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ORIGINAL ARTICLE

Retrospective Study

Prognostic importance of lymph node yield after curative resection of gastroenteropancreatic neuroendocrine tumours

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Abstract

BACKGROUND

The prognostic significance of lymph nodes (LNs) metastases and the optimum number of LN yield in gastroenteropancreatic neuroendocrine tumours (GEP NETs) undergoing curative resection is still debatable. Many studies have demonstrated that cure rate for patients with GEP NETs can be improved by the resection of the primary tumour and regional lymphadenectomy

AIM

To evaluate the effect of lymph node (LN) status and yield on relapse-free survival (RFS) and overall survival (OS) in patients with resected GEP NETs.

Informed consent statement: Patients were not required to give informed consent to the study. We used anonymous clinical data for the analysis.

Conflict-of-interest statement: The authors report no conflict of interest in this work.

Data sharing statement: No additional data are available.

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METHODS

Data on patients who underwent curative resection for GEP NETs between January 2002 and March 2017 were analysed retrospectively. Grade 3 tumours (Ki67 > 20%) were excluded. Univariate Cox proportional hazard models were computed for RFS and OS and assessed alongside cut-point analysis to distinguish a suitable binary categorisation of total LNs retrieved associated with RFS.

RESULTS

A total of 217 patients were included in the study. The median age was 59 years (21-97 years) and 51% (n = 111) were male. Primary tumour sites were small bowel (42%), pancreas (25%), appendix (18%), rectum (7%), colon (3%), gastric (2%), others (2%). Median follow up times for all patients were 41 mo (95%CI: 36-51) and 71 mo (95%CI: 63–76) for RFS and OS respectively; 50 relapses and 35 deaths were reported. LNs were retrieved in 151 patients. Eight or more LNs were harvested in 106 patients and LN positivity reported in 114 patients. Three or more positive LNs were detected in 62 cases. The result of univariate analysis suggested perineural invasion (P = 0.0023), LN positivity (P = 0.033), LN retrieval of ≥ 8 (P = 0.047) and localisation (P = 0.0049) have a statistically significant association with shorter RFS, but there was no effect of LN ratio on RFS: P = 0.1 or OS: P = 0.75. Tumour necrosis (P = 0.021) and perineural invasion (P = 0.016) were the only two variables significantly associated with worse OS. In the final multivariable analysis, localisation (pancreas HR = 27.33, P = 0.006, small bowel HR = 32.44, P = 0.005), and retrieval of ≥ 8 LNs (HR = 2.7, P = 0.036) were independent prognostic factors for worse RFS.

CONCLUSION

An outcome-oriented approach to cut-point analysis can suggest a minimum number of adequate LNs to be harvested in patients with GEP NETs undergoing curative surgery. Removal of ≥ 8 LNs is associated with increased risk of relapse, which could be due to high rates of LN positivity at the time of surgery. Given that localisation had a significant association with RFS, a prospective multicentre study is warranted with a clear direction on recommended surgical practice and follow-up guidance for GEP NETs.

Key words: Well differentiated neuroendocrine tumours; Pancreatic neuroendocrine tumours; Small intestinal neuroendocrine tumours; Ki67; Lymph node ratio; Lymph node retrieval; Lymph node positivity; Relapse-free survival; Overall survival

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Core tip: There is no consensus on the optimal number of lymph node (LN) retrieval in patients undergoing resection for gastroenteropancreatic neuroendocrine tumours (GEP NETs). The purpose of this study was to evaluate the LN status and yield on relapse-free survival and overall survival in patients with resected GEP NETs. By using the outcome-oriented approach to cut-point analysis, this study suggested a retrieval of a minimum of eight or more LNs in patients with GEP NETs undergoing curative surgery. The risk of relapse was high in patients who had ≥ 8 LNs retrieved and a high LN yield and LN positivity were seen in small intestinal NETs and pancreatic NETs. The localisation has a significant association with relapse-free survival, necessitating stricter surveillance especially for intestinal NETs and pancreatic NETs.

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INTRODUCTION

Neuroendocrine tumours (NETs) are a heterogeneous group, accounting for only 0.5% of all malignancies and 2% of all gastrointestinal malignancies, with an incidence of 5.25/100000/year[1,2]. These tumours originate from the neuroendocrine cells anywhere along the gastrointestinal tract (62%-67%) or lung (22%-27%)[3,4]. The incidence and prevalence of NETs are steadily rising, possibly related to increased awareness and detection of early-stage disease. The most common location for gastroenteropancreatic (GEP) NETs is small intestine (41.8%), followed by rectum (19.6%), appendix (16.7%), pancreas (10.8%), colon (10.6%) and stomach (7.6%)[5]. These tumours can be functioning, *i.e*. symptomatic due to hypersecretion of hormones and peptides or non-functioning.

In 2010, the World Health Organisation classified NETs into well differentiated NET Grade 1 (G1) (Ki67 ≤ 2%, Mitotic index < 2/10 HPF), well differentiated NET G2 (Ki67 3%-20%, Mitotic index 2-20/10 HPF), poorly differentiated neuroendocrine carcinoma (NEC) G3 (Ki67 > 20%, Mitotic index > 20/10 HPF), mixed adeno NEC (MANEC) and hyperplastic and preneoplastic lesions[6]. The updated version of World Health Organisation classification in 2017 classified pancreatic neuroendocrine neoplasms into well differentiated NET G1 (Ki67 < 3%, Mitotic index < 2/10 HPF), well differentiated NET G2 (Ki67 3%-20%, Mitotic index 2-20/10HPF), well differentiated NET G3 (Ki67 > 20%, Mitotic index > 20/10 HPF), poorly differentiated NEC G3 (Ki67 > 20%, Mitotic index > 20/10 HPF) and mixed neuroendocrine non-neuroendocrine neoplasms[7]. A working group of the European Neuro Endocrine Tumour Society (ENETS) developed and published a proposal for the first Tumour, Node, Metastases (TNM) staging system for neuroendocrine tumours in 2006. In 2009, the American Joint Committee on Cancer staging (AJCC) included the classification of NETs[8]. The current 8th edition of the AJCC TNM staging for neuroendocrine tumours includes well differentiated GEP NETs but excludes poorly differentiated neoplasms[9]. The staging system of the North American Neuroendocrine tumour society is similar to ENETS TNM staging. However, there is some discrepancy in the staging of pancreas and appendiceal NETs.

Advances in the therapeutic management of these tumours have resulted in improvements in survival over the years[10,11]. Prognosis depends on the location of the primary tumour and presence or absence of regional and distant metastases. A Surveillance, Epidemiology and End Result registry (SEER) based data analysis have reported significant differences in survival amongst various primary sites of NETs, including lung NETs. Neuroendocrine tumours of the rectum had the best prognosis, and NETs of the pancreas (PanNET) had the worse prognosis. Five-year overall survival for stage 1 and 2 GEP NETs without metastasis is 95%-98% following curative surgery, and for NETs with regional metastasis is 54%-75%[12]. Recent SEER data revealed a median survival of 33 mo in G1 and G2 NETs with distant metastasis. The 5-year survival rate in metastatic PanNET is around 40%-60%[13,14]. Several studies have demonstrated that prognosis can be extended if regional metastases are resected along with the primary tumour[15-17]. Hellman *et al*[15] concluded, in a study on patients treated for midgut carcinoid, that patients with resected mesenteric lymph node (LN) metastases survived significantly longer than those with insitu mesenteric metastases (P = 0.05).

The result from an international multicentre study on surgical management of advanced PanNETs has shown that an aggressive approach for locally advanced or metastatic tumours is safe and offers long term survival[18]. Retrospective studies in colorectal cancer have already revealed improved survival rates when a higher number of LNs are examined following curative surgery[19]. This is reflected in colorectal cancer clinical guidelines which recommend evaluation of at least twelve LNs to ascertain LN-status with confidence, as patients with no LN involvement have a favourable prognosis[20-22]. "Adequate" LN clearance is recommended in patients with GEP-NETs undergoing resection of a primary tumour, but there are no clear guidelines about the actual number of nodes that should be resected to achieve favourable survival outcomes.

Several studies in patients with PanNETs have demonstrated that the presence of liver metastases is associated with worse survival[23-25]. Bettini *et al*[26] reported that the presence of nodal metastases in patients with neuroendocrine neoplasms was significantly associated with increased mortality and had a similar prognostic significance to the presence of liver metastases and Ki67 expression. In addition, a number of studies in patients with PanNETs have demonstrated that positive LNs, total LNs examined and the ratio between positive LNs and total LNs examined are important predictors of recurrence after surgery. Boninsegna *et al*[27] reported that a LN ratio (LNR) greater than 0.2 (HR = 2.75) and Ki67% > 5% (HR = 3.39) were significant predictors of recurrence following resection for PanNETs.

This retrospective study was conducted to evaluate the association between LN metastases and survival (relapse-free and overall) in patients with resected well differentiated GEP NETs and to attempt to identify the optimal number of LNs that should be harvested in patients with GEP NETS, undergoing curative surgery.

MATERIALS AND METHODS

Data on patients who underwent curative surgery for GEP NETs between January 2002 and March 2017 were identified and analysed retrospectively. This retrospective study was conducted at a European Neuroendocrine Tumour Centre of Excellence tertiary referral centre, The Christie NHS Foundation Trust, Manchester, United Kingdom, with surgery performed in a high-volume specialised surgical unit at Manchester Royal Infirmary, within the Greater Manchester catchment area serving approximately 2.5 million. Patients with Grade 1 and Grade 2 GEPNETs were included and those with Grade 3 (Ki67 > 20%, poorly differentiated neuroendocrine neoplasms) were excluded as this is a completely different clinical entity with more aggressive biology and behaviour. Data were collected from patient case notes (paper and electronic) and post-operative histopathology reports. Demographic and clinical data were collected, including age, gender, Eastern Co-operative Oncology Group performance status, grade, Ki67, TNM staging, serum Chromogranin A, 5-Hydroxyindoleacetic acid, surgical margin, negative (R0) or positive (microscopic positive margin R1) margins, perineural invasion, lymphovascular invasion, tumour necrosis, total number of LNs retrieved, number of involved LNs and localisation of the tumour. Tumour locations were coded as the stomach, duodenum, small intestine, colon, appendix, rectum, pancreas and rectum. This study was ethically approved by the Quality Improvement and Clinical Audit Committee of The Christie NHS Foundation Trust.

LNR was defined as the ratio between the number of positive LNs (with metastases) and the total number of LNs examined. Relapse-free survival (RFS) was defined as the time between surgery and relapse, or date last seen. Overall survival was defined as the time between surgery and death, or the date the death registry was checked, which was on 23rd February 2018.

Statistical analysis

Descriptive statistics were utilised to check data variability. Kaplan Meier curves were used to identify an empirical estimate of the survival curve, and the Log-rank test was used to evaluate how significant the survival rate difference was between the two categories of a variable. Univariate and multivariable Cox proportional hazard models were used to identify the independent predictors of RFS and OS. A P value of < 0.05 was considered statistically significant.

Univariate Cox proportional hazard models were computed for RFS and OS and assessed alongside cut-point analysis to distinguish a suitable binary categorisation of total LNs retrieved associated with RFS. All statistical analyses were computed in R (version 3.4.2), with cut-point analysis using the function "surv_cutpoint" from the R-package Survminer (version 0.4.2)[28-30]. LN cut-point value was determined using the cut-point determination methods in survival analysis, using *R*[31]. This is an outcome-oriented method providing a value of a cut-point that corresponds to the most significant relationship with survival. Surv cut-point determines the optimal cut-point for each variable.

RESULTS

A total of 217 patients were included in the study. The median age was 59 years (21-97 years) and 51% (n = 111) were male; 77% were G1 and 23% were G2. Primary tumour sites were small bowel (42%), pancreas (25%), appendix (18%), rectum (7%), colon (3%), gastric (2%), others (2%) (Table 1); LN data was not available in 30% [5% PanNETs and 7% small intestinal-NETs (SiNETs)]. Median follow up times for all patients for RFS and OS were 41 mo [95% confidence interval (CI): 36-51] and 71 mo (95%CI: 63-76), respectively, and 50 relapses and 35 deaths were reported.

The total number of patients with LNs retrieved was 151. Data on LNs retrieved were available for 76 patients with SiNETs and 45 with PanNETs, and the rest were grouped as "others" (stomach n = 3, appendix n = 20, colon n = 5, rectum n = 1 and other n = 1). Eight or more LNs were harvested in 106 patients (49 SiNETs, 32 PanNETs); LN positivity was reported in 114 patients; 70 SiNETS and 24 PanNETs. Three or more positive LNs were detected in 62 cases; 43 SiNETs and 13 PanNETs.

Table 1 Characteristics of patients who had curative resection of gastroenteropancreatic neuroendocrine tumours

Variable		*n* (%)
Gender	Male	111 (51)
	Female	106 (49)
Age, yr	Median age	59
ECOG PS	PS 0	140 (65)
	PS 1	64 (30)
	PS 2	8(3.7)
	PS 3	5 (2.3)
Localisation	Small bowel	92 (42)
	Pancreas	55 (25)
	Appendix	39 (18)
	Rectum	15 (7)
	Colon	7 (3)
	Stomach	5 (2)
	Other	4 (2)
Grading	Grade 1	168 (77)
	Grade 2	49 (23)
Surgical margin	R0 resection	186 (86)
	R1 resection	30 (13)
	NA	1 (0.5)
Vascular infiltration	Present	89 (41)
	Absent	109 (51)
	NA	19 (8)
Perineal infiltration	Present	64 (29)
	Absent	133 (62)
	NA	20 (9.3)
Tumour necrosis	Present	10 (5)
	Absent	183 (86)
	NA	24 (10)
Lymph nodes retrieved	≥ 8	106 (49)
	< 8	45 (21)
	NA	66 (31)
Lymph node involvement	Positive	114 (52)
	Negative	37 (17)
Serum CgA Level	≥ ULN	46(21)
	Normal	69 (32)
	NA	102 (47)
Serum 5-HIAA	≥ ULN	17 (8)
	Negative	96 (44)
	NA	104 (48)

ECOG PS: Eastern Co-operative Oncology Group performance status; CgA: Chromogranin A; 5-HIAA: 5-hydroxyindoleacetic acid; ULN: Upper limit of normal; NA: Not available.

There were 29 relapses and 16 deaths reported in patients with SiNETs and 17 relapses and 11 deaths in patients with PanNETs.

Univariate analysis

The result of univariate analysis suggested perineural invasion (P = 0.0023), LN positivity (P = 0.033), LN retrieval of ≥ 8 (P = 0.047) and localisation (P = 0.0049) have a statistically significant association with shorter RFS, but there was no effect of LN ratio (median 1.8) on RFS: P = 0.1 or OS: P = 0.75. Tumour necrosis (P = 0.021) and perineural invasion (P = 0.016) were the only two variables significantly associated with worse OS. Retrieval of ≥ 8 LNs (P = 0.94), localisation (P = 0.44), or surgical margin (P = 0.69) did not significantly affect OS (Table 2). LN cut-point value

associated with RFS was 8.

Multivariable analysis

A total of 140 patients were included in the final multivariable model. Eleven patients (one influential outlier and no data on perineural infiltration in 10 cases) were excluded. The variables included in the final multivariable model for RFS were the presence of perineural infiltration, eight or more LNs retrieved, any positive LNs and localisation: Pancreas and small bowel. The grade wasn't included in multivariable analysis, as it was not statistically significant on univariate analysis. Retrieval of ≥ 8 LNs (HR = 2.70, 95%CI: 1.07-6.84, P = 0.036), tumour localisation: pancreas (HR = 27.33, P = 0.006) and small bowel (HR = 32.44, P = 0.005) were independent prognostic factors for shorter RFS on multivariable analysis. LN positivity was not statistically significantly associated with RFS in the multivariable model. (Table 3 and Figures 1-3).

DISCUSSION

The prognostic significance of LNs metastases and the optimum number of LN yield in GEP NETs undergoing curative resection is debatable. Many studies have already demonstrated that resection of the primary tumour and regional lymphadenectomy results in a high cure rate for patients with GEP NETs. LN positivity and LNRs are independent prognostic factors for survival in patients with resected NETs, but limited evidence is available on the optimal predictive number of resected LNs required[27,32,33]. As per the AJCC TNM staging for NETs, the presence of positive LNs defines stage III disease, regardless of the number of LNs involved. The ENETS guidelines do provide some advice on follow up of patients with GEP NETs post-resection, but to date, there has been no consensus regarding the optimal number of LNs resected, required for the adequate staging of GEP NETs[34].

The main purpose of this study was to identify a cut off value for LN retrieval in resected GEP NETs. By using the outcome-oriented approach to cut-point analysis, this study suggested retrieval of a minimum of eight or more LNs in GEP NETs undergoing curative surgery. The risk of relapse was high in patients who had ≥ 8 LNs retrieved. Previous colorectal studies have demonstrated an increased relapse rate associated with low numbers of LNs harvested[35,36]. Studies in GEP NETs, in particular SiNETs and PanNETs have shown reduced RFS in patients with increased number of involved LNs. The decrease in RFS associated with an increased number of LNs harvested in the current study indicates that by examining more LNs, one increases the chance of finding more involved nodes; thereby staging patients more accurately. Of 151 patients with available information on involved LNs, ≥ 8 LNs were harvested in 70%, and positive LNs were detected in 41%. The majority of LNs were retrieved from SiNETs and PanNETs, and involvement of 3 or more LNs was high in SiNETs and PanNETs.

There are many factors like tumour size, localisation and tumour biology that influence the variability of LN harvest. It has already been reported that the size of the tumour, LN involvement and Ki67 are independent prognostic factors for relapse after potentially curative surgery for NET[37,38]. A relatively large study from the United States neuroendocrine study group identified pre-operative factors, including tumour size ≥ 2 cm, proximal location, moderate differentiation and Ki67 > 3%, as factors predicting LN positivity in resected non-functional PanNETs. LN metastases were reported in patients without these risk factors also, so the conclusion from the study was that routine regional lymphadenectomy should be considered in patients with PanNETs undergoing curative surgery. Pancreatoduodenectomy routinely includes a complete regional lymphadenectomy, whereas distal pancreatectomy should aim to remove ≥ 7 LNs for accurate staging (5-year RFS in LN positive and negative disease was 67% *vs* 86%, P = 0.002)[39]. A recently published study in PanNETs concluded that a regional lymphadenectomy of at least 8 LNs is necessary for optimal staging of PanNETs undergoing curative resection. The study reported patients with ≥ 4 LN metastases had a worse prognosis compared to patients with 1-3 LN metastases or node negative disease[40].

Another study reported on the prognostic role of LN positivity and number of LNs needed for accurate staging of small bowel neuroendocrine tumours[41]. It emphasised the importance of a thorough regional lymphadenectomy to accurately stage patients undergoing curative resection for SiNETs. This study suggested that the minimum requirement of LNs for evaluation after curative resection of SiNET was eight, concurring with the current study; and four or more positive LNs were associated with reduced 3-year recurrence-free survival. Patients with four or more positive LNs

Table 2 Univariate analysis of variables for relapse-free survival and overall survival in patients who had curative resection of gastroenteropancreatic neuroendocrine tumours

Variable	LR *P* value	LR *P* value OS
Production of gut hormones	0.012	0.75
Production of CgA	0.09	0.81
Production of 5 HIAA	0.83	0.098
Genetic predisposition	0.011	0.71
Multiple NET	0.59	0.25
Other active malignancy	0.27	0.96
Vascular infiltration	0.17	0.97
Perineural infiltration	0.0023	0.016
Tumour necrosis	0.66	0.021
≥ 8 lymph nodes retrieved	0.047	0.94
Any lymph nodes positive	0.033	0.78
Gender	0.58	0.87
Localisation	0.0049	0.44
T stage	0.015	0.22
N stage	0.008	0.58
M stage	0.089	0.17
Grade	0.039	1
Surgical margin	0.32	0.69
ECOG performance status	0.75	< 0.0001
ACE comorbidity score	0.39	0.044
Localisation	0.63	0.61
Involved groups	0.062	0.09
TNM stage	0.019	0.19

NET: Neuroendocrine tumours; ECOG: Eastern Cooperative Oncology Group; ACE: Adult Comorbidity Evaluation; CgA: Chromogranin A.

had a worse 3-year recurrence-free survival compared to those with 1-3 or 0 LNs (P = 0.01), and retrieval of > 8 LNs accurately discriminated patients with 4 or more, 1-3 or 0 LNs (3-year RFS 79.7% *vs* 89.6% *vs* 92.9%; P = 0.05)[41]. In addition, Martin *et al*[32] conducted a study involving 16598 patients from the SEER registry, who underwent curative resection for GEP NETs from different primary locations. This study concluded that the extent of LN involvement was associated with survival across most GEP NET primary sites but did not report an optimal LN cut off. However, an LNR of ≥ 2.0 was associated with worse survival.

Compared to these studies the current study included tumours from all gastrointestinal locations and a high LN yield and LN positivity were seen in SiNETs and PanNETs. Associations between LN positivity and RFS might have been found if the numbers of patients included were higher, but ideally, prospective studies should be instituted. Small studies do not have the power to rule out a real difference and avoid a type II error (false negative). The other limitation of this study was that there was variability in the number of LNs resected, and lack of records of LNs harvested in a proportion of patients (30%), highlighting the associated limitations of a retrospective study. The reason that patients with < 8 LNs retrieved had a better RFS may be a reflection of the fact that less pathological LNs were subjectively obvious at the time of surgery in these patients, and thus these patients have a better prognosis with more localised disease. Despite the constraint of study size, this is a relatively large study including patients with resected GEP NETs in a tertiary real-world clinical setting and adds to the limited body of literature in this study area. It does highlight the importance of retrieving adequate LNs during surgery for GEP NETs and indicates the necessity for closer follow up of patients with LN positivity. The current study demonstrated that localisation has a significant association with RFS, necessitating stricter surveillance for small bowel and pancreas primaries, in particular.

In conclusion, this study demonstrated that an outcome-oriented approach to cut-point analysis can suggest a minimum number of adequate LNs to be harvested in patients with GEP NETs undergoing curative surgery. Removal of ≥ 8 LNs is

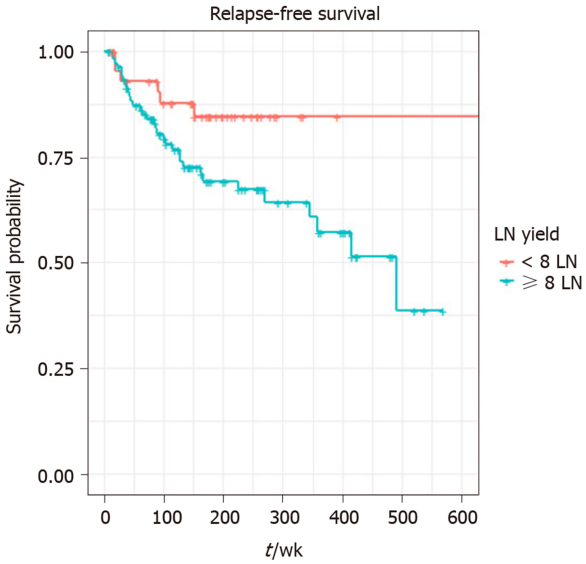

Figure 1 Kaplan Meier curve of relapse-free survival according to lymph node yield in patients with gastroenteropancreatic neuroendocrine tumours who underwent resection of primary tumour and regional lymphadenectomy. Lymph node yield ≥ 8: *P* = 0.0365; Hazard ratio = 2.65; 95%CI: 1.06-6.62.

associated with increased risk of relapse, which could be due to high rates of LN positivity at the time of surgery. However, the current study failed to demonstrate an association between LN positivity and LNR with RFS or OS, due to the small study size. It can be concluded that for accurate staging of GEP NETs, the percentage of positive nodes and LNR should be reported following potentially curative resection and incorporated into TNM staging. Given that localisation (pancreas *vs* small bowel *vs* other) had a significant association with RFS, a prospective multicentre study is warranted with a clear direction on recommended surgical practice and follow-up guidance for GEP NETs.

Table 3 Multivariable analysis of variables associated with relapse-free survival in patients who had curative resection of gastroenteropancreatic neuroendocrine tumours

Variable	HR	95%CI	*P* value
Presence of perineural infiltration: Yes	1.57	0.81-3.06	0.1858
Over 8 lymph nodes retrieved: Yes	2.65	1.06-6.62	0.0365
Any lymph nodes found positive: Yes	2.62	0.88-7.78	0.0840
Localisation category: Pancreas (relative to "others")	10.69	1.95-58.56	0.0063
Localisation category: Small bowel (relative to "others")	12.17	2.19-67.69	0.0043

HR: Hazard ratio; CI: Confidence interval.

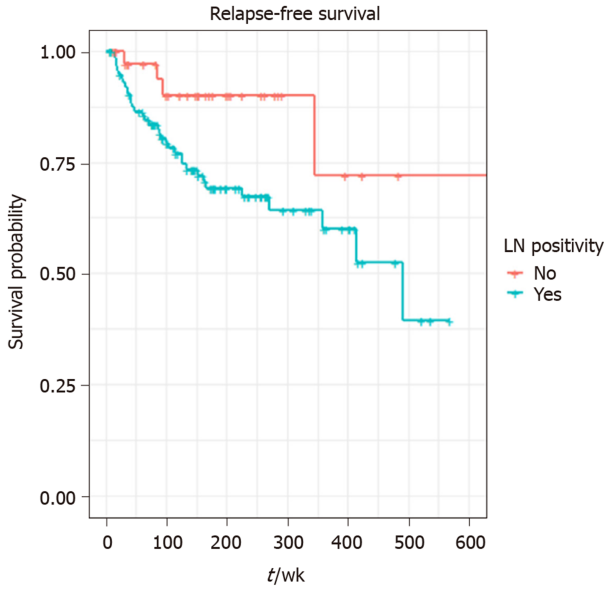

Figure 2 Kaplan Meier plot of relapse-free survival according to LN positivity in patients with gastroenteropancreatic neuroendocrine tumours who underwent curative resection. *P* = 0.0840; Hazard ratio = 2.62; 95%CI: 0.88-7.78.

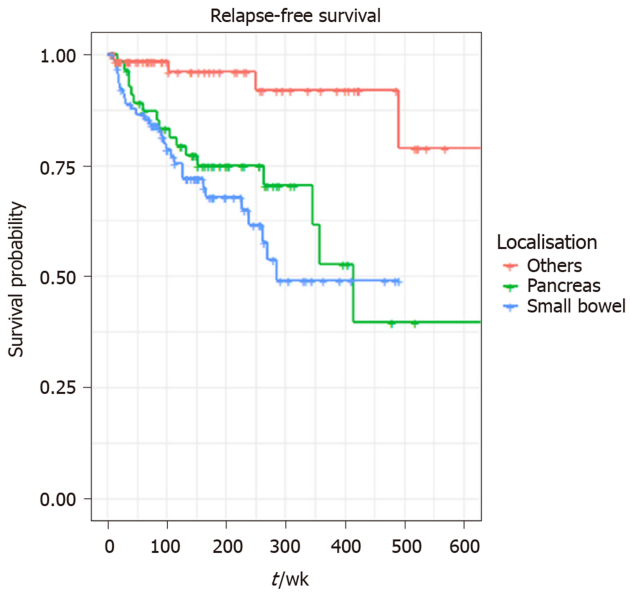

Figure 3 Kaplan Meier plot of relapse-free survival according to tumour localisation: Pancreatic neuroendocrine tumours, small intestinal neuroendocrine tumours and others. Pancreas: *P* = 0.0063; Hazard ratio = 10.69; 95%CI: 1.95-58.56. Small intestine: *P* = 0.0043; Hazard ratio = 12.17; 95%CI: 2.19-67.69.

ARTICLE HIGHLIGHTS

Research background

The prognostic significance of lymph nodes (LNs) metastases and the optimum number of LN yield in gastroenteropancreatic neuroendocrine tumours (GEP NETs) undergoing curative resection is still debatable. Many studies have demonstrated that resection of the primary tumour and regional lymphadenectomy results in a high cure rate for patients with GEP NETs.

Research motivation

LN positivity and LN ratio (LNR) are independent prognostic factors for survival in patients with resected NETs, but limited evidence is available on the optimal predictive number of resected LNs required. Several retrospective studies in Pancreatic NETs (PanNETs) and Small Bowel NETs (SiNETs) have emphasized the importance of adequate resection of regional LNs in patients undergoing curative resection. The current guidelines (AJCC TNM staging 8th edition and ENETS) for the management of GEPNETs do not provide a recommendation regarding LN yield. The main purpose of the study was to identify a cut off value for LN retrieval in resected GEP NETs.

Research objectives

This retrospective study was conducted to identify the optimal number of LNs that should be harvested in patients with GEP NETS undergoing curative surgery and to evaluate the association between LN metastases and survival (relapse-free and overall) in patients with resected well differentiated GEP NETs.

Research methods

Data on patients who underwent curative surgery for GEP NETs between January 2002 and March 2017 were identified and analysed retrospectively. Univariate Cox proportional hazard (CPH) models were computed for RFS and OS and assessed alongside cut-point analysis to distinguish a suitable binary categorisation of total LNs retrieved associated with RFS. LN cut-point value was determined using the cut-point determination methods in survival analysis, using R. This is an outcome-oriented method providing a value of a cut-point that corresponds to the most significant relationship with survival.

Research results

The result of univariate analysis suggested perineural invasion (P = 0.0023), LN positivity (P = 0.033), LN retrieval of ≥ 8 (P = 0.047) and localisation (P = 0.0049) have a statistically significant association with shorter RFS, but there was no effect of LN ratio (median 1.8) on RFS: P = 0.1 or OS: P = 0.75. LN cut-point value associated with RFS was 8. Tumour necrosis (P = 0.021) and perineural invasion (P = 0.016) were the only two variables significantly associated with worse OS. Retrieval of ≥ 8 LNs (HR = 2.70, 95%CI: 1.07-6.84, P = 0.036), tumour localisation: pancreas (HR = 27.33, P = 0.006) and small bowel (HR = 32.44, P = 0.005) were independent prognostic factors for shorter RFS on multivariable analysis.

Research conclusions

The study has concluded that an outcome-oriented approach to cut-point analysis can suggest a minimum number of adequate LNs to be harvested in patients with GEP NETs undergoing curative surgery. A prospective multicentre study is warranted with a clear direction on recommended surgical practice and follow-up guidance for GEP NETs.

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