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Original article

The role of lymph node ratio in recurrence after curative surgery for pancreatic endocrine tumours

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ABSTRACT

Background: The prognostic role of lymph nodes metastasis in pancreatic neuroendocrine tumours is unclear.
Methods: Retrospective study of 53 patients who underwent a curative standard resection for pancreatic neuroendocrine tumours. The endpoint was to define the role of the lymph nodes ratio in recurrence after curative surgery. The following data were considered as possible factors for predicting the risk of recurrence: gender, age, presence of symptoms, hormonal status, site of tumours, type of resection, size of the tumours, radical resection, pathological T, N and M stage, the Ki67 index, the number of lymph nodes harvested, the number of metastatic lymph nodes and the lymph node ratio. Recurrence rate and time of recurrence were evaluated.
Results: Twelve (26.4%) patients developed a recurrence with a median time of 42.8 (1–305) months. At multivariate analysis, the only factors related to recurrence were: size of lesions (HR 1.1, C.I. 95% 1.0–1.1, $P = 0.011$), Ki67 $\geq$ 5% (HR 3.6, C.I. 95% 1.3–10, $P = 0.014$) and LNR $>$ 0.07 (HR 5.2, C.I. 95% 1.1–25, $P = 0.045$).
Conclusions: Our study confirmed that the lymph nodes ratio played an important role in the recurrence rate and suggested that a low number of metastatic lymph nodes reduced the disease free survival.

1. Introduction

The prognostic role of lymph node metastasis is well known in pancreatic ductal adenocarcinoma [1] and, in recent years, the impact of the lymph node ratio (LNR) on survival has been clarified in patients who have undergone pancreatic resection for epithelial malignant disease [2–4]. Regarding pancreatic neuroendocrine tumours (PETs), only a few reports have shown that lymph node (LN) metastasis could play a role in the prognosis [5–9] and only one study [10] reported an LNR $>$ 0.20 as a predicting factor for recurrence after curative surgery. The aim of the present study was to evaluate the role of the LNR in the recurrence after curative surgery in patients with PETs in a single high volume pancreatic centre.

2. Materials and methods

This was a retrospective study of a prospective database regarding 107 consecutive patients affected by sporadic PETs, surgically treated from January 1980 to December 2012. Patients with an R2 resection ($n = 10$), those with an atypical resection (enucleation and middle pancreatectomy) ($n = 26$) and those without information regarding the number of Ki67-positive cells ($n = 18$) were excluded. The remaining 53 patients, who underwent a curative standard pancreatic resection, were retrospectively studied. The endpoint of this study was to define the role of the LNR in recurrence after curative surgery.

The following data were considered as possible factors for predicting the risk of recurrence: gender, age ($<$55 or $\geq$55 years), presence of symptoms, hormonal status (functioning or non-functioning), site of tumours (head or body-tail), type of resection

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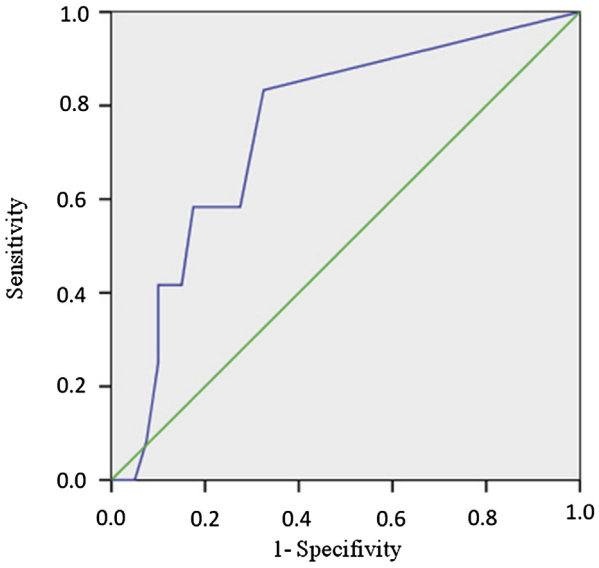
(pancreaticoduodenectomy, distal pancreatectomy or total pancreatectomy), size of the tumours (as a continous variable), radical resection (R0 or R1) [11] pathological T, N and M stage according to the European Neuroendocrine Tumor Society (ENETS TNM) [12], and the Ki67 index. The Ki67 proliferative index was expressed as a percentage based on the number of Ki67-positive cells in 2000 tumour cells in areas of highest immunostaining using MIB1 antibody cells in 2000 tumour cells in these areas (DBA, Milan, Italy). The Ki67 index was included in the analysis as a continuous variable and it was also used to categorize patients in the WHO 2010 classification [13]. Furthermore, the Ki67 index was analysed with the cut-off proposed by Scarpa (Ki67 index > 5%) [14] .The number of lymph nodes harvested, the number of metastatic lymph nodes and the lymph node ratio were included in the study. The LNR was calculated as the ratio of the number of metastatic lymph nodes to the total number of lymph nodes harvested. The LNR was first analysed in the three categories (LNR = 0; LNR between 0 and 0.2; LNR > 0.2) proposed by Boninsegna et al. [10] and it was then analysed in two categories (LNR ≤ 0.07 and LNR > 0.07), calculated using a ROC curve (AUC = 0.768; P = 0.009) for our population (Fig. 1). All specimens were examined by the same high volume pathologist (DS) [15]. Informed consent was obtained for each patient.

The postoperative results were also reported but were not included in the analysis. Postoperative mortality was defined as in hospital or 30-day death.

Follow-up examinations were conducted every 6 months for the first 2 years and annually thereafter with clinical examination, serum CgA with enzyme-linked immunosorbent assay (ELISA) > 21 U/l and immunoradiometric assay (IRMA) > 87 ng/ml and computed tomography (CT). Somatostatin receptor scintigraphic scanning (Octreoscan) was used from 2000 to 2006 and positron emission tomography with 68 Ga-DOTANOC was used from 2006 to 2012 [16] to confirm clinical, laboratory or radiological suspicion of recurrence. Recurrence rate, time and site of recurrence were evaluated. Disease-free survival (DFS) was calculated from the date of surgery to the date of the diagnosis of recurrence. Overall survival (OS) was calculated from the date of surgery to death (both disease related or from other causes).

Means or median, standard deviations or range and frequencies were used to describe the data. OS and DFS were estimated using the Kaplan–Meier method. Risk of recurrence was reported as a Hazard Ratio (HR) with a confidence interval of 95% (C.I. 95%). Cox regression stepwise analyses were used to identify the factors related to recurrence in univariate and multivariate analyses. All variables with P values <0.10 at univariate analysis were incorporated into a multivariate analysis. Two-tailed P values less than 0.05 were considered statistically significant. All statistical analyses were carried out by running the Statistical Package for the Social Science (SPSS, Chicago, IL), version 13.



Area Under Curve	Standar Error	Pvalue
0.751	0.078	0.009

Fig. 1. The optimal cut-off of LNR who predict the recurrence, was calculated using ROC curve. AUC = area under curve; SE = standard error.

3. Results

The characteristics of the 53 patients are summarized in Tables 1 and 2. There were 26 (49.1%) males and 27 (50.9%) females; age was ≥55 years in 36 patients (67.9%). Symptoms were present in 38 (71.7%) patients but only in 11 (20.8%) cases were the tumours functioning. The majority of the tumours were located in the body-tail of the pancreas (38 cases-71.7%). Distal pancreatectomy and pancreaticoduodenectomy were carried out in 35 (66%) and 15 (28.3%) patients, respectively. In three patients (5.7%), having a body-tail neoplasm, a total pancreatectomy was performed due to the presence of suspicious lesions in the head of the pancreas. Liver resection was carried out in only 4 patients (7.5%). The median size of the lesions was 30 (7–50) mm and R1 resection was rarely performed (9.4%). Stage T4 was observed in 6 cases (11.3%) while T2, T3 and T1 were more frequently reported (32.1%, 32.1% and 24.5%, respectively). Twenty-four (45.3%) patients had nodal metastases and 4 (7.5%) had liver metastases. According to the ENETS TNM staging system, 10 (18.9%) patients were in stage I, 19 (35.8%) in stage II, 20 (37.7%) in stage III and 4 in stage IV (7.5%). The mean Ki67 index was 2.4% (0.3–0.61). According to the WHO 2010 classification, 21 (39.6%) were neuroendocrine tumour (NET) G1, 30 (56.6%) NET G2 and only 2 (3.8%) were neuroendocrine carcinomas (NECs). When we applied the Ki67 index modified by Scarpa et al. [14]., 41 (77.3%) cases were <5% and 12 (22.7%) were ≥5%. The median number of lymph nodes harvested was 15 (8–70) and the

Table 1
Demographics, and the clinical and surgical characteristics of 53 patients having pancreatic endocrine tumours (PETs) included in the study.

Characteristics	*N*(%)
Sex	
Male	26 (49.1)
Female	27 (50.9)
Age	
<55 years	17 (32.1)
≥55 years	36 (67.9)
Symptoms	
No	15 (28.3)
Yes	38 (71.7)
Hormonal status	
NF	42 (79.2)
F	11 (20.8)
Tumour site	
Head	15 (28.3)
Body-Tail	38 (71.7)
Type of resection	
PD	15 (28.3)
DP	35 (66)
TP	3 (5.7)

NF = Non-functioning; F = Functioning; PD = Pancreaticoduodenectomy; DP = Distal pancreatectomy; TP = Total pancreatectomy.