumour G1	49	1		–	–
Pancreatic neuroendocrine tumour G2–G3	51	16.543 (2.181,125.457)			
T category[9]			<0.001*	–	–
T1–T2	76	1			
T3–T4	24	6.458 (2.338,17.841)			
N category					
N0	58	1		1	
Nodal micrometastases	16	3.619 (0.509,25.708)	0.199	7.636 (0.777–75.059)	0.081
Nodal macrometastases	26	16.859 (3.758,75.634)	<0.001*	6.281 (1.238–27.419)	0.034*
M category[9]			<0.001*		0.026*
M0	89	1		1	
M1	11	19.023 (6.846,52.855)		5.826 (1.238–27.419)	
Resection margins					
R0	92	1		–	–
R1	5	6.917 (1.900,25.176)	0.003*		
R2	3	15.707 (4.158,59.334)	<0.001*		
Microvascular invasion			0.008*		
No	44	1		–	–
Yes	56	15.613 (2.067,117.927)			
Perineural invasion			0.337		
No	65	1			
Yes	35	1.624 (0.604,4.367)			
Necrosis			0.002*		
No	93	1		–	–
Yes	7	6.131 (1.936,19.416)			

*Statistically significant.

lymphadenectomy was always performed, in accordance with the consensus statement by the International Study Group on Pancreatic Surgery[10], as previously described[6].

Demographics, perioperative features, and pathological details were recorded. Follow-up data were updated in December 2022, providing a minimum follow-up of 12 months for each survivor. Survival probability was estimated according to the Kaplan–Meier method. DFS was compared between groups using the log rank test. Cox regression was performed to identify determinants of disease recurrence. Further details regarding data collection, follow-up, and statistical analysis are reported in the *Supplementary Methods*.

Results

Overall, 100 patients who underwent formal pancreatic resection for NF-PanNETs were included. Nodal involvement was present in 42 patients. Of these, 16 patients (38%) had nodal micrometastases and 26 patients (62%) had nodal macrometastases. Pancreatic resection was performed with curative intent in all but three cases. Other clinicopathological features and their comparisons between patients without nodal metastases, patients with nodal micrometastases, and patients with nodal macrometastases are reported in *Tables S1, S2, Fig. S2* and *Supplementary Results*.

After a median follow-up of 37 (interquartile range 22–50) months, 16 patients (16%) experienced disease relapse and 2 patients died of disease. Patients with N0 NF-PanNETs (that is patients without nodal metastases) had a 4-year DFS rate of 97% compared with 88% for patients with nodal micrometastases ($P = 0.152$) and 43% for patients with nodal macrometastases ($P < 0.001$). Patients with nodal micrometastases had better DFS compared with patients with nodal macrometastases ($P = 0.046$) (*Fig. 1*).

Univariable and multivariable analyses investigating predictors of disease recurrence are reported in *Table 1*. Distant metastases (HR 5.83, 95% c.i. 1.24 to 27.42; $P = 0.026$) and nodal macrometastases (HR 6.28, 95% c.i. 1.24 to 27.42; $P = 0.034$) were identified as independent determinants of disease relapse. Nodal micrometastases were not associated with recurrence either in the univariable analysis ($P = 0.199$) or in the multivariable analysis ($P = 0.081$). Most disease recurrences (12 of 16) occurred in patients with nodal macrometastases. Only two patients with nodal micrometastases experienced disease relapse and, in both cases, liver metastases were present. Disease recurrence occurred in only two patients with N0 neoplasms (one patient with a grade 3 NF-PanNET and one patient with a stage IV NF-PanNET). Two patients eventually died of disease; both had nodal macrometastases and developed distant metastases.

Discussion

Patients with nodal micrometastases had a prognosis that was similar to that of patients without nodal metastases.

Nodal micrometastases could be regarded as a separate clinicopathological entity, with possible implications for postoperative surveillance protocols.

The risk of nodal involvement is a crucial driver for the extent of pancreatic resection and lymphadenectomy, due to its recognized prognostic impact[12–15]. Additional prognostic determinants are needed in the setting of node-positive disease. The LN ratio has recently been associated with an increased risk of recurrence[16,17]. Little is known regarding the importance of the size of nodal metastases.

Concordant with a previous series[7], the present study shows that nodal micrometastases are a common histological finding, being present in nearly 40% of patients with node-positive NF-PanNETs. The high proportion of microscopic nodal involvement explains the relatively high incidence of node-positive NF-PanNETs. The DETECTYON trial demonstrated that the sensitivity of preoperative imaging with regard to the identification of nodal metastases was dismal[6], possibly due to the high rate of microscopic nodal involvement. The chance to critically identify nodal micrometastases depends on the number of retrieved LNs and, consequently, on the amount of adipose tissue examined. A standardized nodal sampling protocol is important.

The presence of pathological features of aggressiveness was more frequent among patients with nodal macrometastases compared with patients without nodal metastases or patients with nodal micrometastases. This suggests that the role of nodal micrometastases as a predictor of poor prognosis is questionable. The risk of disease recurrence was comparable between patients without nodal metastases and patients with nodal micrometastases, but was higher in patients with nodal macrometastases. Consistently, only the presence of nodal macrometastases was identified as an independent determinant of disease relapse.

Surveillance of patients with NF-PanNETs could be stratified according to the type of nodal metastases and could initially be less intensive in patients with nodal micrometastases, as these patients are unlikely to experience early recurrence. Currently, there is no method to distinguish these patients before surgery and tailor the extent of resection.

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Author contributions

Valentina Andreasi (Conceptualization, Data curation, Investigation, Writing—original draft), Stefano Partelli (Conceptualization, Investigation, Supervision, Writing—original draft), Marco Schiavo Lena (Data curation, Investigation, Writing—review & editing), Francesca Muffatti (Data curation, Investigation, Writing—review & editing), Anna Battistella (Data curation, Methodology, Writing—review & editing), Domenico Tamburrino (Investigation, Methodology, Writing—review & editing), Nicolò Pecorelli (Data curation, Investigation, Writing—review & editing), Stefano Crippa (Investigation, Supervision, Writing—review & editing), Gianpaolo Balzano (Investigation, Writing—review & editing), Claudio Doglioni (Methodology, Resources, Supervision, Writing—review & editing), and Massimo Falconi (Conceptualization, Supervision, Writing—review & editing)

Disclosure

The authors declare no conflicts of interest.

Supplementary material

Supplementary material is available at *BJS* online.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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