# Prognostic threshold for circulating tumour cells in patients with pancreatic and midgut neuroendocrine tumours

**Dalvinder Mandair[1,2], Mohid S Khan [1,2,3], Andre Lopes[4], Luke Furtado O'Mahony[5], Leah Ensell[2], Helen Lowe[2], John A Hartley[2], Christos Toumpanakis[1], Martyn Caplin[1], Tim Meyer[2,6]**

[1] Neuroendocrine Tumour Unit, Royal Free Hospital, London

[2] Department of Oncology, UCL Cancer Institute, University College London, London

[3] Department of Gastroenterology, University Hospital of Wales, Cardiff, Wales

[4] Cancer Research UK & UCL Cancer Trials Centre, University College London, London

[5] University College London Medical School, University College London, London

[6] Department of Oncology, Royal Free Hospital, London

Corresponding author: Professor Tim Meyer, UCL Cancer Institute, University College London, 72 Huntley Street, London, WC1E 6DD, UK. Tel 02031082208, email; t.meyer@ucl.ac.uk

Reprint requests: Dr Dalvinder Mandair, Neuroendocrine Tumour Unit, Royal Free Hospital, London, NW3 2QG, email; dalvinder.mandair@nhs.net

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**Abstract**

**Background:** Circulating tumour cells (CTCs) are detectable in patients with NET and are accurate prognostic markers although the optimum threshold has not been defined.

**Objective:** To define optimal prognostic CTC threshold in pancreatic and midgut NET

**Patients and Methods**: CellSearch was used to enumerate CTCs in 199 patients with metastatic pancreatic (PanNET) (90) or midgut NET (109). Patients were followed for progression free survival (PFS) and overall survival (OS) for a minimum of 3 years or until death.

**Results:** AUROC for progression at 12 months in PanNET and midgut NET identified the optimal CTC threshold as ≥1 and ≥2 respectively. In multivariate logistic regression analysis, these thresholds were predictive for 12 month progression with OR of 6.69 ($p< 0.01$) for PanNET and 5.88 ($p<0.003$) for midgut. The same thresholds were found to be optimal for predicting death at 36 months with an OR of 2.87 ($p< 0.03$) and 5.09 ($p<0.005$) for PanNET and midgut NET respectively. In multivariate Cox hazard regression analysis for PFS in PanNET, ≥ 1 CTC had HR 2.6 ($p <0.01$) whilst ≥ 2 CTCs had HR 2.25 ($p < 0.01$) in midgut NET**.** In multivariate analysis OS in PanNET, ≥ 1 CTC had HR 3.16 ($p < 0.01$) and in midgut NET, ≥ 2 CTCs had HR of 1.73 ($p < 0.06$).

**Conclusions:** The optimal CTC threshold to predict PFS and OS in metastatic PanNET and midgut NET is 1 and 2, respectively. These thresholds can be used to stratify patients in clinical practice and clinical trials.

Keywords: Circulating tumour cells, neuroendocrine tumour, PanNET, Midgut NET

## Introduction

Neuroendocrine tumours (NETs) are a heterogeneous group of tumours that arise in diverse anatomic locations but most commonly the gastrointestinal tract and pancreas. According to the US Surveillance Epidemiology and End Research program (SEER), NETs make up 0.9% of all tumours of which 60.5% are gastroenteropancreatic (GEP) and 27% bronchial in origin (Hayat *et al*, 2007) The annual incidence is between 2 and 5 per 100,000 population (Yao *et al*, 2008, but prevalence is higher due to prolonged survival. NETs vary greatly in terms of prognosis and response to treatment but currently the only circulating biomarker recommended by the European Neuroendocrine Tumour Society (ENETs) is Chromogranin A (CgA) (Pavel *et al*, 2012; Modlin *et al*, 2010). The sensitivity of CgA in the diagnosis of GEP-NETS varies between 62-75% with specificity reported between 68-100% (O'Toole *et al*, 2009;Nikou *et al* ,2008 Nehar *et al*, 2004) In retrospective studies, high baseline levels are associated with worse progression free (PFS) and overall survival (OS) (Eklebad *et al*, 2008) . RADIANT 3, a phase III randomised prospective study evaluating everolimus in pancreatic NETs, found that high levels of CgA at baseline were associated with worse outcome (HR 0.42 with P <0.0001) (Yao *et al*, 2008). However, CgA can be elevated in many other common conditions or by the concomitant use of certain drugs and this decreases the sensitivity to between 10-35% (Modlin *et al*, 2016). In up to 40% of GEP- NETs, CgA is normal even in the presence of radiological progression and large volume disease (Walter *et al*, 2012).

Circulating tumour cells (CTCs) have been evaluated as biomarkers in a wide range of tumours. The CellSearch platform, which allows immunomagnetic separation of CTCs expressing epithelial cell adhesion molecule (EpCAM), has

been approved by the Food and Drugs administration (FDA) for use in breast, prostate and colorectal cancer following prospective trials demonstrating the prognostic value of CTCs at defined thresholds (Cristofanilli *et al*, 2004; de Bono *et al*, 2008; Cohen *et al*, 2008) . Pancreatic (PanNET) and midgut NET have been shown to express EpCAM in tissue, and CTCs are detectable in a high proportion of patients using CellSearch (Khan *et al*, 2011). In a prospective study of 176 NET patients, the presence of one or more CTCs was shown to be an independent prognostic factor associated with a significantly increased risk of death. However, the patient population studied was heterogeneous with respect to the primary tumour, and the optimal prognostic CTC according to primary site was not defined. Additionally, the study was limited by short follow-up, with a median of 12.6 months in a patient group which has a 73% survival at 2 years (Khan *et al*, 2013). Here, we have extended the study to allow the prognostic threshold of CTCs to be determined in separate, large cohorts of pancreatic and midgut NET with a minimum follow-up of three years.

## Methods

### Patients

Patients over 18 years of age with histologically proven PanNET or midgut NET and radiological evidence of metastases measurable by Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1) (Eisenhauer *et al*, 2008) were recruited. Both functioning and non-functioning tumours were included. Patients were excluded if they were participating in other clinical trials or had commenced treatment other than somatostatin analogues within the three months prior to sample collection. Ethical approval was obtained for the study from the National Research

Ethics Service (ref 13/LO/0376) and all patients provided written informed consent. Tumour grade was determined according to ENETS and WHO (2010) guidelines (Pape *et al*, 2008) . The presence of metastases was determined using cross-sectional imaging with MRI and CT, and also with somatostatin receptor scintigraphy (SRS) using Octreoscan™ or Gallium 68 DOTATATE PET. The volume of liver metastases was determined from CT and MRI images.

**Enumeration of CTCs**

Blood samples (7.5mL) were collected from patients into CellSave preservative tubes (Menarini Silicon Biosytems, Bologna), stored at room temperature and processed within 96 hours of collection as previously described by Khan et al (Khan *et al*, 2011, 2013). Two operators independently reviewed each sample and both were blind to the clinical details. Where there was disagreement on whether a cell met the criteria for CTC, a third independent operator was required to arbitrate.

**Statistics**

Statistical analyses were performed using Graph Pad Prism Version 6, Microsoft Excel and Stata 14. In the validation study of CellSearch by Allard et al (Allard *et al*, 2004) and the aforementioned study by Khan et al (Khan *et al*, 2013), a training set of 90 patients was used to define a prognostic threshold and a target of 90 was also used for each of the midgut and pancreatic cohorts in this series. To determine optimum CTC threshold, receiver operating characteristic (ROC) curve were plotted for progression at 12 months and death at 36 months for each primary. The optimal threshold was then applied in logistic regression analysis with other clinically significant variables in a univariate and multivariate model for those time points. Kaplan Meier survival curves were plotted and Cox hazards regression analysis was

also performed for overall survival (OS) and progression free survival (PFS) using the optimum CTC threshold for each primary. OS was defined as the time from CTC sample to death, and PFS from the time of CTC sample to death or progression as defined by RECIST 1.1.

## Results

### Patient Characteristics

Overall, 90 patients with PanNET, and 109 midgut NET were recruited between September 2009 and July 2014. Patients were followed up until November 2017 with a median follow-up of 64 months (1-98). All living patients had a minimum follow-up of 3 years. The demographics and clinical characteristics of the patients are shown in Table 1**.** A greater proportion of G1 tumours were seen in the midgut group (69%) than in the PanNET group (28%). There were 16 G3 tumours in the PanNET group compared to 3 in the midgut group.. A higher proportion of midgut patients (27%) had CgA elevated beyond 10x ULN compared to PanNET group (10%). All patients had liver metastases although a greater number of extrahepatic metastatic sites were seen in the midgut group. CTCs were detected in 30 (33%) PanNET and 56 (51%) of midgut NET which is consistent with previously published studies .

### Defining prognostic CTC threshold

In total, 46 patients with PanNET and 41 patients with midgut NET had progressed at 12 months. The AUROC for 12 month PFS in PanNET was 0.69 (95% CI 0.6-0.78) and the optimum CTC threshold was ≥ 1 CTC with a sensitivity of 50% and specificity of 84%. For midgut NET, the AUROC was 0.78(95% CI 0.69-0.87) and the optimal CTC threshold of ≥ 2 CTCs was associated with a sensitivity of 70% and specificity of 83% (Mandair *et al*, 2020).

These thresholds were used to determine the predictive utility of CTCs. Univariate and multivariate logistic regression analysis was applied to predict progression at 12 months (Table 2). For PanNET, grade 3 and CTCs ≥ 1 were both predictive of significantly increased risk of progression at 12 months in multivariate analysis while for midgut NET, grade 2 tumours, CgA > 10x ULN and CTCs ≥ 2 were predictive. The OR for grade 3 midgut NET was 5.47(95% CI 0.13-222.5) but this was not significant likely due to the fact that only three cases of 109 were grade 3.

The optimal CTC threshold was also determined for 36 month survival using ROC analysis (Mandair *et al*, 2020). At 36 months, there were 40 deaths in the PanNET and 43 deaths in the midgut NET cohorts. The AUROC for PanNET was 0.69, (95% CI 0.59, 0.78) with sensitivity of 50% and specificity 80% with optimum CTC threshold ≥ 1. In midguts, the AUROC was 0.75 (95% CI 0.65, 0.86) with the optimum threshold of ≥ 2 CTCs giving a sensitivity of 70% and specificity of 72%. Logistic regression analysis was performed using these thresholds (Table 3). For PanNET, liver volume between 50-75% and the presence of CTC ≥ 1 were predictive of death in multivariate analysis. For midgut NET, CgA 5-10 X ULN and >10 X ULN was predictive as was CTC ≥ 2.

The prognostic performance of CTCs to predict PFS and OS was also estimated using Kaplan-Meier survival curves comparing patients above and below the defined thresholds using the log-rank test (Figure 1A-D). The CTC thresholds were used in Cox hazards regression analysis along with the other clinical variables. The median PFS for PanNET with less <1 CTC was 17.6 months and 6 months in patients with ≥ 1 CTC (HR 2.92, 95% CI 1.79-4.78, p<0.0001)(Figure 1A). For midgut NET, the median PFS was 44.4 months in patients with <2 CTCs, whilst for those with ≥ 2 it was 7.3 months (HR 3.8, 95% CI 2.4-6.01, p<0.0001) (Figure 1B). The univariate and multivariate Cox hazards ratios are summarised for PanNET and midgut NET in table 4. In the multivariate analysis for PanNET, grade 3 and

CTC ≥1 was associated with a significantly worse PFS consistent with the findings for 12 month PFS. Similarly, for midgut NET, CgA elevated beyond 5 X ULN and the presence of ≥ 2 CTCs were associated with significantly worse PFS. The univariate and multivariate Cox hazards ratios for OS are summarised in table 5. The median OS for PanNET with <1 CTC was not reached, compared to 19.2 months for patients with ≥ 1 CTC (HR 3.31, 95% CI 1.87-5.8, p<0.0001) (Figure 1C). Grade 3 and CTC ≥ 1 were significant in multivariate analysis. In midgut NET, the median OS above for patients with ≥2 CTCs was 24.5 months opposed to 77.7 months for those with <2 (HR 3.08, 95% CI 1. 1.9-5, p<0.0001)(Figure 1D). In multivariate analysis CgA >5 x ULN and CTC ≥ 2 were significant.

**Discussion**

The value of CTCs as a prognostic marker in NETs was initially demonstrated in a mixed population of primary tumours (Khan *et al*, 2013). However, a consensus paper on biomarkers in NET, by a panel of international experts concluded that further studies were needed to confirm whether CTCs correlated with prognosis (Oberg *et al*, 2015). To our knowledge, this study represents the largest prospective biomarker study published to date in pancreatic and midgut NET. It also benefits from longer follow-up compared to previously published studies providing robust survival data.

In this study, we have defined the optimal prognostic threshold for PanNET and midgut NET as ≥1 and ≥2 CTCs respectively. Reassuringly the same thresholds were derived using both 12 month PFS and 36 month OS. Applying these thresholds in both logistic regression analysis and Cox hazards regression analysis, we have demonstrated a consistent relationship between CTCs and both PFS and OS. For PanNET, the presence ≥1 CTC is associated with an OR of 6.69 and 2.87 for 12 month PFS and 36 month OS respectively, whilst for midgut

NET the presence of ≥2 CTCs is associated with OR of 5.88 and 5.09 respectively. The Cox hazards ratios for PFS and OS was also significant in univariate analysis for both PanNET and Midgut NET. Significance was maintained in multivariate analysis with the exception of OS for midgut NET which narrowly missed significance (p=0.06). Grade was also an independent prognostic factor as has been widely reported but was more consistent for grade 3 tumours in PanNET. By contrast, CgA levels were not prognostic for PanNET but were informative in midgut NET when elevated 5x ULN or more.

Since the original study by Khan et al (Khan *et al*, 2013), a few smaller prospective studies have evaluated CTCs as prognostic markers in NETs. A phase II study evaluating the effect of pazopanib, a multi-targeted vascular endothelial growth factor and platelet derived growth factor receptor antagonist, in GEP-NETS included measurement of CTCs at baseline. They demonstrated that patients with no CTCs at baseline had a better response and longer PFS compared to those with one CTC or more (Grande *et al*, 2015). However the study did not meet statistical significance and this may be because of the small and heterogeneous patient population. A further prospective study by Khan et al sought to investigate whether changes in CTC count in response to therapy could predict response and overall survival. It was found that patients with no CTCs at baseline or at first follow-up sample had the best OS followed by those that had a more than 50% reduction CTC. Patients that had less than a 50% decrease in CTC count, or an increase, had the worst survival (Khan *et al*, 2016). Molecular characterisation of CTCs in NETs has also been explored and the expression of somatostatin receptors (SSTR) 2 and 5 has been demonstrated on CTCs enriched by CellSearch (Childs *et al*, 2016). The expression of CXCR4 on NET CTCs has also been reported along with observation that bone metastasis were strongly associated with the presence of CTCs (Rizzo *et al*, 2019).

The majority of studies published on the use of CTCs as a prognostic marker in cancer have used the CellSearch platform and it remains the only FDA approved technology for CTC enumeration. There are many other technologies that have been utilised for isolation and detection of CTCs but these studies are limited by the lack of reproducibility, poor correlation with clinical outcome and cost.

Our study also demonstrated that CgA is an independent prognostic biomarker in midgut NET. However, this is only the case for levels at least 5 x ULN which was the case in around 44% midgut patients. For PanNET there was no evidence that CgA had prognostic utility. More recently, the NETest has been developed and evaluated in a number of studies. NETest measures the expression of 51 genes associated with development of neoplasia using RT-PCR to develop a multi-gene signature from peripheral blood (Modlin *et al*, 2015). By matching circulating transcripts with tissue transcripts, 30 of the 51 genes were classified into 9 clusters, and by determining expression across these 9 clusters a score between 0-100% has been derived that can differentiate between stable disease and progressive disease (Kidd *et al*, 2015). A meta-analysis of heterogeneous studies suggest that the NETest may differentiate stable from progressive disease (Oberg *et al*, 2020) but larger prospective studies in well-defined populations are required to define the role of the NETest as an independent prognostic marker.

Circulating microRNAs (miRNA) have been investigated as potential markers of tumour behaviour that can be measured in patient blood samples. In neuroendocrine tumours, 31 candidate miRNAS were found to be similarly expressed in tissue and serum from patents with midgut NET. High circulating levels of miR-22-3p, miR-21-5p and low levels of miR-150-5p when combined predicted worse OS (HR 0.47, $p < 0.002$) (Bowden *et al*, 2017) . The majority of studies to date have evaluated miRNA in tissue samples and although there has been some correlation with tumour response, expression has been reported to be often only

weakly associated with circulating levels (Oberg *et al*, 2015). Currently, based on the published data, circulating miRNA has not been validated as a biomarker in NETS. In conclusion, CTCs enumerated by CellSearch, represent a robust biomarker that can be used to predict outcome in pancreatic and midgut NET. Here, we have defined the prognostic threshold for CTCs in PanNET and midgut NET which allows clinicians to stratify patients in clinical practice or in the context of clinical trials. The technological advances in single-cell sequencing is now being applied to CTCs to extend their utility as liquid biopsies. This is expected to shed new light on tumour evolution and the biology of metastasis (Malihi *et al*, 2020).

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## Data availability

Some or all data generated or analyzed during this study are included in this published article or in the data repositories listed in References

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**Figures**

Figure 1. A-D. Kaplan- Meier survival curves.1A. Progression free survival (PFS) for PanNETs above and below CTC threshold. 1B. PFS for Midgut NETs. 1C.Overall survival (OS) for PanNETs. 1D. OS for Midgut NETs

Tables

| | PanNET n=90 | Midgut NET n = 109 | p value |
|---|---|---|---|
| Age at diagnosis median (range) | 54(23-78) | 51 (30-83) | 0.67 |
| Age at time of sample | 62 (23-89) | 63 (40- 85) | 0.52 |
| < 55 | 34 | 31 | |
| 55-65 | 27 | 30 | |
| >65 | 29 | 48 | |
| Sex male/ female | 46/44 | 59/40 | 0.41 |
| Grade 1 | 28 | 68 | <0.05 |
| Grade 2 | 46 | 38 | 0.36 |
| Grade 3 | 16 | 3 | <0.05 |
| Liver disease <25% | 37 | 47 | 0.88 |
| 25% - 50% | 21 | 42 | <0.05 |
| 50-75% | 20 | 15 | 0.14 |
| >75% | 12 | 5 | <0.05 |
| No. of extrahepatic sites | | | |
| 1 | 13 | 5 | <0.05 |
| 2 | 29 | 34 | 0.88 |
| 3 or more | 48 | 70 | <0.05 |
| Bone metastases | 19 | 23 | 0.98 |
| No Bone metastases | 71 | 86 | |
| CgA < 3 x ULN | 59 | 47 | <0.05 |
| >3xULN - <x5ULN | 12 | 14 | 0.99 |
| >5 x ULN - < 10 X ULN | 10 | 19 | 0.23 |
| > 10 XULN | 9 | 29 | <0.05 |
| CTC = 0 | 60 | 53 | <0.05 |
| CTC ≥ 1 | 30 | 56 | <0.05 |
| CTC ≥ 2 | 18 | 48 | <0.05 |
| Median Length of follow-up months (range) | 84(1-198) | 72 (4 – 324) | 0.18 |
| Previous Treatment | | | |
| SST | 42 | 78 | <0.05 |
| Chemotherapy | 46 | 15 | <0.01 |
| PRRT | 10 | 45 | <0.01 |
| TAE | 5 | 10 | 0.31 |
| IFN | 6 | 15 | <0.05 |
| Sunitinib | 3 | 0 | |
| Everolimus | 1 | 0 | |
| Liver resection | 7 | 6 | 0.51 |
| Resection of Primary | 28/90 (31%) | 55/109 (50%) | 0.12 |

Table 1. Demographics and clinic-pathological characteristics of all pancreatic and midgut NET. SST – somatostatin analogues. PRRT –peptide receptor radio targeted therapy. TAE – Transarterial embolization. IFN – interferon.

| | PanNET | | | Midgut NET | | |
|---|---|---|---|---|---|---|
| Univariate analysis | OR | CI | p value | OR | CI | p value |
| Age < 55 | 1.00 | | | 1.00 | | |
| 55-65 | 1.04 | 0.38-2.87 | 0.933 | 2.08 | 0.65-6.72 | 0.219 |
| >65 | 1.59 | 0.59-4.33 | 0.361 | 4.53 | 1.58-13 | 0.005 |
| Male | 1.00 | | | 1.00 | | |
| Female | 0.59 | 0.25-1.35 | 0.210 | 1.93 | 0.87-4.31 | 0.107 |
| Grade 1 | 1.00 | | | 1.00 | | |
| Grade 2 | 1.12 | 0.43-2.89 | 0.815 | 2.84 | 1.22-6.62 | 0.016 |
| Grade 3 | 5.78 | 1.34-24.92 | 0.019 | 2.36 | 0.14-39.5 | 0.549 |
| Liver disease < 25% | 1.00 | | | 1.00 | | |
| 25-50% | 1.49 | 0.51-4.41 | 0.468 | 3.84 | 1.49-9.88 | 0.005 |
| 50-75% | 4.93 | 1.47-16.54 | 0.010 | 4.83 | 1.39-16.8 | 0.013 |
| >75% | 2.30 | 0.61-8.66 | 0.218 | 16.89 | 1.68-169 | 0.016 |
| Extrahepatic sites | | | | | | |
| 1 | 1.00 | | | 1.00 | | |
| 2 | 1.13 | 0.3-4.31 | 0.859 | 2.31 | 0.98-5.45 | 0.057 |
| 3 or more | 2.44 | 0.69-8.59 | 0.164 | 2.89 | 0.71-8.2 | 0.14 |
| No bone mets | 1.00 | | | 1.00 | | |
| Bone mets | 3.41 | 1.11-10.49 | 0.032 | 2.14 | 0.84-5.45 | 0.109 |
| CgA <3x ULN | 1.00 | | | 1.00 | | |
| 3-5x ULN | 1.66 | 0.47-5.83 | 0.430 | 1.69 | 0.43-6.64 | 0.453 |
| 5-10x ULN | 2.77 | 0.65-11.75 | 0.168 | 7.24 | 2.22-23.6 | 0.001 |
| 10x ULN | 1.48 | 0.36-6.07 | 0.585 | 5.20 | 1.85-14.5 | 0.002 |
| No primary resection | 1.00 | | | 1.00 | | |
| Resection | 0.35 | 0.14-0.9 | 0.030 | 0.48 | 0.22-1.05 | 0.066 |
| CTC < threshold | 1.00 | | | 1.00 | | |
| CTC ≥1 | 5.29 | 1.96-14.27 | 0.001 | - | - | - |
| CTC ≥2 | - | - | - | 9.30 | 3.78-22.9 | <0.0001 |
| Multivariate analysis | | | | | | |
| Grade 1 | 1.00 | | | 1.00 | | |
| Grade 2 | 1.22 | 0.34-4.46 | 0.759 | 4.20 | 1.14-15.52 | 0.031 |
| Grade 3 | 10.16 | 1.33-77.83 | 0.026 | 5.47 | 0.13-225.8 | 0.371 |
| Liver < 25% | 1.00 | | | 1.00 | | |
| 25-50% | 0.69 | 0.11-4.24 | 0.688 | 1.86 | 0.51-6.78 | 0.348 |
| 50-75% | 3.30 | 0.52-20.89 | 0.204 | 1.65 | 0.3-9.2 | 0.567 |
| >75% | 0.97 | 0.14-6.66 | 0.976 | 4.86 | 0.3-78.77 | 0.266 |
| No bone mets | 1.00 | | | 1.00 | | |
| Bone mets | 3.82 | 0.69-21.07 | 0.124 | 2.31 | 0.55-9.77 | 0.254 |
| CgA <3x ULN | 1.00 | | | 1.00 | | |
| 3-5x ULN | 2.12 | 0.36-12.54 | 0.407 | 0.96 | 0.14-6.34 | 0.964 |
| 5-10x ULN | 2.09 | 0.34-12.71 | 0.424 | 3.79 | 0.78-18.38 | 0.098 |
| 10x ULN | 0.34 | 0.04-2.64 | 0.304 | 5.72 | 1.36-24.08 | 0.017 |
| No primary resection | 1.00 | | | 1.00 | | |
| Resection | 0.24 | 0.05-1.08 | 0.064 | 0.79 | 0.27-2.3 | 0.665 |
| CTC < threshold | 1.00 | | | 1.00 | | |
| CTC ≥1 | 6.69 | 1.56-28.69 | 0.01 | - | - | - |
| CTC ≥2 | - | - | | 5.88 | 1.82-19.01 | 0.003 |

Table 2. Summary of univariate and multivariate logistic regression analysis for progression at 12 months from time of sampling for PanNET and midgut NET.

| | PanNET | | | Midgut NET | | |
|---|---|---|---|---|---|---|
| Univariate analysis | OR | CI | p value | OR | CI text | P value |
| Age < 55 | 1.00 | | | 1.00 | | |
| 55-65 | 0.63 | 0.22-1.81 | 0.393 | 3.43 | 1.14-10.35 | 0.029 |
| >65 | 1.56 | 0.58-4.22 | 0.383 | 2.67 | 0.96-7.37 | 0.059 |
| Male | 1.00 | | | 1.00 | | |
| Female | 0.47 | 0.2-1.1 | 0.083 | 1.22 | 0.55-2.7 | 0.620 |
| Grade 1 | 1.00 | | | 1.00 | | |
| Grade 2 | 0.82 | 0.31-2.18 | 0.696 | 1.74 | 0.76-4 | 0.194 |
| Grade 3 | 6.70 | 1.54-29.03 | 0.011 | 1.85 | 0.11-30.74 | 0.669 |
| Liver < 25% | 1.00 | | | 1.00 | | |
| 25-50% | 3.99 | 1.25-12.72 | 0.019 | 2.98 | 1.2-7.37 | 0.018 |
| 59-75% | 10.87 | 3.03-39.09 | 0.0003 | 3.74 | 1.11-12.65 | 0.034 |
| >75% | 3.62 | 0.92-14.35 | 0.067 | 13.09 | 1.32-129.6 | 0.028 |
| 1 extrahepatic site | 1.00 | | | 1.00 | | |
| 2 | 2.04 | 0.46-9.06 | 0.350 | 1.91 | 0.19-19.2 | 0.581 |
| 3 | 3.94 | 0.96-16.13 | 0.057 | 3.18 | 0.34-29.91 | 0.312 |
| No bone mets | 1.00 | | | 1.00 | | |
| Bone mets | 1.99 | 0.71-5.56 | 0.188 | 0.98 | 0.38-2.52 | 0.972 |
| CgA <3x ULN | 1.00 | | | 1.00 | | |
| 3-5x ULN | 2.19 | 0.62-7.74 | 0.223 | 3.17 | 0.88-11.43 | 0.078 |
| 5-10x ULN | 1.57 | 0.41-6.01 | 0.514 | 7.24 | 2.22-23.6 | 0.001 |
| 10x ULN | 1.96 | 0.48-8.05 | 0.353 | 5.20 | 1.85-14.57 | 0.002 |
| No primary resection | 1.00 | | | 1.00 | 0.22-1.05 | 0.067 |
| Resection | 0.41 | 0.16-1.07 | 0.068 | 0.48 | | |
| CTC < threshold | 1.00 | | | 1.00 | | |
| CTC ≥1 | 4.00 | 1.58-10.13 | 0.003 | - | - | - |
| CTC ≥2 | - | - | - | 6.15 | 2.64-14.35 | <0.0001 |
| Multivariate analysis | | | | | | |
| Grade 1 | 1.00 | | | 1.00 | | |
| Grade 2 | 0.53 | 0.13-2.11 | 0.365 | 0.78 | 0.25-2.4 | 0.663 |
| Grade 3 | 5.10 | 0.79-32.74 | 0.086 | 2.26 | 0.07-73.5 | 0.646 |
| Liver < 25% | 1.00 | | | 1.00 | | |
| 25-50% | 3.77 | 0.61-23.24 | 0.152 | 1.15 | 0.36-3.66 | 0.810 |
| 59-75% | 14.30 | 1.98-103.17 | 0.008 | 1.27 | 0.25-6.36 | 0.771 |
| >75% | 3.08 | 0.37-25.58 | 0.298 | 3.45 | 0.16-76.56 | 0.433 |
| No bone mets | 1.00 | | | 1.00 | | |
| Bone mets | 2.18 | 0.45-10.63 | 0.335 | 0.46 | 0.12-1.71 | 0.244 |
| CgA <3x ULN | 1.00 | | | 1.00 | | |
| 3-5x ULN | 1.78 | 0.32-10.03 | 0.513 | 2.35 | 0.47-11.7 | 0.298 |
| 5-10x ULN | 1.10 | 0.16-7.47 | 0.923 | 6.50 | 1.57-26.9 | 0.010 |
| 10x ULN | 0.43 | 0.06-3.25 | 0.410 | 6.26 | 1.67-23.4 | 0.006 |
| No primary resection | 1.00 | | | 1.00 | | |
| Resection | 0.80 | 0.17-3.81 | 0.776 | 0.63 | 0.24-1.64 | 0.343 |
| CTC < threshold | 1.00 | | | 1.00 | | |
| CTC ≥1 | 2.87 | 1.74-11.1 | 0.026 | - | - | - |
| CTC ≥2 | - | - | - | 5.09 | 1.65-15.7 | 0.005 |

Table 3. Summary of univariate and multivariate logistic regression analysis for prediction of death at 36 months from time of sampling for PanNET and midgut NET

| | PanNET | | | Midgut NET | | |
|---|---|---|---|---|---|---|
| Univariate analysis | HR | CI | P value | HR | CI | P value |
| Age < 55 | 1.00 | | | 1.00 | | |
| 55-65 | 1.17 | 0.67-2.04 | 0.574 | 1.39 | 0.76-2.53 | 0.285 |
| >65 | 0.96 | 0.55-1.67 | 0.873 | 1.79 | 1.04-3.09 | 0.037 |
| Male | 1.00 | | | 1.00 | | |
| Female | 0.51 | 0.32-0.82 | 0.006 | 1.29 | 0.83-2.02 | 0.264 |
| Grade 1 | 1.00 | | | 1.00 | | |
| Grade 2 | 1.10 | 0.64-1.88 | 0.737 | 2.17 | 1.35-3.48 | 0.001 |
| Grade 3 | 3.22 | 1.67-6.2 | 0.0005 | 2.50 | 0.6-10.35 | 0.207 |
| Liver < 25% | 1.00 | | | 1.00 | | |
| 25-50% | 1.73 | 0.94-3.17 | 0.079 | 2.61 | 1.57-4.33 | 0.0002 |
| 59-75% | 2.75 | 1.48-5.11 | 0.001 | 2.62 | 1.32-5.2 | 0.006 |
| >75% | 3.00 | 1.48-6.09 | 0.002 | 5.71 | 2.15-15.19 | 0.0005 |
| 1 extrahepatic site | 1.00 | | | 1.00 | | |
| 2 | 1.22 | 0.59-2.51 | 0.586 | 1.47 | 0.44-4.95 | 0.530 |
| 3 | 1.40 | 0.72-2.75 | 0.321 | 2.53 | 0.79-8.11 | 0.118 |
| No bone mets | 1.00 | | | 1.00 | | |
| Bone mets | 1.67 | 0.96-2.89 | 0.067 | 1.35 | 0.81-2.26 | 0.253 |
| CgA <3x ULN | 1.00 | | | 1.00 | | |
| 3-5x ULN | 1.48 | 0.74-2.94 | 0.270 | 1.68 | 0.84-3.39 | 0.145 |
| 5-10x ULN | 2.00 | 1-4.03 | 0.051 | 2.92 | 1.57-5.41 | 0.001 |
| 10x ULN | 2.49 | 1.2-5.19 | 0.014 | 2.83 | 1.63-4.9 | 0.0002 |
| No primary resection | 1.00 | | | 1.00 | | |
| Resection | 0.47 | 0.27-0.82 | 0.007 | 0.64 | 0.41-0.99 | 0.046 |
| CTC<threshold | 1.00 | | | 1.00 | | |
| CTC ≥1 | 2.92 | 1.79-4.78 | <0.0001 | - | - | - |
| CTC ≥2 | - | - | - | 3.80 | 2.4-6.01 | <0.0001 |
| Multivariate analysis | | | | | | |
| Grade 1 | 1.00 | | | 1.00 | | |
| Grade 2 | 1.26 | 0.66-2.4 | 0.490 | 2.18 | 1.26-3.76 | 0.005 |
| Grade 3 | 3.02 | 1.41-6.46 | 0.004 | 5.44 | 1.11-26.76 | 0.037 |
| Liver < 25% | 1.00 | | | 1.00 | | |
| 25-50% | 1.22 | 0.58-2.57 | 0.591 | 1.78 | 0.98-3.23 | 0.060 |
| 59-75% | 1.82 | 0.87-3.8 | 0.112 | 1.84 | 0.85-3.96 | 0.121 |
| >75% | 1.58 | 0.64-3.9 | 0.319 | 2.74 | 0.86-8.67 | 0.087 |
| No bone mets | 1.00 | | | 1.00 | | |
| Bone mets | 1.04 | 0.5-2.14 | 0.919 | 1.19 | 0.64-2.2 | 0.586 |
| CgA <3x ULN | 1.00 | | | 1.00 | | |
| 3-5x ULN | 2.05 | 0.95-4.42 | 0.068 | 1.33 | 0.6-2.97 | 0.482 |
| 5-10x ULN | 1.49 | 0.65-3.41 | 0.350 | 2.13 | 1.03-4.4 | 0.041 |
| 10x ULN | 2.02 | 0.85-4.82 | 0.112 | 2.49 | 1.27-4.91 | 0.008 |
| No primary resection | 1.00 | | | 1.00 | | |
| Resection | 0.56 | 0.27-1.15 | 0.114 | 0.89 | 0.56-1.43 | 0.642 |
| CTC < threshold | 1.00 | | | 1.00 | | |
| CTC ≥1 | 2.60 | 1.37-4.9 | 0.003 | - | - | - |
| CTC ≥2 | - | - | - | 2.25 | 1.32-3.84 | 0.003 |

Table 4. Summary of univariate and multivariate Cox hazards ratios for progression free survival (PFS) for PanNET and midgut NET.

| | PanNET | | | Midgut NET | | |
|---|---|---|---|---|---|---|
| Univariate analysis | HR | CI | P value | HR | CI | P value |
| Age < 55 | 1.00 | | | 1.00 | | |
| 55-65 | 0.57 | 0.27-1.19 | 0.136 | 1.90 | 0.99-3.66 | 0.054 |
| >65 | 1.00 | 0.53-1.92 | 0.989 | 1.89 | 1.03-3.46 | 0.039 |
| Male | 1.00 | | | 1.00 | | |
| Female | 0.51 | 0.28-0.93 | 0.027 | 1.19 | 0.73-1.92 | 0.484 |
| Grade 1 | 1.00 | | | 1.00 | | |
| Grade 2 | 1.08 | 0.54-2.17 | 0.832 | 1.52 | 0.92-2.5 | 0.101 |
| Grade 3 | 4.90 | 2.24-10.7 | <0.0001 | 0.80 | 0.11-5.87 | 0.830 |
| Liver < 25% | 1.00 | | | 1.00 | | |
| 25-50% | 2.66 | 1.19-5.93 | 0.017 | 2.15 | 1.25-3.7 | 0.006 |
| 50-75% | 4.09 | 1.88-8.92 | 0.0004 | 2.29 | 1.09-4.83 | 0.029 |
| >75% | 3.22 | 1.35-7.67 | 0.008 | 6.40 | 2.37-17.3 | 0.0003 |
| 1 extrahepatic site | 1.00 | | | 1.00 | | |
| 2 | 1.44 | 0.55-3.78 | 0.457 | 0.80 | 0.23-2.79 | 0.727 |
| 3 | 2.41 | 0.97-5.99 | 0.059 | 1.96 | 0.61-6.3 | 0.258 |
| No bone mets | 1.00 | | | 1.00 | | |
| Bone mets | 1.59 | 0.84-3 | 0.158 | 1.48 | 0.85-2.57 | 0.162 |
| CgA <3x ULN | 1.00 | | | 1.00 | | |
| 3-5x ULN | 2.24 | 1-5.03 | 0.049 | 1.55 | 0.72-3.36 | 0.263 |
| 5-10x ULN | 1.71 | 0.74-3.93 | 0.206 | 3.24 | 1.67-6.28 | 0.0005 |
| 10x ULN | 2.17 | 0.89-5.29 | 0.087 | 2.78 | 1.53-5.05 | 0.001 |
| No primary resection | 1.00 | | | 1.00 | | |
| Resection | 0.48 | 0.24-0.96 | 0.038 | 0.60 | 0.37-0.97 | 0.037 |
| CTC< threshold | 1.00 | | | 1.00 | | |
| CTC ≥1 | 3.31 | 1.87-5.85 | <0.0001 | - | - | - |
| CTC ≥2 | - | - | - | 3.08 | 1.9-5 | <0.0001 |
| Multivariate analysis | | | | | | |
| Grade 1 | 1.00 | | | 1.00 | | |
| Grade 2 | 0.63 | 0.25-1.58 | 0.325 | 1.23 | 0.7-2.16 | 0.478 |
| Grade 3 | 4.88 | 1.89-12.6 | 0.001 | 1.08 | 0.13-8.75 | 0.939 |
| Liver < 25% | 1.00 | | | 1.00 | | |
| 25-50% | 1.25 | 0.43-3.67 | 0.685 | 1.43 | 0.77-2.68 | 0.261 |
| 50-75% | 3.30 | 1.19-9.11 | 0.022 | 1.51 | 0.65-3.49 | 0.336 |
| >75% | 2.46 | 0.71-8.59 | 0.157 | 2.92 | 0.95-9.23 | 0.06 |
| No bone mets | 1.00 | | | 1.00 | | |
| Bone mets | 0.87 | 0.38-2 | 0.751 | 1.10 | 0.57-2.13 | 0.783 |
| CgA <3x ULN | 1.00 | | | 1.00 | | |
| 3-5x ULN | 4.17 | 1.44-12.1 | 0.008 | 1.25 | 0.53-2.95 | 0.616 |
| 5-10x ULN | 1.20 | 0.4-3.59 | 0.740 | 3.03 | 1.43-6.44 | 0.004 |
| 10x ULN | 1.21 | 0.41-3.62 | 0.729 | 2.02 | 0.97-4.24 | 0.062 |
| No primary resection | 1.00 | | | 1.00 | | |
| Resection | 0.91 | 0.35-2.36 | 0.850 | 0.84 | 0.5-1.41 | 0.502 |
| CTC<threshold | 1.00 | | | 1.00 | | |
| CTC ≥1 | 3.16 | 1.46-6.81 | 0.003 | - | - | - |
| CTC ≥2 | - | - | - | 1.73 | 0.96-3.13 | 0.06 |

Table 5. Summary of univariate and multivariate Cox hazards ratios for overall survival (OS) for PanNET and midgut NET.

Figure