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A rational approach to postoperative surveillance for resected non-functional pancreatic neuro-endocrine tumours

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ABSTRACT

Background: Non-functional pancreatic neuroendocrine tumours (NF-PNETs) are rare and have highly variable outcomes. Current guidelines recommend surveillance for NF-PNETs <2 cm. Patients who ultimately have surgical resection are at risk of disease recurrence, and data to support postoperative surveillance protocols are lacking. The aims of this study were to i) identify post-operative predictors of recurrence and ii) risk stratify patients at risk of recurrence.

Methods: Consecutive patients who underwent surgery for NF-PNETs between 2002 and 2015 were identified retrospectively. Data were collected on demographics, pre-operative laboratory results and histopathological tumour characteristics. Statistical analyses were based on penalised Cox-regression modelling and a decision-tree model. Comparison of the variables identified was performed using ROC curves to identify the most sensitive and specific variable associated with disease recurrence.

Results: We identified 73 patients (38 males) with a median age of 61.5 years (range: 31–79). The median period of follow-up was 49 months (5–131). During follow up, 10 deaths (13.9%) were recorded and disease recurrence occurred in 12 patients (16.4%). The Kaplan-Meier predicted 1-,3- and 5-year recurrence–free survival rates were 98.6% (95% CI = 95.9, 100%), 85.4% (76.9–94.8%) and 72% (58.7–88.2%) respectively. Cox multivariate analysis identified poor tumour differentiation (WHO G3 grade) and lymph node ratio (LNR) as independent predictors for recurrence ($p < 0.05$). A simple criterion of 'tumour grade G3 or LNR $\geq$0.1' was found to be sensitive and specific in detecting disease recurrence.

Conclusion: Our results have identified a simple and sensitive criterion for risk stratifying post-resection surveillance. Prospective validation in larger patient cohort is now warranted.

Introduction

Pancreatic neuroendocrine tumours (NETs) are relatively rare malignancies of the gastrointestinal system, representing approximately 1–2% of all pancreatic neoplasms [1]. However, over the past two decades the incidence of these malignancies is rising as a consequence of the increased use of cross-sectional imaging and endoscopic ultrasound [2,3]. Patients with hormonally active pancreatic NETs such as gastrinomas, insulinomas or glucagonomas, usually require surgery to control patient-reported symptoms attributed to hormone secretion. In contrast clinical decision with regards to proceeding to major pancreatic surgery on subjects with non-functional NETs (NF-PNETs), especially in the context of pancreatic incidentalomas, is challenging due to the lack of supporting evidence on patient selection criteria [4].

NF-PNETs are highly heterogeneous tumours with variable behaviour, and accurately assessing the aggressiveness of these neoplasms in the pre-operative setting has proven difficult for clinicians [5,6]. The management of such neoplasms is complicated by the significant morbidity associated with major pancreatic resection which has to be balanced against the aggressiveness of the tumour and the performance status of the patient. NF-PNETs are considered to be indolent and have a more favourable prognosis compared to pancreatic adenocarcinoma [2]. Nonetheless, only half the patients with localized disease are alive at 10 years after

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diagnosis [7]. In the context of NF-PNETs, tumour size is crucial in the management algorithm. Currently, tumour diameter equal or greater than 2 cm on cross-sectional or endoscopic ultrasound imaging is considered as the cut-off point between radiological surveillance and surgical intervention [8,9]. However, it has been previously reported that tumours smaller than 2 cm may develop distant metastases [7].

Currently, the mainstay of postoperative management of pancreatic NETs following pancreatic resection is to detect disease recurrence at an early stage [7,10,11]. The ability to predict the risk of recurrence following curative pancreatic surgery has been hampered by the absence of a universally accepted staging classification that could help clinicians to identify patients at risk of recurrence. The European Neuroendocrine Tumour Society (ENETS) recently proposed a 4-stage TNM classification for gastroduodenal and pancreatic NETs, combined with a grading classification (low-intermediate-high) based on the mitotic rate and/or Ki-67 proliferation index [12,13]. In the United States, the American Joint Committee on Cancer (AJCC) has introduced a classification system for pancreatic NETs that derives from the staging of pancreatic adenocarcinoma. Post-operative management of patients with pancreatic NETs, unlike other malignancies where the follow-up schedule is based on the expected risk of recurrence, is not mentioned in either the ENETS or AJCC guidelines [12,14]. The evidence available in the literature to date regarding predictors of disease recurrence is limited by the sample size in individual reports and the heterogeneity of subjects included in the analyses (presence of distant metastases at the time of pancreatic surgery, presence of both hormonally active and inactive tumours and patients with hereditary syndromes such as Multiple Endocrine Neoplasia/Von Hippel Lindeau disease) [12–16].

A risk-stratification approach to optimise surveillance intensity is desirable so that the probability of detecting early disease recurrence is maximised whilst such approach would also be beneficial for reducing the financial burden on healthcare resources of unnecessary follow-up. Furthermore, unlike the case of other peri-ampullary malignancies, the role of chemotherapy for pancreatic NETs in the adjuvant setting, is not clearly established, and currently the overall impression is that it is not routinely required [12]. In subjects with evidence of metastatic disease on follow-up, surgical resection (e.g. oligometastatic recurrence), chemotherapy, somatostatin analogues or tyrosine kinase inhibitors are amongst the options currently available to clinicians [18–20]. However, patient selection criteria in the adjuvant setting, especially for subjects at high risk of recurrence, have not been clearly described. It would therefore be highly desirable both from patient and clinician perspective to identify patients at risk of recurrence who would potentially benefit from further therapies using a rational surveillance protocol.

The aims of this study were to i) identify post-operative predictors of recurrence and ii) risk stratify patients at risk of recurrence based on data collected on a well-defined patient cohort.

Methods

Patients

Patients who underwent major pancreatic surgery for non-functional pancreatic NETs between 2002 and 2015 in a tertiary referral centre for hepatopancreatobiliary surgery were identified retrospectively from a prospectively maintained institutional database. All patients underwent pre-operative cross-sectional imaging (Competed Tomography (CT), Magnetic Resonance Imaging (MRI) or Endoscopic Ultrasonography (EUS, +/− Fine Needle Aspiration (FNA)] prior to proceeding to surgery. Patients were included in this study, only if a histologically-proven non-functional pancreatic NET was present upon final histopathological analysis. Non-functional tumours were defined as a NET without clinical symptomatology suggestive of hormonal overproduction. Patients were included in the study if they underwent major pancreatic surgery for non-functional NET with a curative intent. Radical lymphadenectomy was not routinely performed. Subjects who underwent pancreatic enucleation, cases with mixed adeno neuro endocrine carcinoma, or presence of distant metastases at time final pre- or intra-operative staging were excluded from analysis for the purposes of this study.

Data was collected on baseline demographics, pre-operative serum lymphocyte, platelet and neutrophil values, type of pancreatic surgery, pathologic TNM staging, number of lymph nodes harvested, lymph node ratio (calculated as involved/harvested nodes), maximal tumour diameter (based on final histologic report), tumour differentiation, tumour location, presence of perineural or perivascular tumour invasion and surgical resection margin status (R0 or R1). Resection margin status was recorded according to the Royal College of Pathologists [21]. Radiological imaging consisted of abdominal computed tomography (CT), endoscopic ultrasonography and in some cases octreotide scintigraphy (Octreoscan/^{68}Ga PET-CT). The type of pancreatic resection performed (total, distal pancreatectomy or pancreaticoduodenectomy) varied according to the location of the tumour. Completely excised tumours were defined as R0 and specimens with tumour, lymph node or perineural involvement <1 mm from resection margin were deemed as R1 resections. Lymph Node ratio (LNR) was calculated using the involved/harvested nodal ratio. Mitotic count and histologic grade were documented as per the World Health Organization (WHO) 2010 classification (Grades 1 to 3) [22]. Mitotic index was calculated by counting mitoses in 50 high-power fields (hpf) in the most mitotically active area of the tumour and calculating the average number of mitoses per 10 hpf. The area of the tumour with the highest mitotic activity was chosen for Ki-67 immunohistochemistry. The tumour grade was defined as: G1 (well-differentiated), G2 (moderately differentiated) and G3 (poorly differentiated).

Follow-up data were retrieved from our institution's electronic records or from patient records of regional hospitals which carried out the post-resection follow-up and are part of our regional cancer network. Patients were followed-up with every 6 month imaging (CT scan) of chest, abdomen and pelvis, along with clinic review for the first 2 years following resection. Follow-up was reduced to yearly checks thereafter regardless of the location of follow-up (i.e. home institution or regional hospitals). Radiological or cytological findings suggestive of disease recurrence on follow-up (home institution or other regional hospitals) were discussed in the regional multidisciplinary team Meeting where hepatobiliary surgeons, GI radiologists, histopathologists and oncologists constitute the members of the team. Overall survival (OS) was calculated from the date of surgery to the date of death from any cause and censored at the date of last clinical interaction if the patient was still alive. Disease recurrence was defined as local recurrence at the pancreatic resection site, newly identified lymph nodes or development of distant metastases. Recurrence free survival was defined as the percentage of patients without evidence of recurrence from time of surgery to the last clinical interaction or death.

Statistical analysis

Continuous variables are presented as median (range). Categorical variables are presented as absolute frequencies and percentages. Survival was estimated using the Kaplan-Meier method, and differences in survival were ascertained using the Log rank test.

Univariate Cox proportional hazards regression was performed on individual covariates to measure their marginal effect on survival. Subsequently, a penalised Cox model was fitted to the data, with the tuning parameter chosen via ten-fold cross-validation. A multivariate Cox model was refitted on the covariates chosen in the penalised model, to obtain the hazard ratios and confidence intervals of the selected covariates. Furthermore, a decision tree model was developed using a decision-tree analysis. Finally, in order to evaluate the most suitable variable identifying patients at risk of recurrence, sensitivity and specificity analysis was performed by comparing the receiver operating characteristics (ROC) curves of the variables of interest. A p-value <0.05 was considered to be statistically significant. Statistical analysis was performed using the R programming language software (Version 3.2.5, Vienna, Austria).

Results

Study population

The population of patients satisfying the study criteria was 73 patients (38 males:33 females). The median age of the patients included was 61.5 years (range 31–79). Pancreaticoduodenectomy was performed in 39/73 subjects (53.4%); distal pancreatectomy in 27 (37%) and total pancreatectomy in 7 patients (9.6%). The median diameter (maximal) of the neoplasms, after histological analysis, was 2.1 cm (0.5–22), and over half of the tumours (38/73, 52.1%) were originating from the head of pancreas. Nodal involvement (pN1 stage) was present in 30/73 resections (41.1%) and the median number of lymph nodes (LNs) harvested was 12 (0–39). The median number of metastatic LNs per resection specimen was 0.8 (range 0–19) and the median LN ratio (LNR) was 0.1 (0–1). Perivascular and perineural invasion were evident in 44/73 (41.1%) and 11/73 (15.1%) specimens respectively. Surgical resection margin involvement (R1 resection) was present in 29/73 resections (39.7%). Tumour grade (as per the WHO classification) was reported as follows: G1-56/73 (76.7%); G2-13/73 (17.8%) and G3-4 (5.5%). Patient demographic and clinico-pathological characteristics are summarised in Table 1A.

Patient survival and disease recurrence

The median period of patient follow-up was 49 months (5–131). During follow up, 10 deaths were recorded (13.9%) in the study population. The overall Kaplan-Meier predicted 1-, 3- and 5-year overall survival rates were 98.6% [95% CI = (95.9, 100)], 93.6% (87.6, 99.9) and 87.9% (78.9, 98.0) respectively (Fig. 1A). Disease recurrence was recorded in 12 patients (16.4%), with the liver being the site of recurrence in 9 out of 12 patients (75%, Table 1B). The overall Kaplan Meier predicted 1-,3- and 5-year recurrence-free survival rates were 98.6% [95% CI=(95.9100)], 88.7% (80.7,97.0) and 74.6% (61.2,90.9) respectively (Fig. 1B). A sub-analysis on recurrence free survival was performed on patients with tumour diameter <2 cm and those with tumours ≥ 2 cm. Log rank analysis revealed comparable ($p > 0.05$) recurrence-free survival between the two groups (Fig. 1C).

Predictors of recurrence

A multivariate Cox regression analysis was conducted with all measured covariates included in order to identify predictors of disease recurrence. Since there are more covariates than number of recurrences on follow up in our dataset, the classical multivariate Cox regression would overfit. Hence, a penalised Cox model was used where the penalisation parameter, which restricts the model complexity, was chosen with a ten-fold cross-validation. This model selected resection margin status, vascular invasion, tumour differentiation (WHO G3 stage) and LNR as the only relevant covariates. We then refitted a multivariate Cox model on the four selected covariates to obtain de-biased estimates of the coefficients with corresponding confidence intervals (Table 2). However, we remark that, as the multivariate model is fitted after model selection, the confidence intervals constructed are likely to be overly optimistic. We found that tumour grade and LNR≥0.1 are significant predictors of recurrence on univariate and multivariate analyses, and are therefore high-risk factors.

Decision tree analyses

We observed that some covariates exhibited nonlinearity in the Cox model. To capture this, independent of the Cox regression analysis, we fitted a decision tree model, which at each node of the tree selects the most discriminative factors among all measured covariates whereby the effect of these covariates on recurrence depends on whether they exceed computed cut-off thresholds. Each threshold was computed to maximise the odds ratio between the two subbranches beneath the node. A pilot decision tree model to detect post-operative recurrence is therefore generated. We found that the most significant single criterion is based on whether the LNR is ≥ 0.1. Subsequent splitting criteria selected by the decision tree model were the presence/absence of vascular invasion and R0/R1 resection margin involvement (Fig. 2). Based on this model, patients who are at high risk of recurrence on follow-up are those with i) LNR≥0.1 (i.e ≥ 10% of harvested LNs being metastatic), or ii) if LNR<0.1, have both presence of vascular invasion (VI) and R1 resection margin (see Fig. 2).

Performance of models

Finally, we compared the sensitivity and specificity of predicting post-resectional recurrence utilising high-risk factors identified independently by multivariate Cox modelling (i.e. tumour grade G3, LNR≥0.1) and decision tree analyses (i.e. LNR≥0.1 or if LNR<0.1, presence of vascular invasion and R1 margin status, Table 3). High risk factors identified by Cox modelling were used either alone or in combination (i.e. and/or). Based on ROC analyses, our results demonstrated that a criterion based on patient group identified by 'LNR≥0.1 or tumour grade G3' offers the best sensitivity and specificity trade-offs for predicting 3-year and 5-year recurrence rates (Fig. 3A). 'LNR≥0.1 or tumour grade G3' criterion greatly improves the sensitivity of detecting recurrences compared to other parameter or its combinations, and outperforms the decision tree model. Therefore, this criterion is less prone to miss susceptible patients and provides a clear practical criterion for post-operative monitoring. To confirm this finding, we illustrated the recurrence-free Kaplan-Meier curves of patients satisfying the 'LNR≥0.1 or tumour grade G3' criterion versus 'LNR<0.1 or tumour grade G1/2' and those with or without high-risk factors identified by decision tree analyses (Fig. 3B). We therefore conclude that post-resectional NET patients with either LNR≥0.1 or tumour grade G3 are at high risk of recurrent disease and represent a sensitive and specific criterion for closer postoperative surveillance.

Discussion

In this single centre study, we report the resectional and oncological outcomes on 73 consecutive patients with non-functional neuroendocrine pancreatic tumours (NF-NETs) using strict clinico-pathological inclusion criteria. Our results demonstrate the significant effect that lymph node ratio (LNR) and the G3 tumour

Table 1
(A) Patient demographics and clinic-pathological characteristics (n=73). [LNR indicates lymph node ratio, PLR indicates platelet to lymphocyte ratio. (*) indicates median (range) and (¥) indicates frequencies (percentage). **(B) Location and timepoint of disease recurrence following pancreatic surgery**.

A	
Age* (years)	61.5 (31–79)
Male¥	38 (52.1%)
Tumour location¥	
Head	38 (52.1%)
Body	20 (27.4%)
Tail	15 (20.5%)
Type of resection¥	
Pancreaticoduodenectomy	39 (53.4%)
Total pancreatectomy	7 (9.6%)
Distal pancreatectomy	27 (37%)
Tumour size (cm)-*histology*	2.1 (0.5–22)
pT-stage¥	
T1/T2	67 (91.8%)
T3/T4	6 (8.2%)
pN-stage¥	
N0	43 (58.9%)
N1	30 (41.1%)
Lymph nodes harvested*	12 (0–39)
Metastatic lymph nodes*	0.8 (0–19)
LNR*	0.1 (0–1)
Perivascular invasion¥	
Present	44 (60.3%)
Absent	29 (39.7%)
Perineural invasion¥	
Present	11 (15.1%)
Absent	62 (84.9%)
Resection margin status¥	
R0	44 (60.3%)
R1	29 (39.7%)
Pre-operative neutrophil count*	4.89 (1.9–13.54)
Pre-operative platelet count*	241 (123–478)
Pre-operative lymphocyte count*	1.52 (0.72–3.69)
Platelet to lymphocyte ratio*	137.1 (11.6–516.5)
Histological grade¥	
G1	56 (76.7%)
G2	13 (17.8%)
G3	4 (5.5%)
Tumour recurrence¥	12 (16.4%)

B

Patient	Location of disease recurrence	Lymph node ratio	WHO stage	Time to recurrence (*months*)
Patient 1	Liver	0	G3	7
Patient 2	Small bowel mesentery	0.25	G2	27
Patient 3	Liver	0.13	G1	30
Patient 4	Small bowel mesentery	0.14	G3	12
Patient 5	Liver	0.10	G1	40
Patient 6	Liver	0.12	G3	19
Patient 7	Liver	0.33	G1	53
Patient 8	Lung	0.13	G3	48
Patient 9	Liver	0.77	G2	27
Patient 10	Liver & para-aortic nodes	0.42	G2	62
Patient 11	Liver	0.44	G1	58
Patient 12	Liver	0.3	G2	117

grade (based on WHO 2010 classification) have upon disease recurrence. Using high-risk factors identified by multivariate Cox regression analysis and a decision-tree pilot approach, we identified that a criterion of 'tumour grade G3 or LNR≥0.1' identified patients at risk of recurrence and propose post-resectional patient surveillance based on this simple criterion. This criterion now warrants external validation to determine its clinical utility. Our data also demonstrated that tumour size, that has historically had a role on decision making with regards to operative management, is not a predictor of disease recurrence on follow up.

Pancreatic neuroendocrine tumours are considered a rare entity with NF-PNETs accounting for approximately 72% of the cases according to the World Health Organisation [WHO, [22]]. The diagnosis and management of pancreatic neuroendocrine tumours remains challenging for the clinician and a review of the Surveillance, Epidemiology and End Results (SEER) database showed that the survival has not improved over the past 30 years [23]. The European annual incidence of pancreatic NETs is in the region of 1:100,000 and is rising as the number of pancreatic lesions diagnosed incidentally as a consequence of the increasing use of abdominal imaging modalities [24]. Current guidelines recommend a combination of cross-sectional abdominal imaging (Computer-assisted Tomography) and endoscopic ultrasound –assisted fine needle aspiration (EUS-FNA cytology) for detailed evaluation of suspicious pancreatic lesions [25]. EUS in particular, especially when combined with FNA cytology, has been shown to have

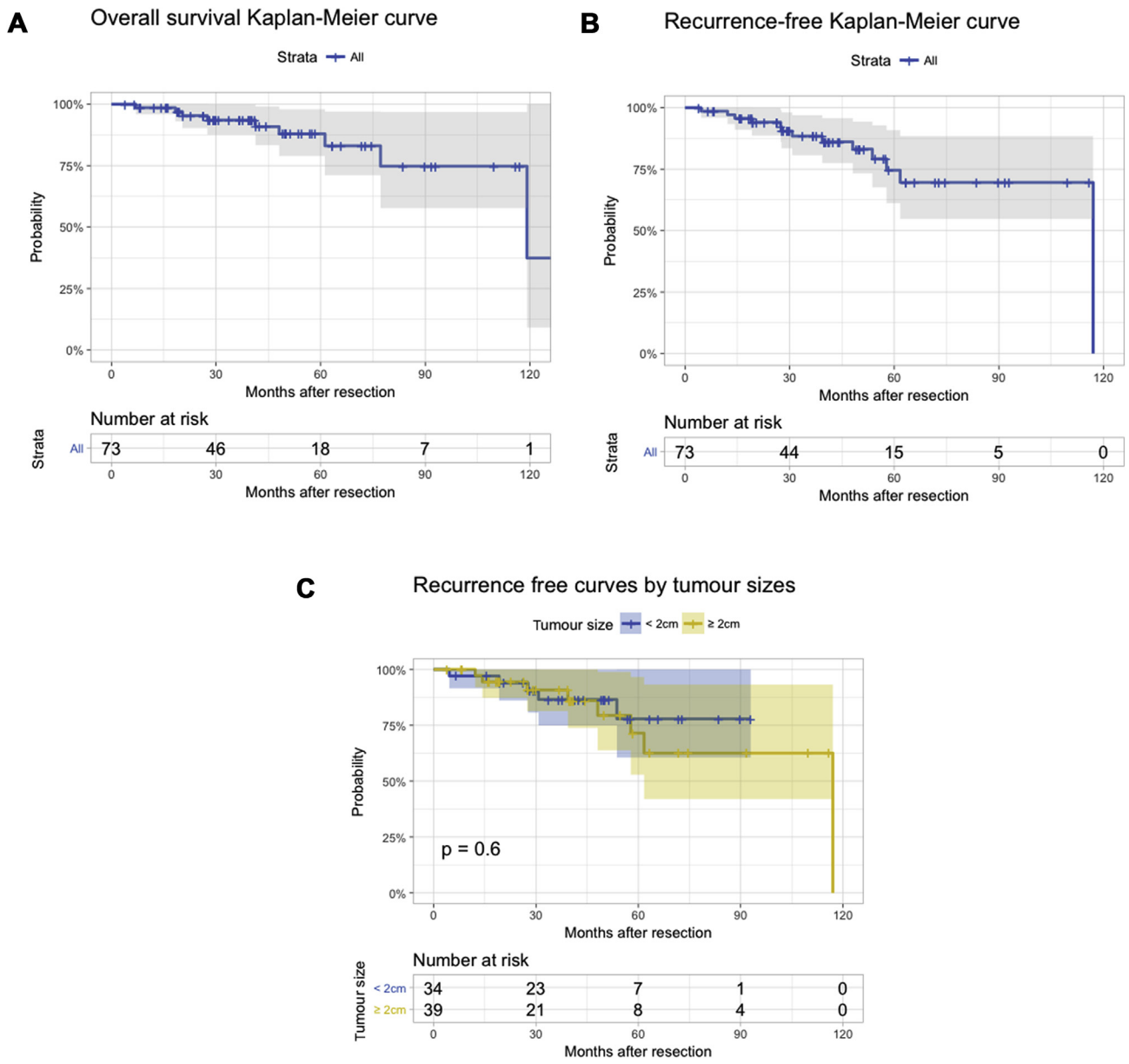

Fig. 1. Overall survival (A) and recurrence-free survival (B-C) rates for the study population (n = 73, 95% CI identified by the shaded area). Recurrence-free survival rates were dichotomised based on tumour size < or ≥2 cm (log rank, p = 0.6) **(C)**.

diagnostic accuracy greater than 80% on assessing the primary tumour and loco-regional nodal involvement [26]. These imaging modalities, as a result of their sensitivity, have gained a crucial role in the management algorithm of patients with NF-PNETs. Pre-operative tumour size greater or equal than 2 cm on pre-operative work-up is currently considered to be the cut-off point between surveillance or surgical intervention [13,27]. However this approach has been questioned by others as recent studies have not reported tumour size to be an important predictor of adverse disease outcome following pancreatic resection [7,11,28]. Similarly, the survival curves in our patient cohort did not demonstrate a lower risk of disease recurrence in those patients with tumours less than 2 cm in diameter ($p > 0.05$).

Attempts have been previously made by others in order to identify predictors of survival or disease recurrence following pancreatic resection of NF-PNETs. Factors such as patient-reported symptoms; presence of distant metastases at time of resection; tumour grade; Ki-67 index; presence of necrosis; radiological appearance (hypovascular vs. hypervascular) and lymph node (LN) involvement have been previously reported. However, we would like to highlight the fact that the study populations in some of the above reports were rather heterogeneous as analyses were performed in some instances regardless of the functioning status of the tumour, the type of pancreatic surgery performed or the presence of synchronous metastases at the time of the original surgery. As such, the findings of these studies are difficult to interpret. In our current study, we have addressed this by a set of stringent inclusion criteria.

In the context of NF-PNETs, the significance of hepatic metastases on patient survival is well established [29,30]. However, unlike the case of other non-endocrine tumours of the gastrointestinal tract (pancreas/gastric/colon) where the number of metastatic LNs confers a burden upon survival [31–33] the role of metastatic nodes in cases of NF-PNETs is yet to be clearly elucidated. The effect of LN

Table 2
Multivariate Cox regression analyses. Tumour G3 grade and LNR≥0.1 are the only significant predictors of disease recurrence upon construction of the final model.

Covariates	Univariate model		Multivariate model (penalised)	Multivariate model (refitted)		
	HR	p-value	HR	HR	95% CI	p-value
Gender (Male)	1.91	0.29	–			
Age (years)	1.04	0.12	–			
Location	–	0.73	–			
Body	1	–				
Head	0.80	–				
Tail	0.43	–				
Tumour size (mm)	1.00	0.88	–			
Tumour stage = T3/T4	3.08	0.09	1.11	1.82	[0.432, 7.67]	0.41
Nodal status (N1)	2.55	0.11	–			
Margin status (R1)	2.76	0.08	1.09	3.67	[0.833, 16.1]	0.09
Vascular invasion (Present)	3.4	0.07	–			
Perineural invasion (Present)	1.39	0.68	–			
WHO Tumour differentiation (G3)	**35.1**	**0.0002**	**14.9**	**59.8**	**[8.92, 400]**	**<0.0001**
No. of metastatic LN	1.12	0.12	–			
LN ratio ≥ 0.1 (LNR)	**8.35**	**0.04**	**1.32**	**4.03**	**[1.06, 15.4]**	**0.04**
Neutrophils	0.91	0.56	–			
Lymphocytes	1.02	0.96	–			
Platelets	1.00	0.67	–			
PLR	1.00	0.52	–			

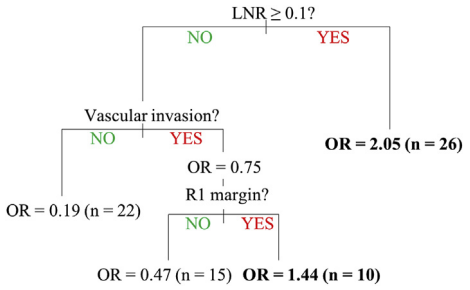

Fig. 2. A decision tree for prediction of post-resection disease recurrence. Odds ratios (OR) compared to the whole study population are reported at all leaf (terminal) nodes in the decision tree. Leaf nodes with the highest risk of disease recurrence are highlighted in bold.

metastases on the outcome of patients with NF-PNETs has not been reported with consistency. Prior studies have reported that the presence of lymph node metastases is not a significant determinant of survival [17,18,34–36] and not associated with disease recurrence post resection [37,38] or disease progression [39]. On the contrary, other reports have suggested that LN positivity adversely affects survival and is associated with recurrence post-resection or progressive disease [11,40,41]. As such, the true effect of lymph node involvement on patient survival, in the case of NF-PNETs, remains poorly understood and controversial. The prognostic value of LNR in the context of recurrence following radical surgery for PNETs has been previously reported elsewhere [41]. The authors of the study demonstrated that patients with LNR ≥0.2 were at greatest risk of disease recurrence on follow-up. However, the significance of the findings of that study is limited by the relatively small number of patients (n = 58), the presence of synchronous liver metastases at the time of pancreatic resection (11% of cases), the presence of both functioning/non-functioning tumours in the study's cohort and by that fact that the cut-off LNR of 0.2 was chosen arbitrarily.

In our current study, we have identified two factors that predict biological aggressiveness of disease (i.e. tumour grade G3 or LNR≥0.1) can be utilised to predict with sensitivity and specifity postoperative disease recurrence. This has clinical implications as such a strategy could aid clinicians risk stratify patients and cater for more frequent surveillance for those subjects at risk of recurrence. Furthermore, it would facilitate the decision making of the multidisciplinary approach of patients post-pancreatic surgery and could potentially target those subjects in need of adjuvant therapies (chemotherapy, biological therapies). Critically, patients with oligometastatic recurrence, can undergo further resectional surgery or ablative procedures that may prolong survival if a curative intent can be achieved [24]. Currently, no consensus exists on the use of adjuvant therapies following radical resection of NF-PNETs. Chemotherapy and biological therapies have been employed in cases of advanced disease [42,43].

We acknowledge the limitations of the reported findings in this study. First of all the retrospective approach limits to an extent the value of the results reported. Furthermore, the decision tree approach we propose, although it is based on a well defined population, is reported on a pilot basis and validation in larger patient cohorts is required. Finally although the proportion of patients with disease recurrence is similar to figures presented elsewhere, it remains relatively small in terms of absolute numbers. This has not enabled us to analyse the data further with the aim of proposing a follow-up protocol based on presence of variables predictors of recurrence and timing of the event (disease recurrence) on follow-up.

Table 3
Sensitivity and specificity of various strategies for predicting 3-year and 5-year recurrences, based on factors identified by Cox modelling and decision tree analysis.

		LNR≥0.1	Grade III	LNR≥0.1 and Grade III	LNR≥0.1 or Grade III	Decision tree high risk factors: *if LNR≥0.1 or if LNR<0.1, presence of VI and R1 margin*
3-year recurrence	sensitivity	0.71	0.43	0.14	1.00	0.86
	specificity	0.69	1.00	1.00	0.69	0.60
5-year recurrence	sensitivity	0.73	0.27	0.09	0.91	0.82
	specificity	0.67	1.00	1.00	0.67	0.67

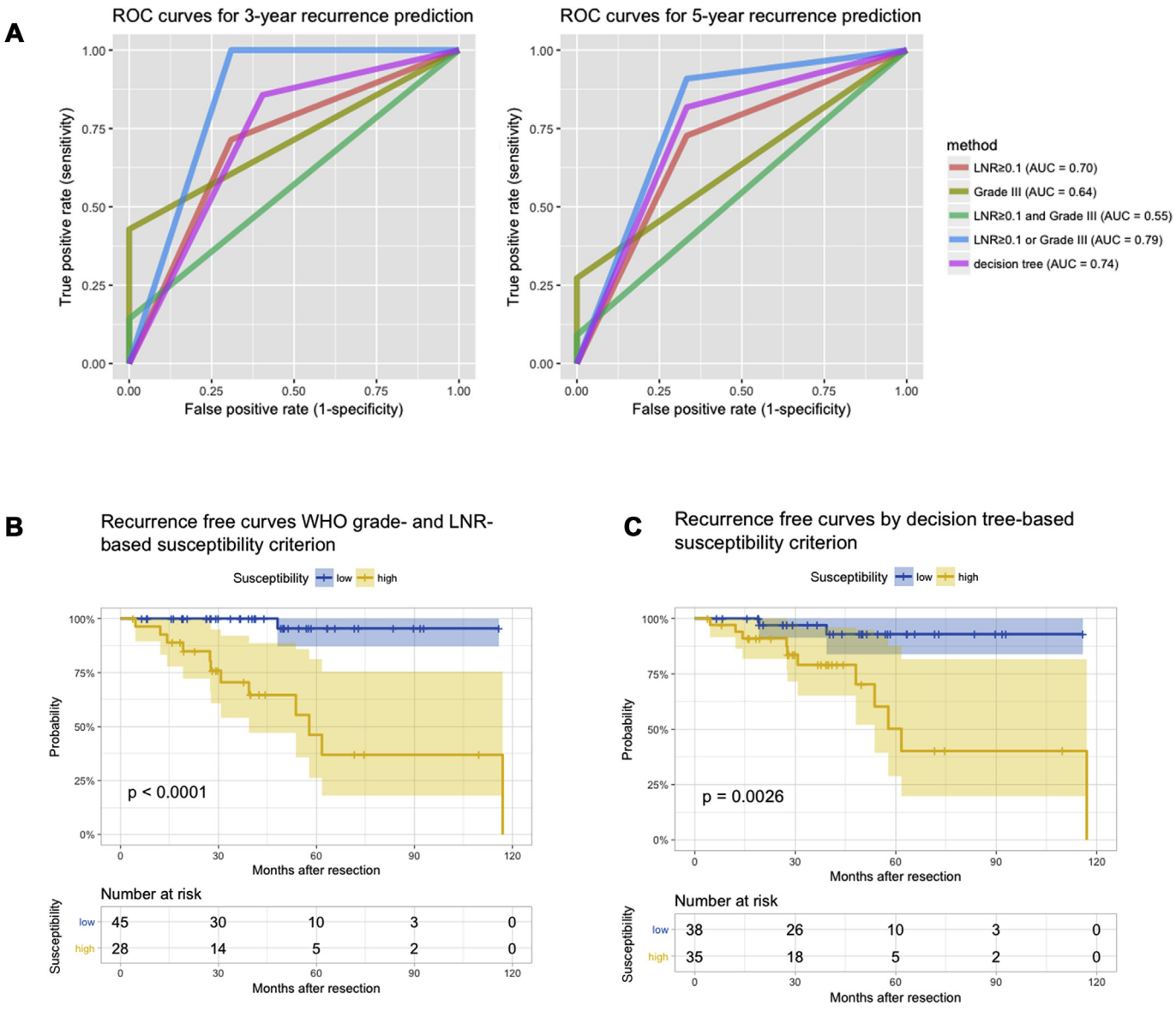

Fig. 3. (A) ROC curves for 3-year and 5-year recurrence predictions using different parameters. (B &C) Comparison of recurrence-free survival curves of groups with or without high risk factors identified from Cox modelling and decision tree modelling. (B. High risk factors from Cox modelling: recurrence-free survival curves of patients who have high susceptibility to recurrence (yellow, LNR≥0.1 or WHO Grade III) and patients who have low susceptibility (blue, LNR<0.1 and WHO Grade I/II). Log rank, $p < 0.0001$) (C. High risk factors from decision tree modelling: recurrence-free survival curves of patients who have high susceptibility to recurrence (yellow, LNR≥0.1 or if LNR<0.1 and with vascular invasion and R1 margin) and patients who have low susceptibility (blue, LNR<0.1 and without vascular invasion and has R0 margin). Log-rank, $p = 0.0026$.

In summary, this report presents the findings of a well-defined patient cohort with no evidence of distant organ metastases at the time of surgery. A simple criterion of 'tumour grade G3 or LNR ≥0.1' was found to be sensitive and specific in detecting disease recurrence on follow-up. We have demonstrated that the Kaplan-Meier predicted time to recurrence analysis differed significantly between those subjects who fulfilled the criterion and those who did not. The utility of this clinical relevant surveillance criterion now warrants external validation in a larger patient population.

Conflicts of interest

None declared.

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