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Malignant pancreatic neuroendocrine tumour: Lymph node ratio and Ki67 are predictors of recurrence after curative resections ☆

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ABSTRACT

Introduction: Malignant pancreatic neuroendocrine tumours (PNENs) are generally associated with a good prognosis after radical resection. In other pancreatic malignancies predictors of recurrence and the role of lymph node ratio (LNR) are well known, but both have been scarcely investigated for malignant PNETs.

Methods: The prospective database from the surgical Department of Verona University was queried. Clinical and pathological data of all patients with resected malignant PNET between 1990 and 2008 were reviewed. Univariate and multivariate analysis were performed.

Results: Fifty-seven patients (male/female ratio = 1) with a median age of 58 years (33–78) entered in the study. Twenty-nine (51%) patients underwent pancreaticoduodenectomy and 28 (49%) distal pancreatectomy. Postoperative mortality was nil with a 37% morbidity rate. There were 36 (63%) patients with lymph node metastases (N1). Of these, 23 (64%) had a lymph node ratio (LNR) >0 and ⩽0.20 and 13 (36%) had a LNR >0.20. The median overall survival and the median disease free survival (DFS) were 190 and 80 months, respectively. Recurrent disease was identified in 24 patients (42%) with a 2 and 5-year DFS rate of 82% and 49%, respectively. On multivariate analysis, LNR >0.20 (HR = 2.75) and a value of Ki67 >5% (HR = 3.39) were significant predictors of recurrence ($P < 0.02$).

Conclusions: After resection for malignant PNETs, LNR and a Ki67 >5% are the most powerful predictors of recurrence. The presence of these factors should be considered for addressing patients to adjuvant treatment in future clinical trials.

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1. Introduction

Malignant pancreatic neuroendocrine tumours (PNETs) are generally associated with good prognosis when resected with radical intent, also when liver metastases are present.[1–5] Predictors of poor prognosis include: non-functioning tumour, tumour size, tumour differentiation, patients' age and distant metastases. However, these predictors have been identified from heterogeneous series which included both benign and malignant forms.[6–18] Moreover, the prognostic role of the lymph node ratio (LNR), i.e. the ratio between the number of metastatic lymph nodes over that of examined lymph nodes, is being increasingly recognised as powerful prognostic factor in other pancreatic malignancies, including pancreatic ductal adenocarcinoma (PDA), intraductal papillary mucinous and ampullary carcinomas.[19–22] The prognostic role of LNR in malignant PNET is still unknown. Despite the usually good survival of patients resected with curative intent a proportion of patients recur, but rate, time and type of failure have been scarcely investigated. Currently, no indication to adjuvant therapy exists after radical resection for malignant PNETs, and chemo or biological therapies are only indicated for patients affected by advanced PNETs.[23–25] Moreover, the lack of data regarding recurrence rates and median time to recurrence, represents a major problem in the development of clinical studies.[26] The identification of patterns and predictors of recurrence in PNETs with malignant behaviour could help in stratifying and selecting subgroups of patients for adjuvant treatments. Aims of the present work were to (1) evaluate rate, time and patterns of recurrence in a consecutive series of patients who underwent surgical resection with radical intent for malignant PNETs and to (2) recognise predictors of recurrence.

2. Patients and methods

2.1. Data collection

The prospective database maintained at the Department of Surgery of the University of Verona was queried to identify all the patients who underwent a resection with radical intent between 1990 and 2008 for malignant PNET. All patients with MEN1 syndrome or Von Hippel–Lindau disease were excluded from the study. Patients with tumours arising from the papilla of Vater, bile duct, or duodenum were also excluded, as well as both those with macroscopic residual tumour at the end of the operation (R2 resections) and those in whom an atypical resection was performed. Patients with poorly differentiated tumours were not included. Clinical presentation, demographics, data regarding surgical procedures, postoperative course and complications, pathology and follow-up were collected. Perioperative mortality was defined as in hospital or 30-day death.

2.2. Pre-operative work up and surgical procedures

All patients underwent a routine evaluation that included clinical, laboratory and imaging assessments. From 1998, laboratory analyses included chromogranin A (evaluated by IRMA SCHERING-CIS®, normal value (n.v.) <98 ng/mL), neuron specific enolase (NSE, n.v. <12.5 ng/mL), and CA19.9 (n.v. <25 U/mL). tumour staging was performed by conventional high-resolution imaging techniques including ultrasonography (US), computed tomography (CT) and/or magnetic resonance imaging (MRI). From 1998 all patients underwent somatostatin receptor scintigraphy (Octreoscan®) as part of their preoperative workup. In keeping with the anatomic location of the neoplasm, pancreaticoduodenectomy or left-pancreatectomy with splenectomy were performed. As regard tumour localised in the head of the pancreas, Whipple resection was performed in all cases before 1996, while pylorus-preserving pancreaticoduodenectomy (PPPD) was carried out whenever possible since that year. Standard lymphadenectomy was routinely performed.

2.3. Pathology

Quality of resection was determined according to the R-classification by the International Union Against Cancer. The UICC 2002 classification was used.[27] The diagnosis of PNET was based on conventional histology and immunohistochemistry (chromogranin A, synaptophysin) on surgical specimen. All cases were reviewed and classified according to the latest WHO-2010 classification[28] and were assigned to a TNM-based stage and grading score according to Rindi et al.[30] tumour (T) status was also determined using 'T' classification according to UICC classification (seventh edition).[31] PNETs were defined malignant when invasion of extrapancreatic structures/organs or metastasis was present. The Ki67 proliferative index was expressed as a percentage based on the count of Ki67- positive cells in 2000 tumour cells in areas of the highest immunostaining using the MIB1 antibody (DBA, Milan, Italy) and were stratified into two categories G1 (Ki67 <2%) and G2 (Ki67 $\geqslant$2% and <20%). Moreover the value of Ki67 was dichotomised at 5% according to Scarpa et al.[32] Data on the total number of resected lymph nodes and the number of positive lymph nodes were obtained. LNR was determined by dividing the total number of lymph nodes harbouring metastases by the total number of examined nodes. Patients were divided in three groups based on their LNR, including one group of patients with LNR = 0, one group with LNR >0 and $\leqslant$0.20 and one group with LNR >0.20.

2.4. Follow-up

Follow-up consisted of physical examination, laboratory tests including tumour markers (specific tumour hormone in case of functioning tumour, chromogranin A and NSE), and imaging techniques, including an abdominal ultrasound, computed tomography and somatostatin receptor scintigraphy, when required. Follow-up was routinely carried out every 6 months for the first 5 years and yearly thereafter. Follow-up tests were performed at any time if there was the suspicion of disease recurrence. Failure sites were recorded only when a lesion was visible at imaging procedures and classified as local (nodal, around the remnant or reappearance of the disease in the surgical bed), and distant (liver, non regional lymph nodes, peritoneum or systemic). Time to

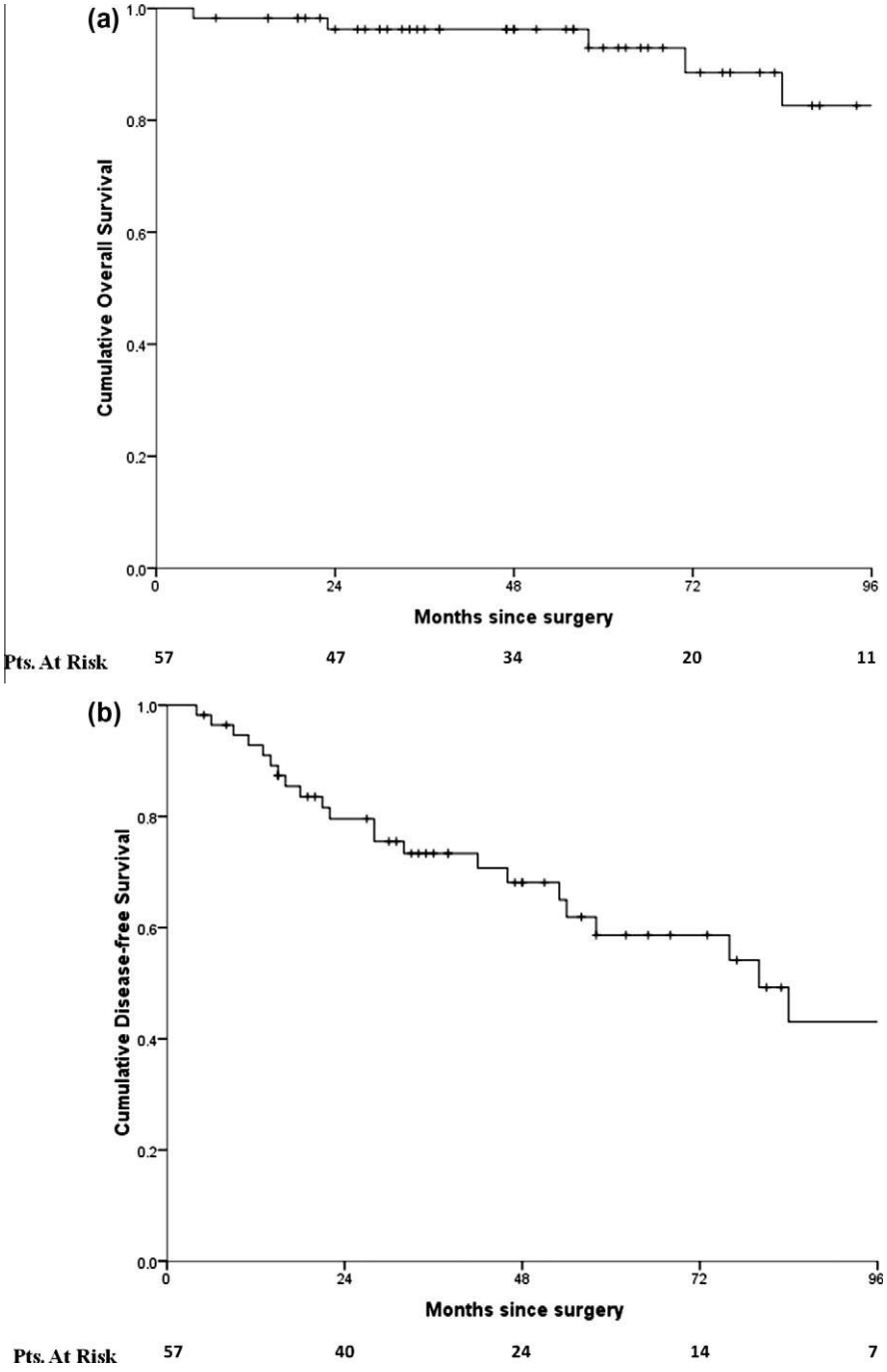

Fig. 1 – (a and b) Overall (a) and disease free survival (b) after resection for malignant pancreatic neuroendocrine tumour (Kaplan–Meier).

recurrence was considered as the interval between resection and disease recurrence. Death of patients was defined as disease-related or for other causes, in order to evaluate disease-specific survival. Follow up was updated for all the alive patients in January 2011.

2.5. *Statistical analysis*

Results are presented as frequencies and percentages for categorical variables and as median (range) for continuous variables. Categorical variables were compared using a Chi Square test and Fisher's exact test as appropriate. When comparing two groups, normally distributed continuous variables were analysed using a two-sample Student *t* test, while the Mann-Whitney *U* test was used for non-normally distributed variables. Survival analysis was done using the Kaplan–Meier method and Log-Rank test. A stepwise Cox proportional hazard model was used to evaluate significant recurrence predictors. All *p* values were two sided and considered significant when less than 0.05. For all the tests a specific software was used (Medcalc 9.6 ® www.medcalc.be).

3. Results

3.1. Demographic and perioperative results

From a total of 218 patients affected by malignant PNET, referred for possible pancreatic resection to our institution, 211 patients underwent surgery for sporadic malignant PNET and 74 were resected with a 35% overall resectability rate (Fig. 1). Among those 74 patients, 7 (9%) underwent an atypical resection and were then excluded from the study as were 10 (13.5%) with a poorly differentiated tumour at histology (PNEC G3). Thus, 57 (26%) patients underwent a pancreatic resection with radical intent and were included in the present study. The male/female ratio was 1 with a median age of 58 years (33–78 years). The most common presenting symptom was abdominal pain (n = 23, 40%). Among the 57 patients, 54 (95%) had a non-functioning malignant PNET, two had a gastrinoma and one a glucagonoma. In the 29 patients (51%) with a PNET localised in the pancreatic head, a pancreaticoduodenectomy with pancreatico-jejunostomy was performed whereas the remaining 28 (49%) underwent distal pancreatectomy with en-bloc splenectomy. In seven patients (10.5%) an additional resection was required due to the presence of liver metastases or adjacent organs involvement. In particular, five patients (7.5%) had a hepatic resection for liver metastases, while a left nephrectomy with adrenalectomy and a right colectomy were carried out in the remaining two. In 2 cases a vascular resection was performed because of superior mesenteric vein invasion. Postoperative mortality was nil whereas overall morbidity was 37%. Pancreatic fistula was the most common postoperative complication (n = 14, 25%), followed by abdominal collection in 4 (7%) cases. Only one case (2%) required a reoperation because of massive postoperative bleeding. None of the patients underwent adjuvant treatments after the resection.

Table 1 – Demographic, presenting symptoms and perioperative details of the 57 patients resected with radical intent for malignant pancreatic endocrine tumours (PNETs).

Variable	n (%)
Age, median (years) (range)	58 (33–78)
Gender	
Male	26 (45.6)
Female	31 (54.4)
Diagnosis	
Incidental	21 (36.8)
Symptomatic	36 (63.2)
Functioning	3 (5.3)
No Functioning	54 (94.7)
Symptoms	
Pain	23 (40.4)
Weight loss	18 (31.6)
Jaundice	6 (10.5)
Type of resection	
PD	29 (50.9)
DP	28 (49.1)
Abdominal complications	
None	36 (63.2)
Pancreatic fistula	14 (24.6)
Abdominal collection	4 (7)
Other	3 (5.3)

PD, pancreaticoduodenectomy.
DP, distal pancreatectomy.

3.2. Pathology results

Histopathological findings are shown in Table 1. According to the 2010 WHO classification,[29] 24 cases were PNET G1 (42%) and 33 were PNET G2 (58%). According to the TNM staging

Table 2 – Histological findings of the 57 patients resected with radical intent for malignant pancreatic neuroendocrine tumours (PNETs).

Variable	n (%)
Tumour site	
Head	29 (50.9)
Body–tail	28 (49.1)
Tumour size (mm) (range)	45 (12–135)
Microvascular angioinvasion	
Yes	42 (73.7)
No	15 (26.3)
Perineural invasion	
Yes	38 (66.7)
No	19 (33.3)
Peripancreatic tissue invasion	
Yes	33 (57.9)
No	24 (42.1)
Necrosis	
Yes	6 (11.9)
No	51 (89.5)
TNM staging[30]	
T1	4 (7)
T2	4 (7)
T3	30 (52.6)
T4	19 (33.3)
N1	36 (63.2)
N0	21 (36.8)
M1	5 (8.8)
M0	52 (91.2)
UICC T staging[31]	
T1	4 (7)
T2	19 (33)
T3	18 (32)
T4	16 (28)
Nodes harvested median (range)	17 (3–57)
LNR	
LNR = 0	21 (36.8)
0 < LNR $\leqslant$ 0.2	23 (40.4)
LNR > 0.2	13 (22.8)
Stage	
Stage II	12 (21.1)
Stage III	40 (72)
Stage IV	5 (9)
WHO 2010 classification[28]	
PNET G1	24 (42.1)
PNET G2	33 (57.9)
Ki 67% median (range)	3 (1–20)
Ki 67 >5%	
Yes	14 (24.6)
No	43 (75.4)
Resection margins	
R1	4 (7)
R0	53 (93)

Table 3 – Univariate analysis on determinants of recurrence in 57 patients after resection with radical intent for malignant pancreatic neuroendocrine tumours (PNETs).

Variable	HR	95% CI	P
Gender (male)	1.28	0.56–2.91	0.557
Age > 50 years	2.30	0.98–5.42	0.057
Functioning tumour (F-PNET)	0.05	0.00–122.97	0.444
Symptoms at diagnosis in NF-PNET			
Weight loss	1.24	0.52–2.92	0.629
Pain	1.33	0.58–3.05	0.498
Jaundice	2.01	0.76–5.35	0.160
Tumour size (mm)[a]	1.00	0.99–1.01	0.808
Microvascular angioinvasion	4.70	1.10–20.06	***0.037***
Perineural invasion	1.65	0.61–4.48	0.324
Peripancreatic tissue infiltration	3.56	1.21–10.49	***0.022***
Gross vessels infiltration	1.99	0.88–4.52	0.100
TNM classification[30]			
T4 versus other T	2.11	0.27–16.51	0.476
N1	0.81	0.40–1.66	0.565
M1	2.12	0.74–6.11	0.163
UICC T classification[31]			
T4 versus other T	1.99	0.88–4.52	0.100
Lymph nodes examined > 12	0.94	0.38–2.36	0.899
Metastatic lymph nodes > 3	1.70	0.83–3.49	0.150
LNR = 0	1	–	–
LNR >0 and ⩽0.20	1.24	0.66–2.33	***0.513***
LNR >0.20	2.74	1.19–6.33	***0.018***
WHO 2010 classification[28]			
PNET G2 versus PNET G1	3.65	1.34–9.94	***0.011***
Ki67 (%)[a]	1.02	1.00–1.04	***0.011***
Ki67 > 5%	3.47	1.52–7.94	***0.003***
R1	1.20	0.28–5.16	0.803

NF-PNET, No-functioning pancreatic neuroendocrine pancreatic tumour; LNR, lymph node ratio. Bolditalic is for P values <0.05.
[a] Expressed as continuous value.

system,[30] 12 cases (21%) were classified as stage II, 40 (72%) as stage III and 5 (9%) as stage IV. Negative margins (R0) were achieved in 53 cases (93%) and the remaining 4 pancreatectomies (7%) resulted in a microscopic involvement of the surgical margins (R1). The median number of lymph nodes harvested was 17 (3–57), and 36 patients (63%) had lymph node metastases. Of these latter, 23 patients (64%) had a LNR ⩽0.20 and 13 (36%) had a LNR >0.20. The median value of Ki67 was 3% (1–20%), and 24 tumours (36%) had a Ki67 >5% (Table 2).

3.3. *Recurrence and long-term outcomes*

The median follow up was 54 months (5–202 months) with no patient lost. After a median time of 28 months (4–158 months) from surgery, 24 patients (42%) developed recurrence of the disease. In these patients, hepatic recurrence was observed in 20 patients (83%) whereas 4 (17%) developed local recurrence. The median time to recurrence was 25 months when liver metastases occurred and 19 months in case of local recurrence ($p = 0.53$), respectively. Among 4 patients with R1 resection, 2 developed local recurrence and the remaining 2 patients are presently free of disease.

Among the 24 patients with recurrence, 7 (29%) eventually died of disease after a median time of 25 months (1–114 months) from recurrence diagnosis.

The median overall survival (OS) of 57 patients calculated from the time of pancreatic resection was 190 months with an OS rate at 5 years of 93% (Fig. 1a). The disease-free survival (DFS) rate at 2 and 5 years was 80% and 59%, respectively, with a median of 80 months (Fig. 1b). Among patients with recurrence, the median OS was 125 months with a 5-year rate of 89.5%.

By univariate analysis (Table 3), factors significantly associated with recurrence after pancreatic resection included: microvascular invasion (HR 4.70), peripancreatic fat invasion (HR 3.56), a G2 tumour (HR 3.65), LNR >0.20 (HR 2.74.) and a Ki67 value >5% (HR 3.47).

Table 4 – Significant predictors of recurrence in 57 patients resected for malignant pancreatic endocrine tumours (PNETs) with radical intent (Cox regression analysis adjusted for microvascular angioinvasion, peripancreatic tissue infiltration and number of positive nodes).

Variable	Hazard ratio	95% CI	P
Microvascular angioinvasion	2.86	0.63–13.05	0.176
Peripancreatic tissue infiltration	1.27	0.36–4.48	0.714
Ki67 > 5%	3.39	1.45–7.93	***0.005***
LNR = 0	1	–	–
LNR >0 and ⩽0.20	1.24	0.66–2.33	0.513
LNR >0.20	2.75	1.19–6.33	***0.018***

LNR, lymph node ratio. Bolditalic is for P values <0.05.

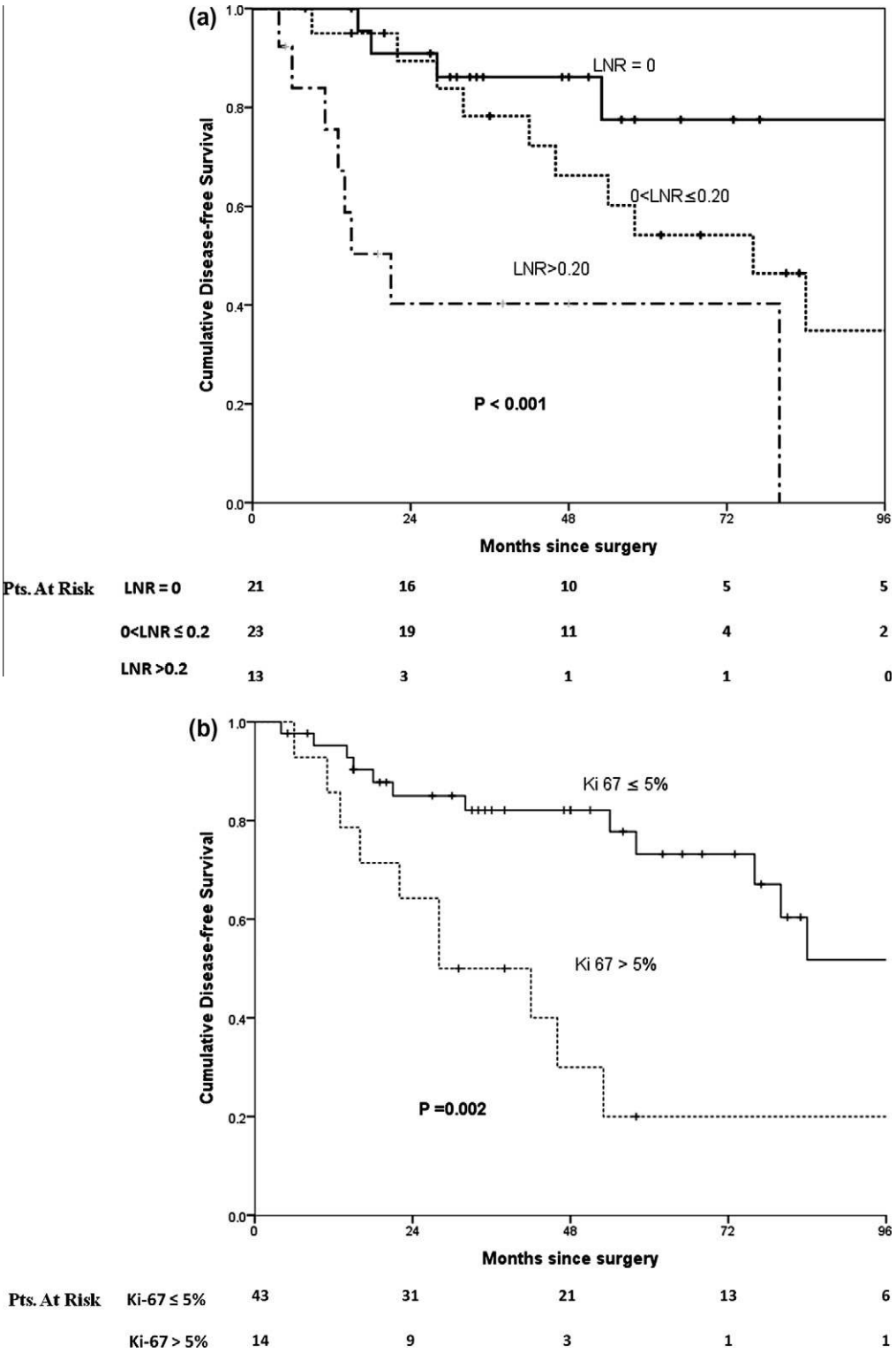

Fig. 2 – (a and b) Disease free survival after resection for malignant pancreatic neuroendocrine tumour comparing patients with a LNR = 0 (n = 21), 0 < LNR ⩽ 0.20 (n = 44) and LNR > 0.20 (n = 13) (P < 0.001) (a) and comparing patients with a Ki67 ⩽5% (n = 43) and Ki67 >5% (n = 14) (P = 0.002) (b) (Kaplan–Meier).

Multivariate analysis (Table 4) confirmed both LNR >0.20 and Ki67 >5% as significant and independent predictors of recurrence. Specifically, patients with a LNR >0.20 had a 2 and 5-year DFS rate of 40% compared with 89% and 54% in those with a LNR ⩽0.20 (P < 0.001) (Fig. 2a). The 2- and 5-year DFS rate for patients with a Ki67 >5% were 64% and 21% compared with 85% and 73% of patients with Ki67 ⩽5% (p = 0.002)(Fig. 2b).

4. Discussion

In the present study, the analysis of the largest single-institution series of malignant PNETs treated with radical intent surgery showed that nearly half of patients experienced recurrence of the disease after a median time of 28 months, 83% had liver involvement while 17% had local recurrence. Our study disclosed that LNR >0.20 and Ki67 >5% were significant predictors of recurrence. Previous reports on prognosis after curative resection for PNETs included large series with a wide heterogeneity regarding both histological type and surgical treatment and considered overall survival as primary endpoint.[6–18] We used a homogeneous series that only included pancreatic neuroendocrine tumours with malignant behaviour and recurrence of disease as primary end-point. The inclusion of overtly malignant forms, as defined by the invasion of extrapancreatic structures/organs or metastasis,(defined as well differentiated carcinomas by the WHO-2000 classification[29]) alone with the exclusion of all cases of neuroendocrine tumour without evidence of malignancy (defined as well differentiated tumour benign or borderline by the WHO-2000 classification[29]) allowed us to focus on parameters predicting recurrence of a disease when it is already a cancer and has been tentatively cured by radical surgery. The choice of recurrence of disease resides in that it seems more appropriate than overall survival to describe the history of malignant PNETs and overcomes the limitation of those studies linked to the long life expectancy which characterises endocrine tumours. The observed median DFS time was of 80 months. The resectability rate among our malignant PNET patients was 35%, which is a figure similar to that of Lo et al.[8] who reported a resection rate of 26% in a cohort of 64 malignant PNET patients. Thus our data confirm that the majority of malignant PNETs are not amenable of curative resection at the time of diagnosis, suggesting that, despite a more indolent biological behaviour, an early diagnosis is demanding also in patients with malignant PNET. In the current series, nearly half of the patients experienced recurrence. This fact raises the question of how we could identify patients at higher risk of recurrence, and therefore potential candidates to adjuvant therapies. Our study suggests that the parameters able to stratify these patients are LNR and Ki67. At present, only patients affected by advanced PNETs are candidates to antitumoural therapies and the rarity of these tumours, along with the low rate of resections, makes it difficult to find prognostic parameters to stratify patients at risk for recurrence.

At present, both the TNM staging system proposed by the European Neuroendocrine Tumor Society (ENETS)[30] and the WHO classification[28], consider a Ki67 value of 2% as cut-off for prognosis. However, a recent study from our institution[32] demonstrated that a Ki67 cut-off value of 5% was able to efficiently prognosticate among pancreatic endocrine tumours at the same stage, while a 2% cut-off was not.

Our study showed that lymph node ratio is the strongest predictor of recurrence in malignant PNET, while the simple data of lymph node involvement and number of positive nodes were not significant in predicting recurrence. Three previous studies[12,13,16] have shown a correlation between survival and nodal involvement. However, these reports considered patients affected by both benign and malignant PNET. We report that patients with a LNR >0.20 had a 5-year DFS rate of 40% compared with 54% of those with a LNR >0 and ⩽0.20. Moreover, nearly all patients with a LNR >0.20 had recurrence within only 2 years after surgery. The ratio between positive and examined lymph nodes has been shown as a powerful prognostic tool in other pancreatic malignancies such as ductal adenocarcinoma and intraductal papillary mucinous carcinoma[19,20,22] as well as in ampulla of Vater carcinomas.[21] Besides its role in stratifying patients for adjuvant treatments, LNR has been shown useful in reducing stage migration effect in the aforementioned malignancies. The prognostic value of LNR in malignant PNETss is even more meaningful considering that the number of both positive and examined lymph nodes seems to have an influence on disease-stage. In this setting, both the current TNM staging systems[30,31] could be improved taking into account the prognostic value of LNR for malignant PNET resected with radical intent. In conclusion, we showed here that LNR and Ki67 are parameters helping in the assessment of risk of recurrence of disease in malignant PNET patients after radical surgery. TNM staging systems for pancreatic endocrine tumours might result improved by the introduction of the LNR parameter instead of the simple record of nodal involvement (N1 versus N0).[30,31] Ki67 is the second most powerful predictor of recurrence of disease in patients undergoing curative intent surgery for malignant PNET, when a cut-off of 5% is used.[32] Patients at high risk of recurrence might deserve adjuvant therapies and appropriate clinical studies should be devised.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2011.10.030.

REFERENCES

1. Norton JA, Kivlen M, Li M, et al. Morbidity and mortality of aggressive resection in patients with advanced neuroendocrine tumors. *Arch Surg* 2003;**138**(8):859–66.
2. Norton JA, Warren RS, Kelly MG, et al. Aggressive surgery for metastatic liver neuroendocrine tumors. *Surgery* 2003;**134**(6):1057–63.
3. Sarmiento JM, Que FG. Hepatic surgery for metastases from neuroendocrine tumors. *Surg Oncol Clin N Am* 2003;**12**(1):231–42.

4. Touzios JG, Kiely JM, Pitt SC, et al. Neuroendocrine hepatic metastases: does aggressive management improve survival? *Ann Surg* 2005;**241**(5):776–83.
5. Kulke M. Advances in the treatment of neuroendocrine tumors. *Curr Treat Options Oncol* 2005;**6**:397–409.
6. Venkatesh S, Ordonez NG, Ordonez NG, et al. Islet cell carcinoma of the pancreas. A study of 98 patients. *Cancer* 1990;**65**:354–7.
7. Thompson GB, Van Heerden JA, Grant CS, et al. Islet cell carcinomas of the pancreas: a twenty-year experience. *Surgery* 1988;**104**:1011–7.
8. Lo CY, Van Heerden JA, Thompson GB, et al. Islet cell carcinoma of the pancreas. *World J Surg* 1996;**20**:878–84.
9. White TJ, Edbey JA, Thompson JS, et al. Is there a prognostic difference between functional and nonfunctional islet cell tumors? *Am J Surg* 1994;**168**:627–30.
10. Madeira I, Terris B, Voss M, et al. Prognostic factors in patients with endocrine tumors of the duodenopancreatic area. *Gut* 1998;**43**:422–7.
11. La Rosa S, Sessa F, Capella C, et al. Prognostic criteria in nonfunctioning pancreatic endocrine tumours. *Virchows Arch* 1996;**429**:323–33.
12. Tomassetti P, Campana D, Piscitelli L, et al. Endocrine pancreatic tumors: factors correlated with survival. *Ann Oncol* 2005;**16**:1806–10.
13. Hochwald SN, Zee S, Conion KC, et al. Prognostic factors in pancreatic neoplasms: an analysis of 136 cases with a proposal for low grade and intermediate-grade groups. *J Clin Oncol* 2002;**20**(11):2633–42.
14. Fischer L, Kleeff J, Esposito I, et al. Clinical outcome and long-term survival in 118 consecutive patients with neuroendocrine tumours of the pancreas. *Br J Surg* 2008;**95**:627–35.
15. Bilimoria KY, Talamonti MS, Tomlinson JS, et al. Prognostic score predicting survival after resection of pancreatic neuroendocrine tumors. Analysis of 3851 patients. *Ann Surg* 2008;**247**(3):490–500.
16. Bettini R, Boninsegna L, Mantovani W, et al. Prognostic factors at diagnosis and value of WHO Classification in a mono-institutional series of 180 non-functioning pancreatic endocrine tumours. *Ann Oncol* 2008;**19**:903–8.
17. Gullo L, Migliori M, Falconi M, et al. Nonfunctioning pancreatic endocrine tumors: a multicenter clinical study. *Am J Gastroenterol* 2003;**98**:2435–9.
18. Solorzano CC, Lee JE, Pisters PW, et al. Nonfunctioning islet cell carcinoma of the pancreas: survival results in a contemporary series of 163 patients. *Surgery* 2001;**130**:1078–85.
19. Pawlik TM, Gleisner AL, Cameron JL, et al. Prognostic relevance of lymph node ratio following pancreaticoduodenectomy for pancreatic cancer. *Surgery* 2007;**141**(5):610–8.
20. Slidell MB, Chang DC, Cameron JL, et al. Impact of total lymph node count and lymph node ratio on staging and survival after pancreatectomy for pancreatic adenocarcinoma: a large, population based analysis. *Ann Surg Oncol* 2008;**15**(1):165–74.
21. Falconi M, Crippa S, Dominguez I, et al. Prognostic relevance of lymph node ratio and number of resected nodes after curative resection of ampulla of Vater carcinoma. *Ann Surg Oncol* 2008;**15**(11):3178–86.
22. Partelli S, Fernandez-Del-Castillo C, Bassi C, et al. Invasive intraductal papillary mucionous carcinomas of the pancreas: predictors of survival and the role of lymph node ratio. *Ann Surg* 2010;**251**(3):477–82.
23. Vilar E, Salazar R, Perez-Garcia, et al. Chemotherapy and role of the proliferation marker ki-67 in digestive neuroendocrine tumors. *Endocr Relat Cancer* 2007;**14**(2):221–32.
24. Rougier P, Mitri E. Chemotherapy in the treatment of neuroendocrine malignant tumors. *Digestion* 2000;**62**:73–8.
25. Kaltsas GA, Besser GM, Grossman AB. The diagnosis and medical management of advanced meuroendocrine tumors. *Endocr Rev* 2004;**25**:458–511.
26. Kulke MH, Siu LL, Tepper JE, et al. Future directions in the treatment of neuroendocrine tumors: consensus report of the national cancer institute neuroendocrine tumor clinical trials planning meeting. *J Clin Oncol* 2011;**29**(7):934–43.
27. American Joint Committee on Cancer. *AJCC cancer staging manual*. 6th ed. New York, NY: Springer; 2002. pp. 157–164.
28. Bosman. *WHO classification of tumor of the digestive system*. Lyon: IARC Press; 2010.
29. Solcia E, Kloppel G, Sobin LH. *Histological typing of endocrine tumours. WHO international histological classification of tumours*. 2nd ed. Berlin, New York: Springer-Verlag; 2000.
30. Rindi G, Kloppel G, Alhman H, et al. TNM staging of foregut (neuro) endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 2006;**449**:393–401.
31. Sobin LH, Gospodarowicz MK, Wittekind C. *UICC: TNM classification of malignant tumors*. 7th ed. Ofxord: Wiley-Blackwell; 2009.
32. Scarpa A, Mantovani W, Capelli P, et al. Pancreatic endocrine tumors: improved TNM staging and histopathological grading permit a clinically efficient prognostic stratification of patients. *Mod Pathol* 2010;**19**:1–10.