Endocrine CONNECTIONS

Predicting the survival of patients with small bowel neuroendocrine tumours: comparison of 3 systems

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Abstract

Neuroendocrine tumours (NET) are clinically challenging due to their unpredictable behaviour. Nomograms, grading and staging systems are predictive tools with multiple roles in clinical practice, including patient prognostication. The NET nomogram allocates scores for various clinicopathological parameters, calculating percentage estimates for 5- and 10-year disease-specific survival of patients with small bowel (SB) NET. We evaluated the clinical utility of three prognostic systems in 70 SB NET patients: the NET nomogram, the World Health Organisation (WHO)/European Neuroendocrine Tumour Society (ENETS) grading system and the American Joint Commission on Cancer (AJCC)/Union Internationale Contre le Cancer (UICC) TNM staging method. Using Kaplan–Meier methodology, neither the WHO/ENETS grade ($P=0.6$) nor the AJCC/UICC stage ($P=0.276$) systems demonstrated significant differences in patient survival in the cohort. The NET nomogram was well calibrated to our data set, displaying favourable prediction accuracy. Harrel's C-index for the nomogram (a measure of predictive power) was 0.65, suggesting good prediction ability. On Kaplan–Meier analyses, there were significant differences in patient survival when stratified into nomogram score-based risk groups: low-, medium- and high-risk tumours were associated with median estimated survivals of 156, 129 and 112 months, respectively ($P=0.031$). Our data suggest that a multivariable analysis-based NET nomogram may be clinically useful for patient survival prediction. This study identifies the limitations of the NET nomogram and the imperfections of other currently used single or binary parameter methodologies for assessing neuroendocrine disease prognosis. The future addition of other variables to the NET nomogram will likely amplify the accuracy of this personalised tool.

Key Words
- small bowel
- neuroendocrine
- tumour
- nomogram
- prediction

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Introduction

Small bowel (SB) neuroendocrine tumours (NET) are accruing significant clinical attention due to their increasing incidence (1, 2) in addition to recent advances in their molecular biology (3, 4, 5, 6) and treatment (7, 8). Despite such progress, SB NET may still present notable challenges such as the high rate of metastasis at the initial presentation (9), as well as the optimal selection of therapeutic strategies from a diverse armamentarium for disseminated disease (10, 11, 12). Furthermore, the limitations of currently available mono-analyte biomarkers for predicting disease activity and behaviour; for example, the poor sensitivity and specificity of chromogranin A, are appreciated in the literature (13, 14). This is arguably partly attributable to the diverse functionalities of NET cells of origin, in addition to divergences between the clinical behaviour of different sub-types. Tumour classification methods based on tumour grade and stage have been developed for SB NET, namely the World Health Organisation (WHO)/European Neuroendocrine Tumor Society (ENETS) staging and grading system (15) and the American Joint Committee on Cancer/Union Internationale Contre le Cancer (AJCC/UICC) staging and grading system (16). Although these have been shown to correlate with survival in large cohorts of patients (17, 18), precise prognostication and definition of management strategies for individual patients remain elusive. Significant effort has been expended in the development of novel approaches to rectify these shortcomings, such as PCR-based multi-analyte methods of assessing disease activity (19), analysis of miRNAs (5), metabolomic profiling (20) and prognostic nomograms (21).

Nomograms mathematically assimilate various clinicopathological parameters to yield patient-specific information capable of influencing their clinical management or informing clinicians about the patient journey. Indeed, a plethora of nomograms have been developed within the realm of oncology aiming to predict various facets of malignant disease processes such as patient survival (22), risk of disease recurrence (23), risk of drug toxicity in clinical trials (24), presence of specific activating mutations (25) or to identify triggers for treatment decisions (26, 27). However, these tools must be rigorously validated and scrutinised prior to their translation into clinical practice (28).

A SB NET nomogram (NET nomogram) was developed in 2010 to enable the imputation of a number of patient- and tumour-related values to calculate an estimate for 5- and 10-year disease-specific survival of patients with SB NET, with the inclusion of prognosticators based on Cox regression, hazard ratio and Kaplan–Meier analyses of published data and also information from the Surveillance, Epidemiology and End Results (SEER) registry (21) (Fig. 1). Here, we undertake an evaluation of this predictive tool, assessing its utility in a larger cohort of SB NET patients. Furthermore, we assess the patient prognostication ability of the WHO 2010/ENETS grading and AJCC/UICC staging in our patient cohort as comparators.

Methods

Our cohort comprised patients with small bowel neuroendocrine tumours treated at Imperial College London NHS Healthcare Trust, UK (ICLNHT), which is an ENETS Centre of Excellence, and also the University Hospital, Essen, Germany (UHE). Patients with histologically confirmed SB NET (either on tumour specimen or biopsy material) were identified from a prospectively maintained database. All patients were staged and graded according to WHO/ENETS (15) and AJCC/UICC (16) criteria. Tumour staging was based on results of standard cross-sectional imaging and somatostatin receptor-based imaging; in the initial phase of the study this was somatostatin receptor scintigraphy and more recently, positron emission tomography/computed tomography (PET/CT). As the same physician (A.F.) oversaw patients at the two institutions, consistency of the results in relation to the study was assured. Furthermore, all patients were discussed within the setting of a multidisciplinary team regarding treatment selection.

Consent has been obtained from each patient or subject after full explanation of the purpose and nature of all procedures used.

Data required for calculation of the NET nomogram scores were retrieved via examination of individual case notes. All histology reports were re-reviewed to ascertain consistency in describing the variables in the nomogram. Standard assays for determination of biochemical variables were used. Tumour size was measured either using pathological analysis of surgical specimens or in the case of those who did not receive surgical treatment for their primary tumour, radiology. For patients with multifocal primary tumours, the largest tumour was used. Only patients with all data required for the nomogram were included in the study cohort. After collation and

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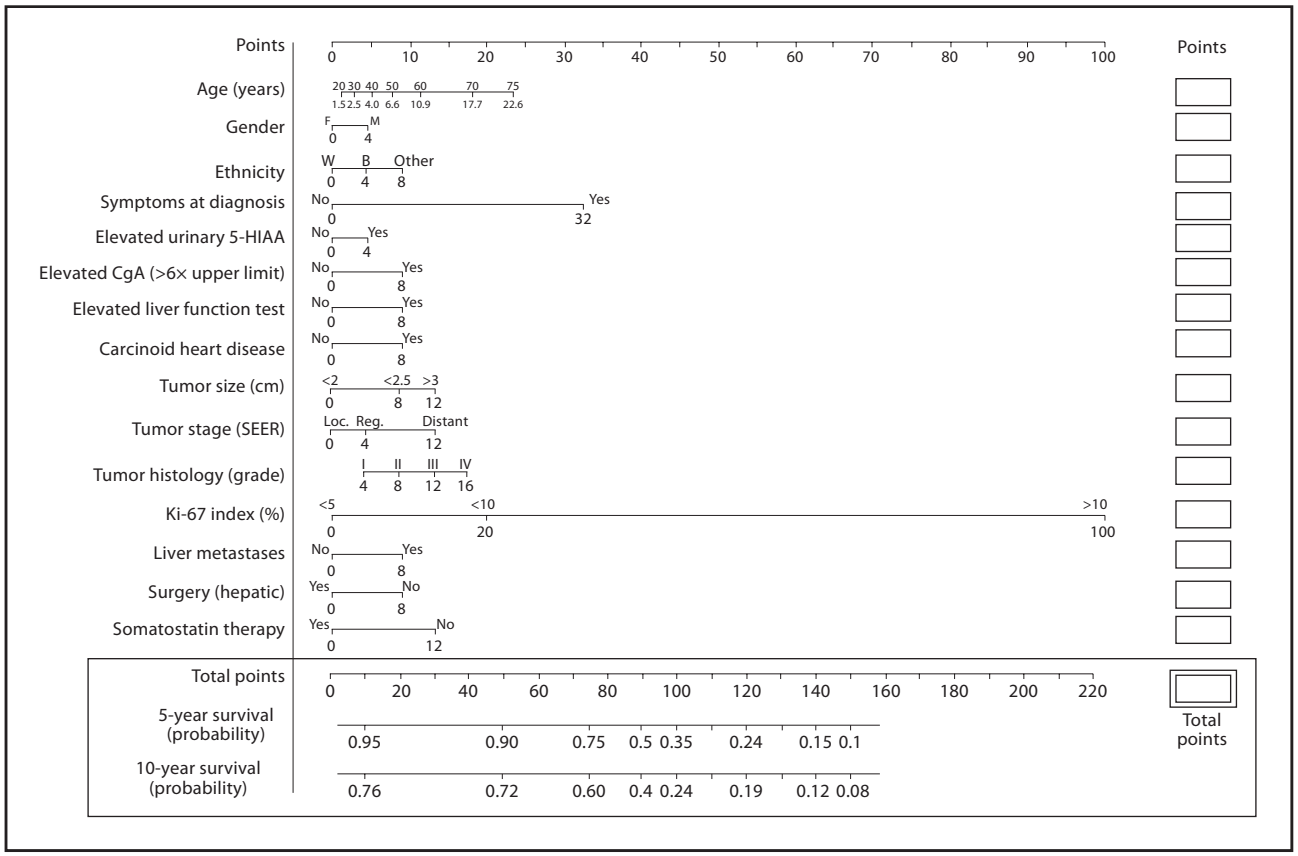

Figure 1
Modified NET nomogram. Reproduced, with permission, from Modlin IM, Gustafsson BI, Pavel M, Svejda B, Lawrence B & Kidd M (2010) A nomogram to assess small-intestinal neuroendocrine tumor ('carcinoid') survival, *Neuroendocrinology*, volume **92**, pages 143–157. Copyright 2010 Karger Publishers, Basel, Switzerland. (21).

analysis of the data, nomogram scores were calculated for individual patients. On the basis of nomogram score, patients were separated into three risk groups as specified in the original report, specifically: low risk (score <75), medium risk (score 75–95) or high risk (score >95). The original paper-based nomogram was converted into a Microsoft Excel spreadsheet-based calculator. Briefly, using the paper-based nomogram, scores were plotted against corresponding percentage survival estimations and curve-fitting functions utilised to derive an equation for converting nomogram score into 5- and 10-year percentage disease-specific survival estimates. This enabled parameter entry and expedited calculations. Each patient was followed up at 3-to 6-month intervals. Our institutional protocol follow-up consider the recommendations of ENETS and include standard cross-sectional imaging, somatostatin receptor-based imaging, serum tumour markers and urinary 5-hydroxyindoleacetic acid. Depending upon individual clinical situations, additional procedures such as endoscopies might be considered. Date of death was confirmed by documentation in the patient files and/or contact with the referring physician. Patient data were analysed according to the standard institutional review board protocols in accordance with the World Medical Association Declaration of Helsinki pertaining to the ethical conduct of research involving human subjects.

Comparison of means utilised the unpaired *t* test, and associations between categorical variables were assessed using Pearson's chi-square or Fisher's exact tests. Discrimination of the nomogram was quantified overall using Harrell's C-index (a measure of predictive power, in which a C-index greater than 0.5 suggests good predictive ability), in addition to utilising receiver-operating characteristic (ROC) analyses based on survival at 5 and 10 years; the area under the curve (AUC) was calculated for each outcome with corresponding 95% confidence intervals (CI) (29). These specific time points were selected given the nomogram's function to provide percentage estimates for disease-specific survival at 5- and 10-year follow-up. Calibration plots were used to assess calibration of the NET nomogram to our data set, i.e., how predicted and observed survivals compared – patients were grouped

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Table 1 Basic demographics of our study cohort. Grading and staging according to the WHO/ENETS system (15).

Parameter	*N* (%)
Total number of patients	70
Median age at diagnosis (range)	57 years (32–82)
Gender	
Male	39 (55.7)
Female	31 (44.3)
Tumour grade	
G1	62 (88.6)
G2	6 (8.6)
G3	2 (2.8)
Tumour stage	
$T_{1-4}N_0M_0$	7 (10)
$T_{1-4}N_1M_0$	19 (27.1)
$T_{1-4}N_0M_1$	1 (1.4)
$T_{1-4}N_1M_1$	43 (61.4)
Liver metastases	
Yes	40 (57.1)
No	30 (42.9)
Primary tumour focality	
Multifocal	10 (14.3)
Unifocal	60 (85.7)

on the basis of their nomogram-predicted overall survival estimates then compared with the mean Kaplan–Meier survival for that group. For all 3 prognostic systems, the Breslow test was employed to compare the overall survival curves generated with Kaplan–Meier methodology.

All statistical analyses were performed using SPSS software, v22 or R software, v3.2.0, with the significance level set at $P<0.05$.

Results

Our patient cohort comprised 70 consecutive patients (ICLNHT $n=44$, UHE $n=26$; 39 male, 31 female), with a median age of 57 years at diagnosis treated between 1998 and 2015 (UHE 1998–2007, ICLNHT 2010–2015). Both groups of patients were comparable regarding demographics and parameters analysed, with no statistically significant differences in, for example, age, tumour grade and tumour stage, thus enabling analysis as one cohort. Basic demographics of our cohort are demonstrated in Table 1, and clinicopathological characteristics of the study cohort in terms of the parameters in the NET nomogram are shown in Table 2.

Sixty-four (91.4%) patients underwent surgery at some stage of their treatment, 4 of which were emergency cases comprising laparotomy with small bowel resection ($n=3$) or right hemicolectomy ($n=1$). Additional treatment modalities employed in our cohort included Lutetium

Table 2 Clinicopathological characteristics of study cohort in terms of NET nomogram parameters.

Parameter	*N* (%)
Total number of patients	70
Median age at diagnosis	57 years (range 32–82)
Gender	
Male	39 (55.7)
Female	31 (44.3)
Ethnicity	
White	55 (78.6)
Black	8 (11.4)
Other	7 (10)
Symptoms at diagnosis (carcinoid syndrome)	
Yes	29 (41.4)
No	41 (58.6)
Elevated urinary 5-HIAA	
Yes	19 (27.1)
No	51 (72.9)
Elevated serum chromogranin A (6× upper limit)	
Yes	18 (25.7)
No	52 (74.3)
Elevated liver function tests	
Yes	7 (10)
No	63 (90)
Tumour size*	
<2 cm	47 (67.1)
2–2.5 cm	9 (12.9)
>2.5 cm	14 (20)
Tumour stage (SEER)	
Localised	7 (10)
Regional	19 (27.1)
Distant	44 (62.9)
Tumour histology	
I (well differentiated)	62 (88.6)
II (moderately differentiated)	7 (10)
III (poorly differentiated)	1 (1.4)
Tumour grade (Ki67%)	
<5	65 (92.9)
5–10	2 (2.9)
>10	3 (4.3)
Carcinoid heart disease	
Yes	8 (11.4)
No	62 (88.6)
Liver metastases	
Yes	40 (57.1)
No	30 (42.9)
Resection of liver metastases	
Yes	15 (21.4)
No	55 (78.6)
Treatment with somatostatin analogue	
Yes	18 (25.7)
No	52 (74.3)

Upper limit of serum chromogranin A = 60 µmol/L. Carcinoid heart disease confirmed by echocardiography. Note that Ki67 value cut-offs are derived from statistical methods used in the original report of the NET nomogram and are not according to standard ENETS/WHO grade criteria (15).
*For multifocal tumours, size of the largest lesion was used.
5-HIAA, 5-hydroxyindoleacetic acid; SEER, Surveillance, Epidemiology and End Results program.

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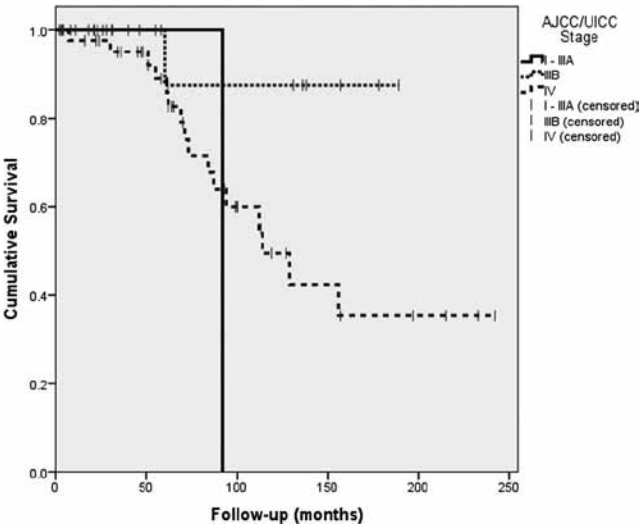

Figure 2
Kaplan–Meier plot of patient survival stratified by AJCC/UICC tumour stage ($P=0.276$). Stages I–IIIA ($n=7$), stage IIIB ($n=19$), stage IV ($n=44$).

177 peptide receptor radionuclide therapy (PRRT) ($n=15$), somatostatin analogues ($n=18$), transarterial chemoembolization ($n=5$), radiofrequency ablation of liver metastases ($n=3$), selective internal radiotherapy ($n=2$) and standard chemotherapy ($n=2$). Overall, 26 patients (37.1%) received multimodal treatment.

Of the entire cohort, 3 patients underwent exploratory laparotomy only, 16 underwent a small bowel resection and 40 underwent a right hemicolectomy due to primary tumour location in the terminal ileum. Additionally, 4 patients received concurrent right hemicolectomy and small

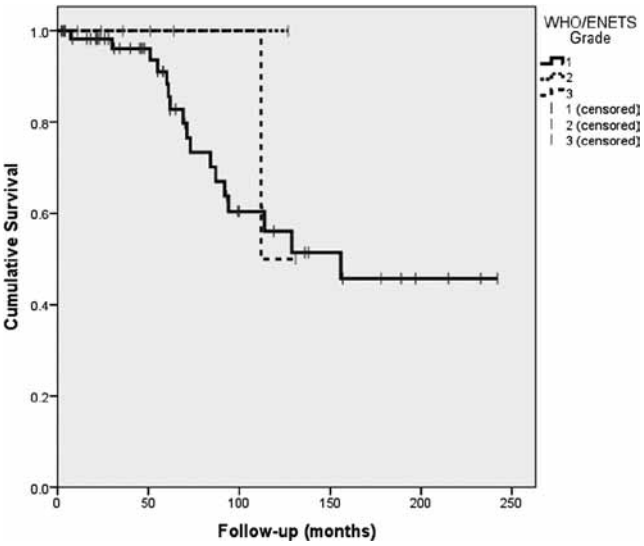

Figure 3
Kaplan–Meier plot of patient survival stratified by WHO/ENETS tumour grade ($P=0.6$). Grade 1 ($n=62$), Grade 2 ($n=6$) and Grade 3 ($n=2$).

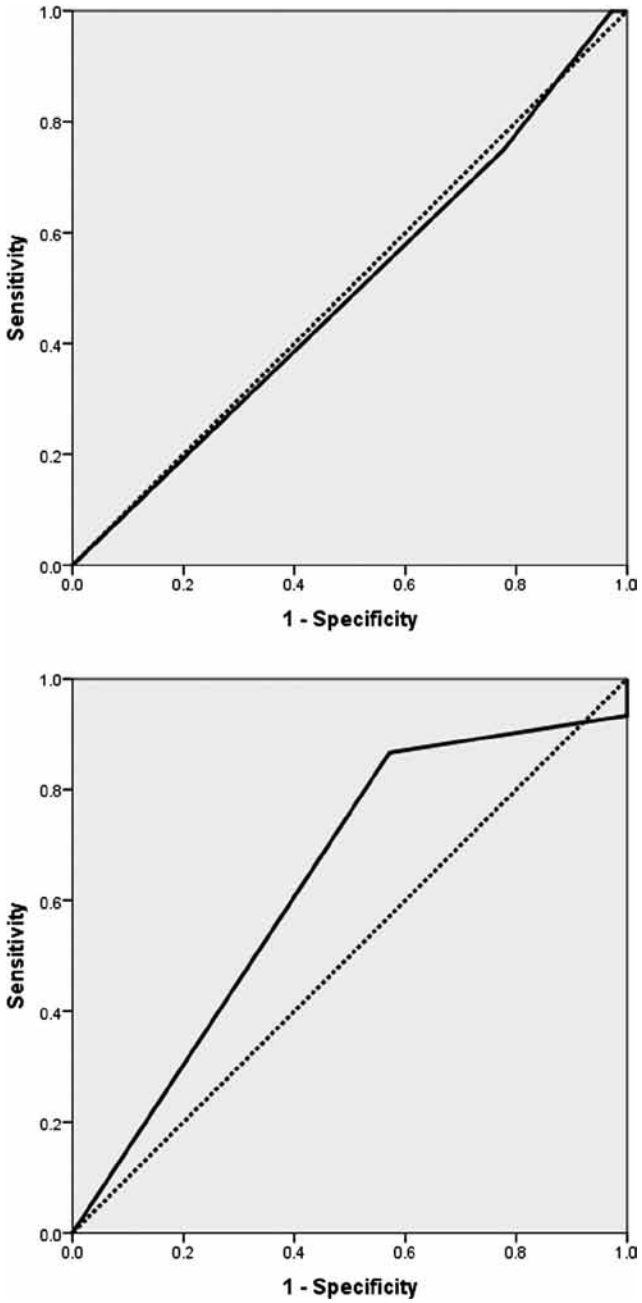

Figure 4
Receiver-operating characteristic curves for 5- (top) and 10-year (bottom) survival (AJCC/UICC disease stage). Area under curves (95% confidence intervals) are 0.49 (0.188–0.791) and 0.425 (0.425–0.842), respectively.

bowel resection. Fourteen patients received liver resection; one underwent small bowel resection and two underwent right hemicolectomy with a liver resection within the same procedure, respectively.

Transplantation techniques were utilised in two patients: one underwent resection of the primary tumour prior to orthotopic liver transplantation. Another patient

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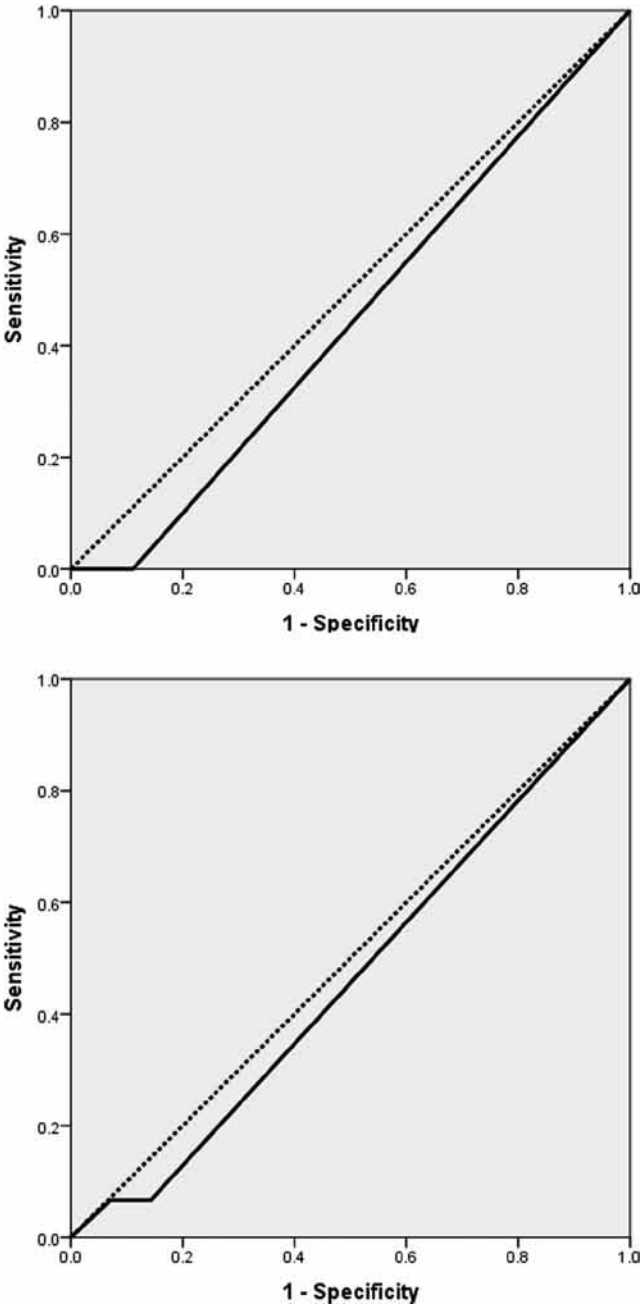

Figure 5
Receiver-operating characteristic curves for 5- (top) and 10-year (bottom) survival (WHO/ENETS tumour grade). Area under curves (95% confidence intervals) are 0.444 (0.169–0.720) and 0.464 (0.251–0.678), respectively.

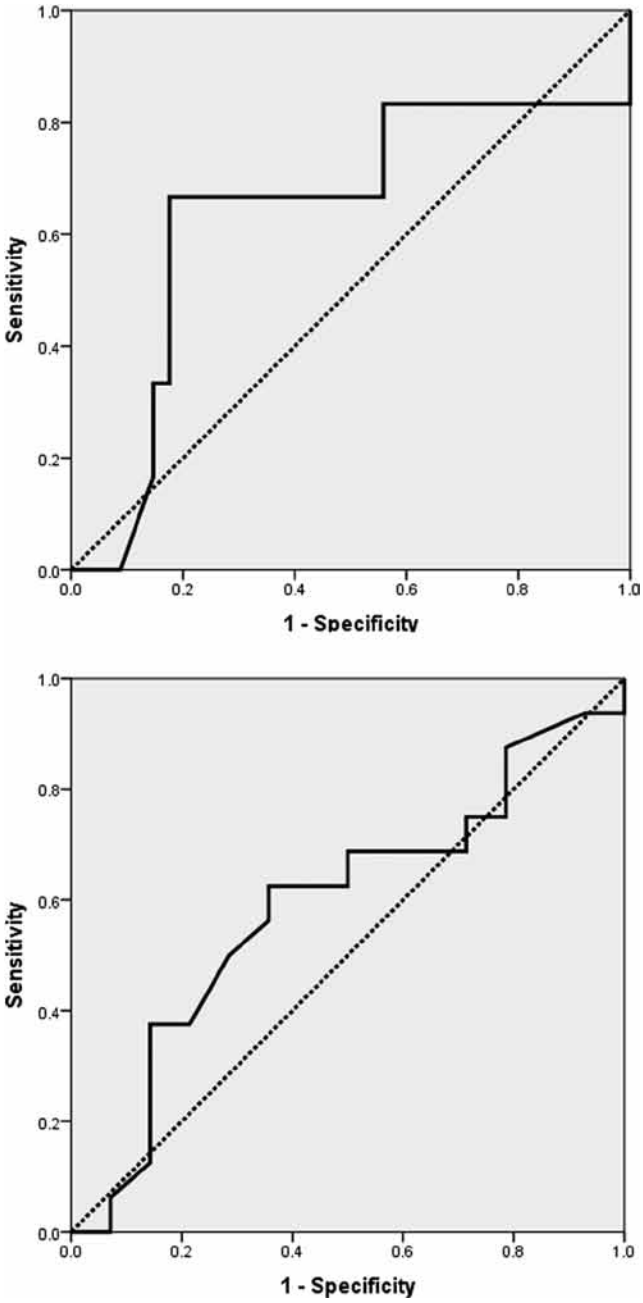

Figure 6
Receiver-operating characteristic curves for 5- (top) and 10-year (bottom) survival (nomogram). Area under curves (95% confidence intervals) are 0.637 (0.362–0.912) and 0.587 (0.277–0.797), respectively.

with a multifocal SB NET with extensive mesenteric disease underwent multivisceral transplantation after neo-adjuvant PRRT (30). There was no mortality in our cohort within 30 days. Five patients (7.1%) experienced grade I surgical morbidity as assessed using the Clavien–Dindo classification system (31). The 6 patients who did not undergo any surgical intervention received somatostatin analogues, PRRT, or a combination of both ($n=3$, $n=2$ and $n=1$, respectively). Median follow-up for the entire cohort was 61.5 months (range 2–242), during which time there were 18 deaths (all of which were disease-specific). No patient was lost to follow-up.

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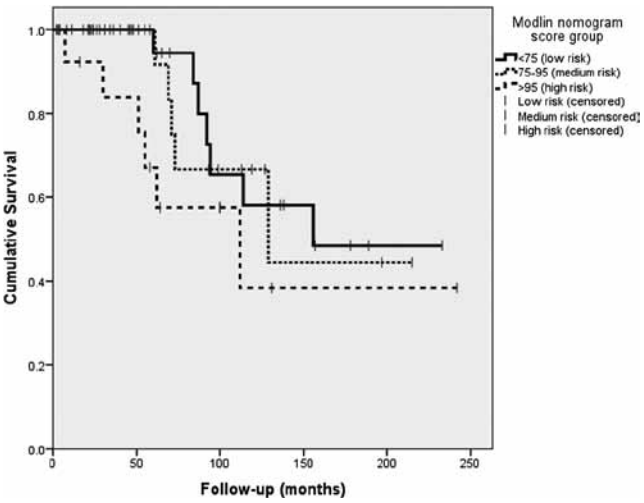

Figure 7
Kaplan–Meier plot of patient survival stratified by NET nomogram score risk group ($P=0.031$). Low risk ($n=42$), medium risk ($n=15$) and high risk ($n=13$).

WHO/ENETS and AJCC/UICC systems

All patients had sufficient clinicopathological data to be analysed under the WHO/ENETS grading criteria and the AJCC/UICC staging system (Supplementary Tables 1 and 2, respectively, see section on supplementary data given at the end of this article). Sixty-two patients (88.6%) had grade (G) 1 tumours, 6 (8.6%) had G2 tumours and 2 (2.8%) had G3 tumours. Regarding AJCC/UICC staging, 2 patients (2.9%) were stage I, 3 (4.3%) were stage II, 2 (2.9%) were stage IIIA, 19 (27.1%) were stage IIIB and 44 (62.9%) were stage IV at the time of initial presentation.

On Kaplan–Meier analysis, the median estimated survival for patients with G1 tumours was 156 months. For G2 tumours, no median estimated survival could be calculated due to no patient deaths within the follow-up period; for G3 tumours, a median estimated survival of 112 months was calculated; however, this is derived from a very small sample size ($n=2$). Given the small size of, and/or low numbers of patient deaths in the samples of patients with AJCC/UICC stages I, II, and IIIa tumours, no reliable median survival estimates could be calculated for these individual patient sets. However, when combined into a single group, median estimated survival was 92 months. For stage IIIb and IV tumours, median estimated survivals were 172 months and 114 months, respectively. There were no significant differences in survival when patients were stratified according to disease stage ($P=0.276$) or according to grade ($P=0.6$) (Figs 2 and 3).

Regarding ROC analysis for disease stage: for 5- and 10-year disease-specific survival, the corresponding AUCs were 0.49 (95% CI: 0.188–0.791, $P=0.44$) and 0.633 (95% CI: 0.425–0.842, $P=0.22$), respectively (Fig. 4). Regarding ROC analysis for tumour grade: for 5- and 10-year disease-specific survival, the corresponding AUCs were 0.44 (95% CI: 0.169–0.720, $P=0.718$) and 0.46 (95% CI: 0.251–0.678, $P=0.74$), respectively (Fig. 5).

NET nomogram

Calculated nomogram scores ranged from 26.6 to 208, with a median score of 66.2. Forty-two patients had a low risk score (<75), whereas 15 and 13 had medium (75–95) and high (>95) risk scores, respectively.

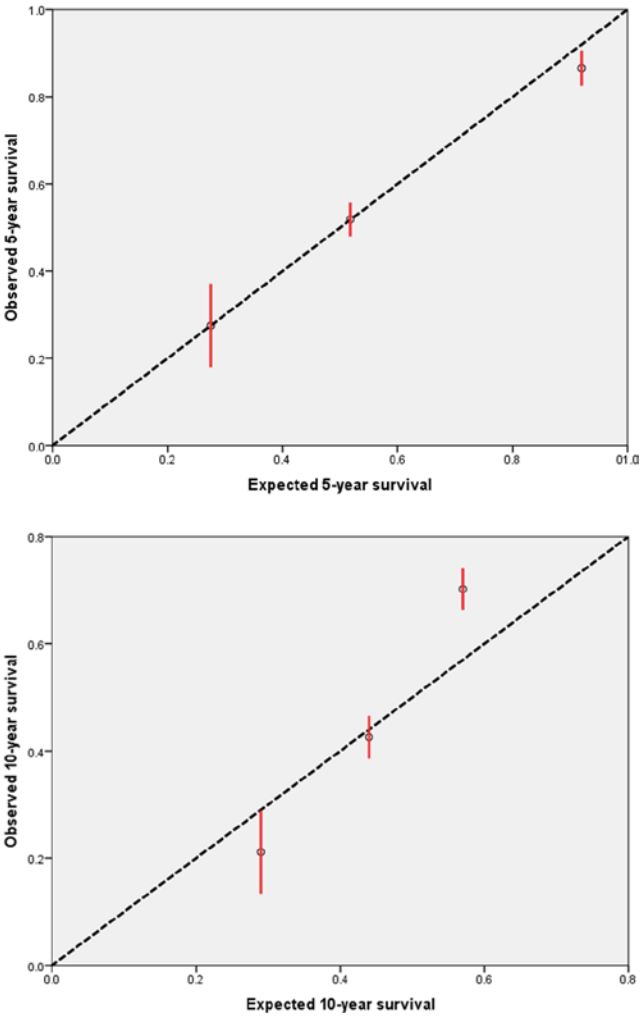

Figure 8
Calibration plots comparing observed and expected survival at 5 (top) and 10 years (bottom). Vertical bars represent S.E.M. Data for all patients are included. The data marks in each plot from left to right represent high-, medium- and low-risk groups, respectively.

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Regarding the discrimination of the NET nomogram, the C-index equalled 0.65; ROC analysis demonstrated that for 5-year disease-specific survival, the AUC was 0.637 (95% CI: 0.362–0.912, P=0.289), whereas for 10-year disease-specific survival, the AUC was 0.587 (95% CI: 0.277–0.797, P=0.418) (Fig. 6). However, there were significant differences in patient survival between low-, medium- and high-risk score groups (χ^2=6.98, P=0.031, Fig. 7), suggesting the ability of the nomogram to meaningfully stratify patients and predict patient outcomes. Median estimated survival in the low-, medium- and high-risk score groups was 156, 129 and 112 months, respectively. Furthermore, the numbers of deaths that occurred during the study period in the low-, medium- and high-risk groups were 7 (16.7%), 5 (33.3%) and 6 (46.2%), respectively. The calibration plots (Fig. 8) demonstrated that expected and observed survivals were comparable.

Discussion

NET patient prognosis prediction is limited by the paucity of systems in existence, which are able to integrate precise and individualised disease parameters. Thus, accurate prognostication of the specific disease of an individual remains elusive. Indeed, it is often more reflective of a Delphic pronouncement or a personal anecdotal assessment than a science. Systems classifying NET on the basis of individual parameters such as tumour proliferative activity or extent of disease dissemination have been demonstrated to have substantial power in distinguishing quality of outcomes either in their original (32, 33) or revised formats (34). In a cohort of 93 patients with intestinal NET assessed by Araujo and coworkers (32), disease-specific survival was 165.8 months for patients with grade 1 tumours compared to 15.8 months for grade 3 tumours. Although no deaths were seen in patients with stage I or stage II NET, disease-specific survival decreased to 112.8 months in those with stage IV disease. Jann and coworkers reported a 5-year survival of 100% for both stages 1 and 2 midgut and hindgut NET, compared to 89.5% and 83.3% for stages 3 and 4 tumours, respectively (17). However, such single-parameter systems exhibit a substantial limitation, namely that they inherently ignore a plethora of patient- and tumour-specific characteristics relevant to the biology of the disease or its clinical management. Of note, in contrast to requirements for staging of other cancers (35) a necessity for a minimum number of lymph nodes resected in NET disease to allow accurate nodal staging has not been addressed as a measure for surgical quality. Thus, disease understaging in the present assessment for small bowel tumours represents a significant limitation.

The NET nomogram is based on an optimised construct of literature-curated data and with some prognostic weightings derived from studies not exclusively examining SB NET. Despite the limitations inherent to the data available for developing this type of mathematical construct, this represents a useful step forward from the pathology-based single or binary parameter systems currently used. Such a nomogram offers the potential of a multivariate analysis of a given individual's disease and offers numerous potential clinical utilities including formal patient stratification, objective patient counselling, guidance of therapeutic strategies and evaluation of the efficacy of such clinical decisions (21). The original report described its utility in an internal validation cohort of 33 patients with SB NET drawn from 3 institutions with follow-up ranging between 0.5 and 19 years. Indeed, the authors demonstrated a significant increase in the nomogram scores of deceased patients vs. those alive at last follow-up, and the ability of the nomogram to effectively predict survival.

Our study encompassed a cohort of 70 SB NET patients, and our results are in agreement with those reported in the original study insofar as the NET nomogram offers a basis for patient prognostication, albeit modestly powerfully with regards to differences in survival time between patients deemed as low, medium and high risk. Nevertheless, several aspects of this predictive tool are amenable to future optimisation to reflect intuition and developments in clinical knowledge. These include refinement of the allocation of points based on metastatic disease. As aforementioned, patients may be assigned points for LM, but the nomogram also assigns 12 points for distant disease stage (according to the SEER classification). Thus, one hypothetical patient with liver metastases may receive 20 points, whereas another with only osseous metastases receives 12 – i.e. LM are 'counted twice'. Although the ability of NET to metastasise to bone is appreciated in the literature (36, 37), there are no clear data comparing the relative detriment of differential sites of disease dissemination in SB NET patients. Furthermore, the prognostic relevance of peritoneal metastases is not well reflected. More recently, several groups have shown that peritoneal spread significantly worsens the prognosis of patients with SB NET, notably Gonzales and coworkers

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who demonstrated that discrete mesenteric nodules >1 mm in size that were distinguishable from mesenteric lymph nodes occurred in 60% of their SB NET patient group and were associated with poorer survival (38).

Potential additions to the nomogram could include indices for other therapeutic strategies and their effectiveness, such as the trans-arterial liver-directed approaches, PRRT and measurement of circulating neuroendocrine gene transcripts (13, 39, 40, 41), all of them not considered originally. However, as noted by Modlin and coworkers, the incorporation of prognostic indices is critically dependent upon data availability, and not all of these novel technologies are broadly available (21). Although such strategies have demonstrated clinical promise, the hazard ratio data necessary for inclusion in a nomogram are not currently available.

The fact that the WHO/ENETS and AJCC/UICC systems failed to effectively predict prognosis in our cohort may appear initially surprising. This could partly be attributable to our sample size; however, an equally (if not more) accountable basis could be that the vast majority of our patients harboured low grade, yet metastatic disease and that only a few patients had intermediate- or high-grade tumours. Small bowel NETs do indeed have a particular proclivity to present with metastasis despite the vast majority of primary tumours being of low grade. The recent series of Lardiere-Deguelte and coworkers reported a median Ki67 of 2±2.8% (range 1–15) in their cohort of SB NET patients (42), and Gonzalez and coworkers demonstrated a 75% rate of G1 tumours in their report (38) (both $n=72$). In their retrospective analysis of over 600 patients with small bowel NET (68% of whom had G1 disease), the Uppsala group reported that 88% demonstrated mesenteric lymph-node metastases and 61% harboured liver metastases at initial presentation (43). Strikingly similar results have also been reported by our group in a multi-centric cohort of 84 patients; 83.3% of these patients had G1 disease, yet, 88.1% of patients had lymph node involvement and 60.7% had distant metastases at presentation (9). Of course, one must consider the caveat of potential referral bias with regards to the rate of distant metastases in NET patients treated at tertiary centres. Nevertheless, based on the reported data, we believe that the rates of metastasis encountered in this cohort is reflective of clinical reality. Such observations strongly underscore the potential clinical utility of a prognostic tool, which can successfully assimilate multiple tumour parameters as opposed to depending on a single aspect of tumour status, i.e., grade or stage, which alone in actuality may not appear greatly helpful.

It should be noted that analysis of the WHO/ENETS grading and AJCC/UICC staging systems demonstrated that ROC analyses exhibited non-significant AUC values for discrimination in both. Although the ROC analyses for assessing discrimination of the nomogram in our cohort also returned low AUC values, it is well recognised in mathematical literature that a single nomogram may deliver rather different AUC values when tested in separate cohorts and that AUC is not a critical value in the estimation of prediction accuracy (28). Our data suggest a limited usefulness of classifying small bowel NET purely on the basis of grade or stage. Although prognostically valid, a single-dimensional representation of a complex disease process is sub-optimal and is further encumbered by the fact that the majority of SB NET patients exhibit low-grade disease and the majority have distant tumour spread.

Thus, the NET nomogram may present a viable alternative to these 'classical' systems as it includes multiple different aspects of neuroendocrine disease biology specific to each patient. This strategy logically provides a platform that is not only more supportive for accurate prognostication but also far more embracing of the complexities of these tumours. Although the NET nomogram at this time exhibits imperfections, it possesses potential clinical utility that exceeds other monodimensional strategies. We have succeeded to accrue a cohort over twice the size of that used in the initial internal validation of the nomogram; nevertheless, the low number of patients may present the 'Achilles heel' of our study and the interpretation of data herein. Such limitations are commonplace in this clinical arena given the relative rarity of NET. Furthermore, the addition of sophisticated molecular and biological information from each tumour will likely enhance the nomogram such that it functions as an enhanced tool combining both clinical and molecular genomic information, consistent with the development of a personalised prognostic mathematical algorithm for an individual patient.

Supplementary data

This is linked to the online version of the paper at http://dx.doi.org/10.1530/EC-16-0114.

Declaration of interest

M K and I M were co-authors of the original report describing the NET nomogram. Otherwise, we declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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