High Grade Gastroenteropancreatic Neuroendocrine Neoplasms and Improved Prognostic Stratification with the New World Health Organization 2019 Classification: A Validation Study from a Single-Institution Retrospective Analysis

Running title: High Grade GEP NEN and the WHO Classification

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ABSTRACT

Objectives

There is a pressing need to develop clinical management pathways for grade 3 (G3) gastroenteropancreatic neuroendocrine neoplasms (GEP NEN).

Methods

We performed a retrospective study in patients with metastatic G3 GEP NEN. The relationship between baseline characteristics and progression-free and overall survival was analyzed using the Kaplan-Meier method. Univariate and multivariate analyses were performed using the Cox proportional hazards model.

Results

We included 142 patients (74 well-differentiated neuroendocrine tumors [WDNET], 68 poorly differentiated neuroendocrine carcinomas [PDNEC]). There was a survival benefit in patients with WDNET compared to PDNEC (median 24 vs. 15 months, hazard ratio, 0.46; 95% confidence interval, 0.31-0.86; *P* = 0.0001) which persisted in both pancreatic and non-pancreatic cohorts. Well-differentiated morphology, Ki-67 <50% and positive somatostatin receptor imaging were independently associated with prolonged survival. Of the subgroup treated with first-line platinum-based chemotherapy, response rates were favorable (partial response 47%, stable disease 30%); there was no significant difference in response rates nor progression-free survival between WDNET and PDNEC despite significantly prolonged overall survival in the WDNET cohort.

Conclusions

Our study corroborates the knowledge of two prognostically distinct subgroups within the World Health Organization 2019 G3 GEP NEN population, observed in both pancreatic and non-pancreatic gastrointestinal cohorts. Definitive management pathways are needed to reflect the differences between G3 WDNET and PDNEC.

Key Words: Gastroenteropancreatic, neuroendocrine tumor, neuroendocrine carcinoma, WHO classification, high grade, grade 3

INTRODUCTION

Gastroenteropancreatic (GEP) neuroendocrine neoplasms (NEN) are classified based on morphology and proliferation index. According to the World Health Organization (WHO) 2010 classification,[1] GEP NEN are defined as either well-differentiated and low or intermediate grade (G1 and G2) or poorly differentiated and high grade (G3, large cell or small cell type). All high grade neuroendocrine neoplasms are defined by a mitotic count >20 per 10 high-power fields (2.0 mm^2) and/or Ki-67 >20%. Nevertheless, not all G3 GEP NEN have morphology that is poorly differentiated leading to potential limitations of the WHO 2010 classification. There are little published data on G3 well-differentiated neuroendocrine tumors (WDNET); however, they are estimated to represent 15-20% of G3 GEP NEN, most frequently originate from the pancreas and have better survival compared to poorly differentiated neuroendocrine carcinomas (PDNEC).[2] Recently, the WHO defined a new classification for G3 NEN of pancreatic origin: G3a for G3 WDNET and G3b for PDNEC.[3] In October 2019, this new classification for G3 NEN was formally endorsed by the WHO for the entire gastrointestinal tract and hepatobiliary system.[4]

There are lack of quality data regarding high grade GEP NEN, but emerging studies indicate heterogenous biological behavior, likely influenced by primary site of origin, morphology, proliferation indices and molecular alterations.[2,5–7] In a retrospective study, a separation of the grade 3 population based on the proliferation index (Ki-67 >55%) has been shown to have a significant impact on response to treatment, as well as prognosis.[8] Higher objective response rates to platinum-based chemotherapy were seen in the population with Ki-67 ≥55% compared with those with Ki-67 21-55% (42% vs. 15% respectively, $P < 0.001$), albeit with poorer overall survival (median 10 vs. 14

months, $P < 0.001$). Further retrospective studies support the concept of two prognostically distinct subgroups within the G3 GEP NEN population determined by Ki-67 and morphology.[9–12]

There is no clear consensus on which molecular markers should be used to distinguish G3 WDNET and PDNEC however genetic sequencing studies suggest they should be considered distinct neoplastic entities. Studies have identified alterations in p53 and Rb expression in PDNEC which were not present in WDNET, and these may have a clinical impact in the future.[7,10,13] In addition, mutually exclusive inactivating mutations of *DAXX* and *ATRX*, a frequent molecular abnormality found in pancreatic WDNET, have not been observed in PDNEC.[10,14–16] *DAXX* and *ATRX* loss are associated with shorter progression-free and overall survival in patients with pancreatic WDNET[17] and more research on the prognostic or predictive effects of molecular alterations in the G3 GEP NEN population is needed.

There is a pressing need to develop clinical management pathways in the G3 GEP NEN population. In this study, our aim was to investigate the determinants of survival and response to treatment in both G3 WDNET and PDNEC of GEP origin and to validate the new WHO 2019 classification system.[4]

METHODS

Population

Patients with histologically confirmed, metastatic G3 GEP NEN or unknown primary suggestive of GEP origin, were retrospectively identified from our institution database between January 2005 and December 2018. All histology was reviewed by an

experienced NET histopathologist and re-classified according to the WHO 2019 classification of G3 GEP NEN.[4] Mixed neuroendocrine non-neuroendocrine neoplasms (i.e. MiNEN) were excluded. Data collected comprised demographics (sex, age at diagnosis, date of histological diagnosis), tumor characteristics (primary site of origin, presence of hepatic metastases), pathology (morphology, proliferative indices, immunohistochemistry), imaging (computed tomography [CT] or magnetic resonance imaging [MRI], somatostatin receptor imaging [SSRI] including ^{68}Gallium [^{68}Ga]-DOTATATE positron emission tomography [PET] or octreotide scan and ^{18}F-fluorodeoxyglucose FDG [^{18}F-FDG] PET) and treatment (first-line therapy, treatment outcomes). SSRI positivity was defined as octreotide scan or ^{68}Ga-DOTATATE PET avidity above background liver and ^{18}F-FDG positivity was defined as disease avidity above the background mediastinal blood pool. This study was registered with the Quality Governance and Clinical Audit Committee of the Royal Free Hospital NHS Foundation Trust.

Treatment and assessment

Patients that received platinum-based chemotherapy in the first-line setting were analyzed separately. The regimens included cisplatin or carboplatin and etoposide, FCarboStrep (5-fluorouracil 500 mg/m^2, folinic acid 45 mg, carboplatin AUC 5, streptozocin 1000 mg/m^2) or FCiSt[18] (5-fluorouracil 500 mg/m^2, folinic acid 45 mg, cisplatin 70 mg/m^2, streptozocin 1000 mg/m^2) administered every 21 days. Patients who had concurrent external beam radiotherapy or chemotherapy in the adjuvant or neoadjuvant setting were not included. Patients were followed up and reviewed for disease progression and survival every 3 months. Tumor assessment was performed with contrast-enhanced computed tomography (CT) or magnetic resonance imaging

(MRI) at baseline and then every 3 months. Radiological response was assessed in the multidisciplinary tumor board according to RECIST version 1.1.[19]

Statistical analysis

Categorical variables were expressed as percentages and compared with the Fisher's exact test. Continuous variables were expressed as median and range and compared with the Mann Whitney U-test. Progression-free survival (PFS) and overall survival (OS) were estimated by the Kaplan-Meier method and comparison of curves was performed using the log-rank test. The continuous variables Ki-67 and age were analyzed in quartiles with cut-off points chosen in order to create four groups with approximately equal numbers of events or failures. Univariate and multivariate analyses were performed using the Cox proportional hazards model to determine the relationship between baseline characteristics and OS. Variables with a *P* value < 0.1 were included in the multivariate Cox model. Variables with high collinearity (e.g. morphology and Ki-67) were not included in the same regression model. Of the entire cohort, OS was calculated from the date of histological diagnosis to date of death. Survivors were censored at last date of known alive. In the subgroup that received first-line platinum-based chemotherapy, PFS was calculated from the date of cycle 1 chemotherapy to the date of first radiological disease progression. Patients without disease progression were censored at the date of last imaging assessment. OS was calculated in this subgroup from date of cycle 1 chemotherapy until death. A two-sided *P* value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC). Optimal Ki-67 cut-off points were explored using cut-off determinations in survival analysis using R software version 2.15.0 (R Foundation for Statistical Computing, Vienna, Austria).

This is an outcome-oriented method that provides a value of a cut-off point that corresponds to the most significant relationship with survival.[20]

RESULTS

Patients

One hundred and forty-two patients were included (74 WDNET, 68 PDNEC); their characteristics are summarized in Table 1. The majority of patients were male (63%). The median age at diagnosis was lower in the WDNET cohort as opposed to the PDNEC cohort (54 vs. 62 years, $P = 0.027$). Overall, the most frequent site of primary was pancreas (51%) followed by hindgut (11%), midgut (10%) and esophageal (8%). Site of primary was unknown in 13% of patients but this group had a distribution of disease and tumor immunostaining suggestive of gastrointestinal primary. The WDNET cohort had a significantly higher proportion of patients with tumors of pancreatic origin compared with the PDNEC cohort (64% vs. 37%, Table 1). The PDNEC cohort had a higher proportion of patients with tumors of non-pancreatic gastrointestinal origin, especially of esophageal and hindgut origin, compared to the WDNET cohort (54% vs. 19%, Table 1). As anticipated, the median Ki-67 in the WDNET cohort was significantly lower compared to that of the PDNEC cohort (30% [range, 21-70] vs. 70% [range, 21-95] respectively, $P < 0.0001$). In the WDNET cohort, there was a significantly higher incidence of SSRI positivity (80% vs. 39%) and lower incidence of ^{18}F-FDG avidity (59% vs. 89%), compared with the PDNEC cohort. However, SSRI and ^{18}F-FDG PET were not performed in 39% and 61% of patients, respectively.

Overall survival

After a median follow-up of 16 months (range, 3-62), 80% of patients had died. Of the entire cohort, there was prolonged survival in patients with WDNET compared to PDNEC (median OS 24 vs. 15 months, hazard ratio [HR], 0.46; 95% confidence interval [CI], 0.31-0.86; *P* = 0.0001, Fig. 1a). This was more marked in the cohort of patients with non-pancreatic gastrointestinal primary (median OS WDNET 36 months vs. PDNEC 15 months, HR, 0.38; 95% CI, 0.19-0.74; *P* = 0.005, Fig. 2a), as opposed to pancreatic primary (median OS WDNET 20 months vs. PDNEC 17 months, HR, 0.56; 95% CI, 0.32-0.99; *P* =0.039, Fig. 2b). Of the entire cohort, a cut-off point of 50% for Ki-67 was found to have the highest log-rank test statistic for OS (Ki-67 <50% vs. Ki-67 ≥50%; median OS 28 months vs. 15 months, HR, 0.46; 95% CI, 0.30-0.70; *P* = 0.0003, Fig. 1b). Variables that were associated with OS on univariate analysis included morphology, Ki-67, SSRI and ^{18}F-FDG PET characteristics (Table 2 and Fig. 1). There was a large proportion of patients that did not have SSRI or ^{18}F-FDG PET imaging performed, however we included these patients in the univariate model to minimize selection bias.

To further analyze the survival of patients with missing SSRI or ^{18}F-FDG PET data and to inform the appropriate multivariate model, we performed bivariate analyses including morphology and SSRI or ^{18}F-FDG PET. The WDNET population showed a clear survival benefit in patients with SSRI avidity compared with WDNET patients who did not have SSRI available (median 33 vs 14 months, HR, 0.31; 95% CI, 0.15-0.63; *P* = 0.001, Fig. 3). Furthermore, the patients with SSRI negativity had a similar median OS (15 months) compared with those patients who did not have SSRI available (14 months) (Fig. 3). The cohort of patients with WDNET and ^{18}F-FDG PET scans (27/74; 36%) however, was too small to allow further interpretation because of wide and

overlapping confidence intervals of the survival curves. Similarly, of the PDNEC population, the number of patients with SSRI (27/68; 40%) or ^{18}F-FDG PET (28/68; 41%) available were too small for further interpretation. It was concluded that ^{18}F-FDG PET was not a candidate variable for the multivariate model due to significant missing data.

For the multivariate model, we included SSRI, age, morphology and Ki-67; the latter two variables were handled separately given known collinearity. SSRI, morphology and Ki-67, but not age, remained independently associated with OS (Fig. 1 and Table 2).

Treatment and response evaluation

Fifty-nine patients with evaluable data received first-line therapy with platinum-based chemotherapy (33 WDNET, 27 PDNEC). The characteristics of this subgroup are summarized in Table 3. The WDNET cohort tended to be younger in age (median 51 vs. 64 years, P = 0.01) and included a higher proportion of patients with pancreatic primary compared with the PDNEC cohort (55% vs. 35% respectively). The WDNET cohort also had a higher proportion of patients with avid SSRI imaging (81% vs. 43%, Table 3), although the number of SSRI studies performed in this PDNEC subgroup was small (7/26). The majority of patients in both the WDNET (67%) and PDNEC (69%) cohorts received chemotherapy with FCarboStrep or FCiSt.

There was shorter PFS in patients with PDNEC compared with WDNET, but this did not attain statistical significance (median 5 vs. 7 months; log-rank P = 0.07) (Table 4). When the cohort was stratified by a Ki-67 cut-off point of 50% rather than morphology,

the median PFS estimates were similar to the WDNET and PDNEC cohorts respectively, but with greater separation of the curves leading to statistical significance (Ki-67 <50% PFS 5.5 months vs. Ki-67 ≥50% PFS 7 months; log-rank *P* = 0.003). Predictors of prolonged PFS on univariate analysis included Ki-67 <50% (*P* = 0.003) and SSRI positivity (*P* = 0.008) but not age, sex, morphology or site of primary. Similar to the entire cohort, patients with WDNET had a significantly longer OS compared with the PDNEC cohort (median 22 vs. 14 months; HR, 0.36; 95% CI, 0.19-0.68; *P* =0.002).

Radiological response was evaluable in 57 patients (33 WDNET, 24 PDNEC) (Table 4). Twenty-seven (47%) patients had a partial response, 17 (30%) patients had stable disease and 13 (23%) had progressive disease. Of the WDNET and PDNEC cohorts respectively, the rate of partial response (42% vs. 54%; *P* = 0.43) and progressive disease (18% vs. 29%; *P* = 0.36) were not statistically different. There was a trend towards a higher rate of stable disease in the WDNET group (39% vs. 17%; *P* = 0.08), however this did not attain statistical significance.

DISCUSSION

This retrospective study validates the knowledge of two prognostically distinct subgroups within the WHO 2017 pancreatic G3 NEN[3] and WHO 2019 G3 GEP NEN[4] populations. Similar to previous studies,[9,11,12] the WDNET cohort comprised tumors of predominantly pancreatic origin and demonstrated improved OS compared with the PDNEC cohort. The variables that were independently associated with OS included tumor morphology, Ki-67 and SSRI avidity. Although previous WHO classifications[1] for GEP NEN have placed more emphasis on the proliferative index to delineate G3 GEP NEN from G1 or G2, evolving evidence indicates that morphological

differentiation is also important.[9,11,12,21,22] Our study demonstrates a clear survival benefit in patients with WDNET compared to PDNEC (median 23 vs. 15 months, HR, 0.46; 95% CI, 0.31-0.86; *P* = 0.0001). Interestingly, this finding was more prominent in the cohort of patients with non-pancreatic gastrointestinal primary as opposed to pancreatic primary (Fig. 2), and this may reflect a more favorable inherent biology in well-differentiated G3 NET of midgut origin which constituted the majority of the non-pancreatic gastrointestinal WDNET population. Furthermore, 16% of patients with poorly differentiated morphology had a Ki-67 <50% and 7% of patients with well-differentiated morphology had a Ki-67 >50% indicating the hazard of interpreting proliferative indices in isolation. Nevertheless, a Ki-67 with a cut-off point of 50% was a strong predictor of OS, and proliferation index remains an important component of the prognostic algorithm.

Previous retrospective studies[10,21] have highlighted the inadequacy of relying on pure morphologic or proliferation rate criteria to distinguish between G3 WDNET and PDNEC. In a pathology study of 33 G3 pancreatic NEN[10] assessed at a specialist NET center, initial morphologic assessment was performed prior to immunohistochemical staining for surrogate biomarkers of known genotypes for WDNET (i.e. *DAXX* or *ATRX* loss) and PDNEC (i.e. p53 overexpression, Rb or *SMAD4* loss). In 20 (61%) of the 33 cases, three NET specialist pathologists were not able to agree on the morphological classification. Furthermore, of the confirmed WDNET cases, 35% had a Ki-67 >55% and of the confirmed PDNEC cases, 33% had a Ki-67 <55%.

New biomarkers are urgently needed to distinguish between G3 WDNET and PDNEC given the potential limitations of morphology and proliferation indices. Furthermore,

intra- and inter-tumor heterogeneity with regard to Ki-67 is well described in GEP NEN[23–25] which highlights the limitation of relying on a biopsy from a single site to predict disease behavior. In clinical practice, the complement of ^{68}Ga-DOTATATE and ^{18}F-FDG PET is increasingly being used in patients with suspected high grade disease to guide the most optimal site for biopsy (i.e. to sample the most aggressive site of disease). In our study, the G3 WDNET cohort had a higher incidence of SSRI positivity and a lower incidence of ^{18}F-FDG positivity compared with the PDNEC cohort. Moreover, SSRI positivity and ^{18}F-FDG negativity were both associated with prolonged OS on the univariate analysis and the concept of using SSRI and ^{18}F-FDG PET as prognostic biomarkers has been demonstrated in previous studies.[26–30] The complement of SSRI and ^{18}F-FDG PET may also potentially act as a biomarker to predict treatment response in the G3 NEN population and prospective studies are warranted. Our study showed a surprisingly high incidence of SSRI positivity, particularly in the G3 WDNET cohort (47/59, 80%), and peptide receptor radionuclide therapy (PRRT) may be a potential treatment option in select patients.[31]

Previous retrospective studies have demonstrated a relatively poor objective response rate to platinum/etoposide chemotherapy in the G3 WDNET cohort or G3 cohort with Ki-67 <55%, compared with PDNEC, despite improved survival.[8,9,11,32] In our study, the majority of patients treated with first-line chemotherapy received a 5-fluorouracil/platinum/streptozocin regimen. Overall, the best predictors of prolonged PFS included Ki-67 <50% and SSRI positivity. Objective response rates were relatively high in the G3 WDNET cohort and were not statistically different to the PDNEC population (partial response 42% vs. 54% respectively, P = 0.43). This may potentially be explained by the high proportion of tumors of pancreatic origin in the

WDNET cohort, as well as the majority of the population receiving streptozocin in their treatment schedule which has shown clear activity in well-differentiated pancreatic NET in previous studies.[33–37] Similar to the entire cohort, the WDNET population had prolonged OS compared with the PDNEC population (median 22 months vs. 14 months, log-rank $P = 0.008$). Prospective, randomized studies assessing the efficacy of alkylating agents, such as streptozocin or temozolomide, in the G3 WDNET population are warranted.

Particular strengths of our study include the review of histopathology by an expert NET pathologist and, thus far, the highest number of G3 WDNET patients studied in a single institution. The newly defined G3 WDNET cohort has little descriptive data in the current literature and we encourage other large NET centers to analyze the characteristics, treatment response and prognosis of this population. Our study also contributes knowledge of platinum/streptozocin-based chemotherapy in the G3 NEN cohort. The predominant limitations include its retrospective design and inherent biases including potential unmeasured confounders, the single-institution setting and the relatively small patient numbers, especially with complete SSRI and ^{18}F-FDG PET data, limiting the statistical power of the analyses. Prospective, multi-center studies are therefore needed to validate our findings. In addition, the median age of the WDNET cohort was statistically lower compared to that of the PDNEC cohort and this could have contributed to the finding of prolonged survival in the former group, however the findings were not materially affected in a multivariate survival analysis that included age as a covariate.

In conclusion, our study corroborates the knowledge of two prognostically distinct subgroups within the WHO 2019 G3 GEP NEN[4] population. This finding was not limited to G3 NEN of pancreatic origin but also demonstrated in NEN of non-pancreatic gastrointestinal origin, and this supports the adoption of the improved WHO 2017 pancreatic NEN classification[3] for the remaining gastrointestinal sites.[4] Further research is urgently needed to develop prognostic biomarkers and guide optimal treatment pathways for G3 WDNET versus PDNEC; this will require incorporation of tumor characteristics (morphological differentiation, Ki-67, primary site of origin), molecular imaging (SSRI and ^{18}F-FDG PET), as well as tumor molecular profiling.

Authors' contributions

Conception and design: ARH, DM; data collection: ARH, MF, RS, CR, GM; data analysis: ARH, HMD; drafting of the manuscript: ARH; result interpretation and critical revision of the manuscript: ARH, HMD, TVL, MEC, DK, CT, DM; final approval of the version to be published: all authors.

Ethics approval and consent to participate

This study was approved by the Quality Governance and Clinical Audit Committee of the Royal Free Hospital NHS Foundation Trust.

Consent for publication

Not applicable

Data availability

The data sets used and/or analyzed in the current study are available from the corresponding author on reasonable request.

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Conflict of interest

The authors have no conflicts of interest to declare with regards to this manuscript.

C. Toumpanakis reports advisory board and speaker honoraria from Ipsen, Novartis and AAA; outside the submitted work. He has received education grants from Ipsen, Novartis and AAA for the Royal Free NET unit.

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The remaining authors declare no competing interests.

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Figure legends

Figure 1. Kaplan-Meier plots for overall survival with patients stratified by A) morphology, B) Ki-67, C) SSRI avidity, and D) ^{18}F-FDG PET avidity.

NA not available

SSRI somatostatin receptor imaging

^{18}F-FDG PET, ^{18}F-fluorodeoxyglucose positron emission tomography

Figure 2. Kaplan-Meier plots for overall survival in patients with A) non-pancreatic gastrointestinal primary stratified by morphology and B) pancreatic primary stratified by morphology.

Figure 3. Kaplan-Meier plot for overall survival in patients with G3 well-differentiated neuroendocrine tumors stratified by SSRI avidity.

NA not available

SSRI somatostatin receptor imaging

Table 1. Patient Characteristics				
Characteristic	**All cases**	**WDNET**	**PDNEC**	***P***
Number	142	74	68	
Median age in years (range) at diagnosis	59 (13-89)	54 (13-81)	62 (15-89)	**0.027***
Sex, n (%)				0.86†
Male	89 (63)	45 (61)	44 (65)	
Female	53 (37)	29 (39)	24 (35)	
Site of Primary, n (%)				**<0.0001**‡
Pancreas	72 (51)	47 (64)	25 (37)	
Gastrointestinal	51 (36)	14 (19)	37 (54)	
Midgut	*14*	*9*	*5*	
Esophageal	*11*	*0*	*11*	
Gastric	*9*	*2*	*7*	
Ampullary	*2*	*1*	*1*	
Hindgut	*15*	*2*	*13*	
Unknown§	19 (13)	13 (18)	6 (9)	
Ki-67, median (range)	40% (21-95)	30% (21-70)	70% (21-95)	**<0.0001***
SSRI avidity, n (%)				**0.0005**†
Yes	58 (41)	47/59 (80)	11/28 (39)	
No	29 (20)	12/59 (20)	17/28 (61)	
Not available	55 (39)	15	40	
FDG PET avidity, n (%)				**0.014**†
Yes	41 (29)	16/27 (59)	25/28 (89)	
No	14 (10)	11/27 (41)	3/28 (11)	
Not available	87 (61)	47	40	

** Mann Whitney test; †Fisher's exact test; ‡Fisher-Freeman-Halton exact test; §tumor immunostaining and distribution of disease suggestive of gastrointestinal primary. WDNET, well-differentiated neuroendocrine tumor; PDNEC, poorly differentiated neuroendocrine carcinoma; SSRI, somatostatin receptor imaging; FDG PET, 18F-fluorodeoxyglucose positron emission tomography. Bold values denote statistical significance at the P < 0.05 level.*

Table 2. Univariate and Multivariate Analyses Assessing the Relationship Between Baseline Characteristics and Overall Survival					
Variable	**Univariate analysis**	**Multivariate Cox regression analysis**			
	Log-rank p value	**Model 1 HR (95% CI)**	***P***	**Model 2 HR (95% CI)**	***P***
Sex, M vs F	0.85				
Morphology, PD vs WD	<0.0001			**2.07 (1.37-3.11)**	**0.0005**
Ki-67, quartiles by event	<0.0001				
Ki-67, ≥50% vs <50%	0.0002	**2.25 (1.46-3.46)**	**0.0002**		
SSRI positivity, yes vs no vs NA	<0.0001	**1.43 (1.05-1.95)**	**0.03**	**1.40 (1.05-1.88)**	**0.02**
FDG PET positivity, yes vs no vs NA	0.006				
Age, quartiles by event	0.095	1.00 (0.99-1.01)	0.97	1.00 (0.99-1.02)	0.59
Hepatic metastases at diagnosis, yes vs no	0.67				
Site of primary, pancreas vs non-pancreatic	0.98				
PD, poorly differentiated; WD, well-differentiated; NA not available; SSRI somatostatin receptor imaging; FDG PET, 18F-fluorodeoxyglucose positron emission tomography. Bold values denote statistical significance at the P < 0.05 level.					

Table 3. Cohort that Received First-Line Platinum-Based Chemotherapy

Characteristic	**All cases**	**WDNET**	**PDNEC**	***P***
Number	59	33	26	
Median age in years (range) at diagnosis	59 (20-79)	51 (20-75)	64 (23-79)	**0.01***
Sex, n (%)				0.79†
Male	36 (61)	21 (64)	15 (58)	
Female	23 (39)	12 (36)	11 (42)	
Site of primary, n (%)				**0.016‡**
Pancreas	27 (46)	18 (55)	9 (35)	
Gastrointestinal	20 (34)	6 (18)	14 (54)	
Unknown§	12 (20)	9 (27)	3 (12)	
Ki-67, %, median (range)	40 (21-90)	30 (21-70)	70 (21-90)	**<0.0001***
SSRI avidity, n (%)				**<0.0001†**
Positive	24 (41)	21/26 (81)	3/7 (43)	
Negative	9 (15)	5/26 (19)	4/7 (57)	
Not available	26 (44)	7	19	
FDG PET avidity, n (%)				0.17†
Positive	18 (31)	8/14 (57)	10/11 (91)	
Negative	7 (12)	6/14 (43)	1/11 (9)	
Not available	34 (58)	19	15	
Chemotherapy, n (%)				1.0†
FCiSt/FCarboStrep	40 (68)	22 (67)	18 (69)	
Cis/carboplatin/etoposide	19 (32)	11 (33)	8 (31)	

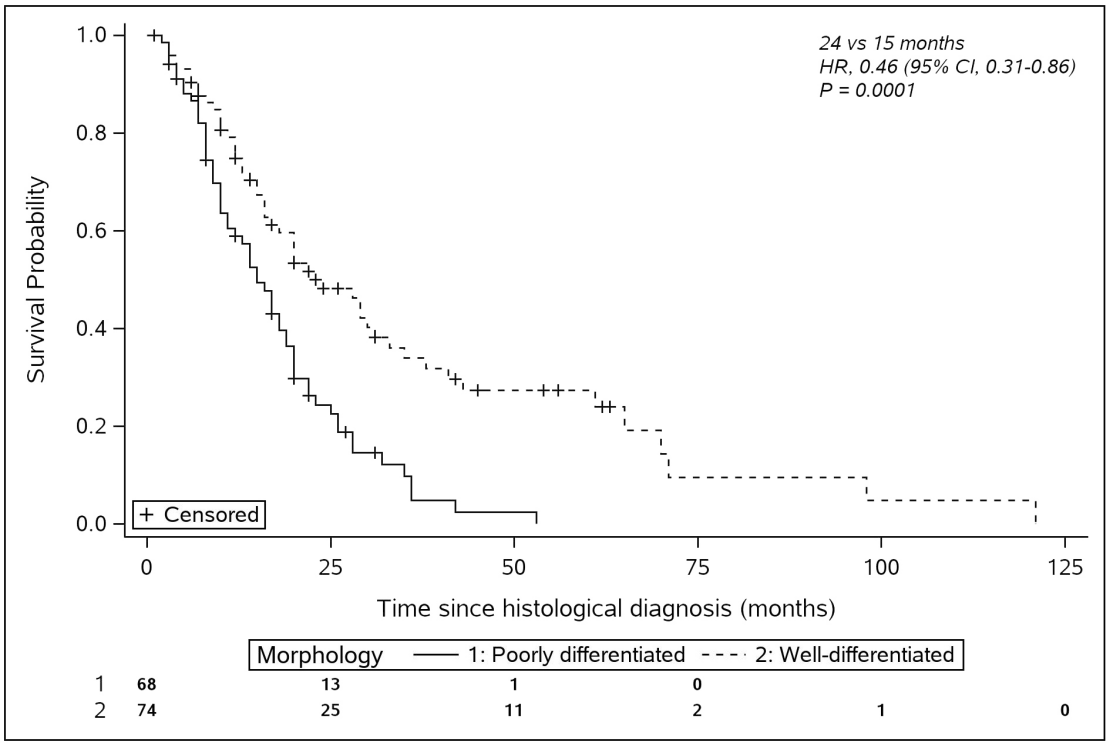
** Mann Whitney Test; †Fisher's exact test; ‡Fisher-Freeman-Halton exact test; §tumour immunostaining and distribution of disease suggestive of gastrointestinal primary. WDNET, well-differentiated neuroendocrine tumour; PDNEC, poorly differentiated neuroendocrine carcinoma; SSRI, somatostatin receptor imaging; FDG PET, 18F-fluorodeoxyglucose positron emission tomography; FCiSt, 5-fluorouracil/cisplatin/streptozocin; FCarboStrep, 5-fluorouracil/carboplation/streptozocin. Bold values denote statistical significance at the P < 0.05 level.*

Table 4. Response in Patients Treated With First-Line Platinum-Based Chemotherapy in Evaluable Patients				
	WDNET n (%)	**PDNEC n (%)**	**Overall n (%)**	***P***
Best objective response				
Partial response	14 (42)	13 (54)	27 (47)	0.43*
Stable disease	13 (39)	4 (17)	17 (30)	0.08*
Progressive disease	6 (18)	7 (29)	13 (23)	0.36*
Total	33	24	57	
Progression-free survival (months)	7	5		0.07†
Overall survival (months)	22	14		**0.008**†

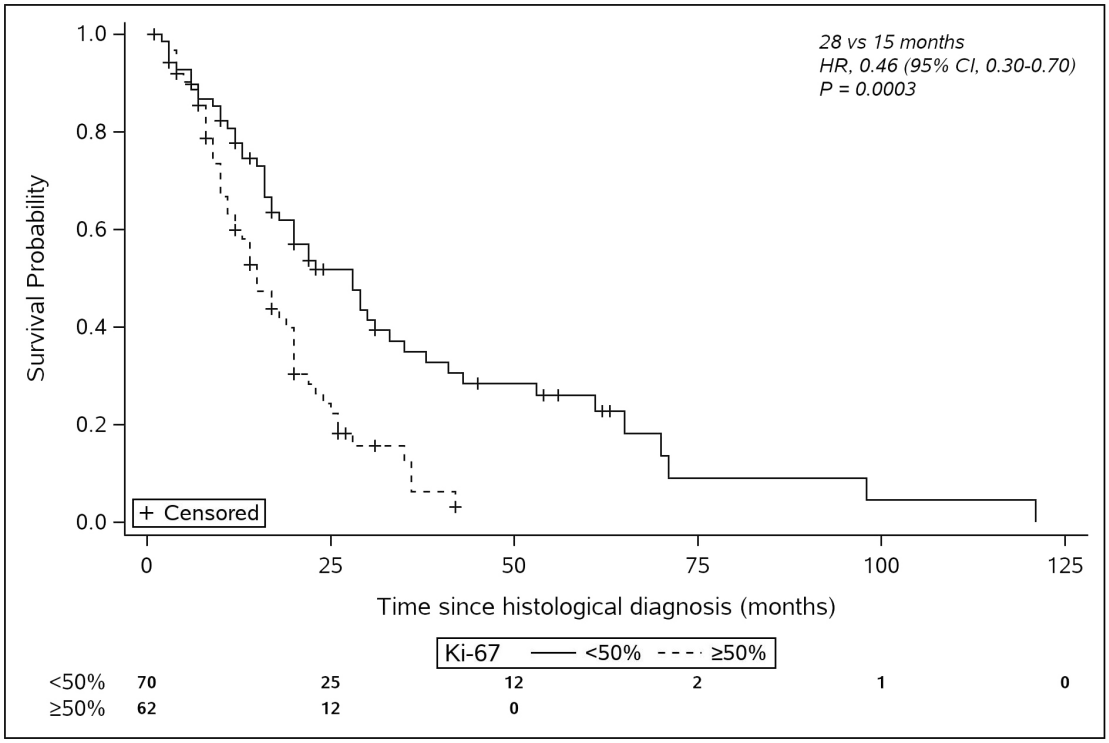
**Fisher's exact test; †Log-rank test. WDNET, well-differentiated neuroendocrine tumor; PDNEC, poorly differentiated neuroendocrine carcinoma. Bold values denote statistical significance at the P < 0.05 level.*

Figure 1.

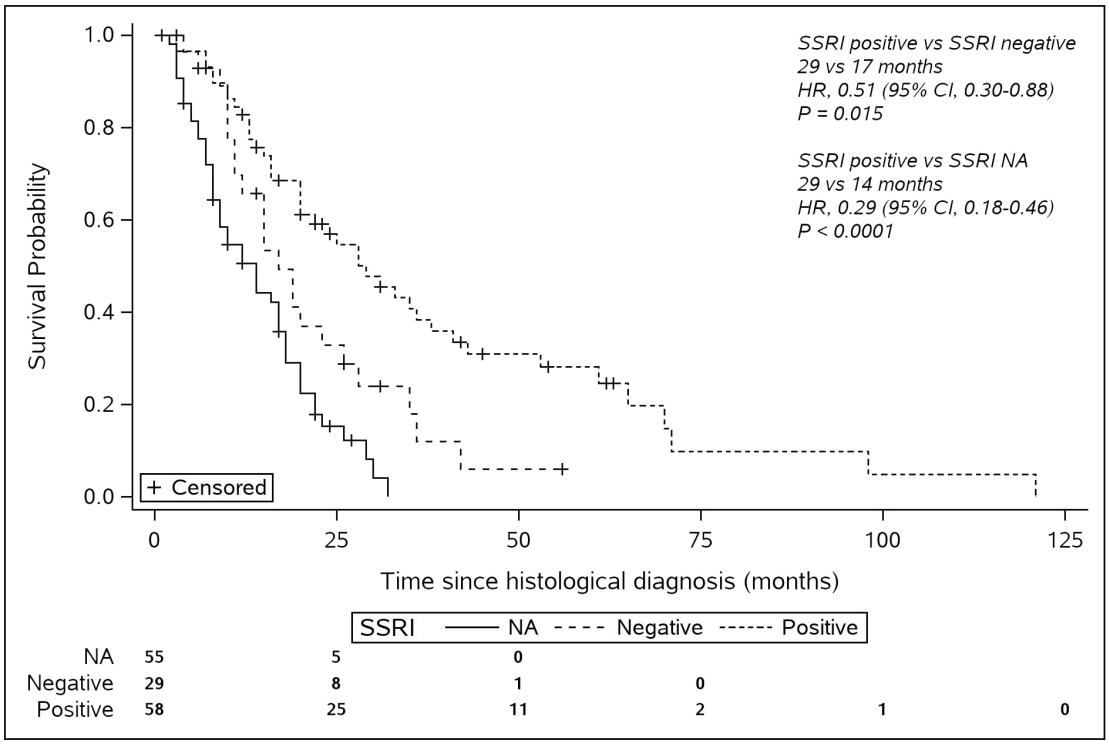
A


24 vs 15 months
HR, 0.46 (95% CI, 0.31-0.86)
P = 0.0001
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
+ Censored
0
25
50
75
100
125
Time since histological diagnosis (months)
Morphology
1: Poorly differentiated
2: Well-differentiated
1 68 13 1 0
2 74 25 11 2 1 0

B


28 vs 15 months
HR, 0.46 (95% CI, 0.30-0.70)
P = 0.0003
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
+ Censored
0
25
50
75
100
125
Time since histological diagnosis (months)
Ki-67
<50%
≥50%
<50% 70 25 12 2 1 0
≥50% 62 12 0

C


SSRI positive vs SSRI negative
29 vs 17 months
HR, 0.51 (95% CI, 0.30-0.88)
P = 0.015
SSRI positive vs SSRI NA
29 vs 14 months
HR, 0.29 (95% CI, 0.18-0.46)
P < 0.0001
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
+ Censored
0
25
50
75
100
125
Time since histological diagnosis (months)
SSRI NA Negative Positive
NA 55 5 0
Negative 29 8 1 0
Positive 58 25 11 2 1 0

D

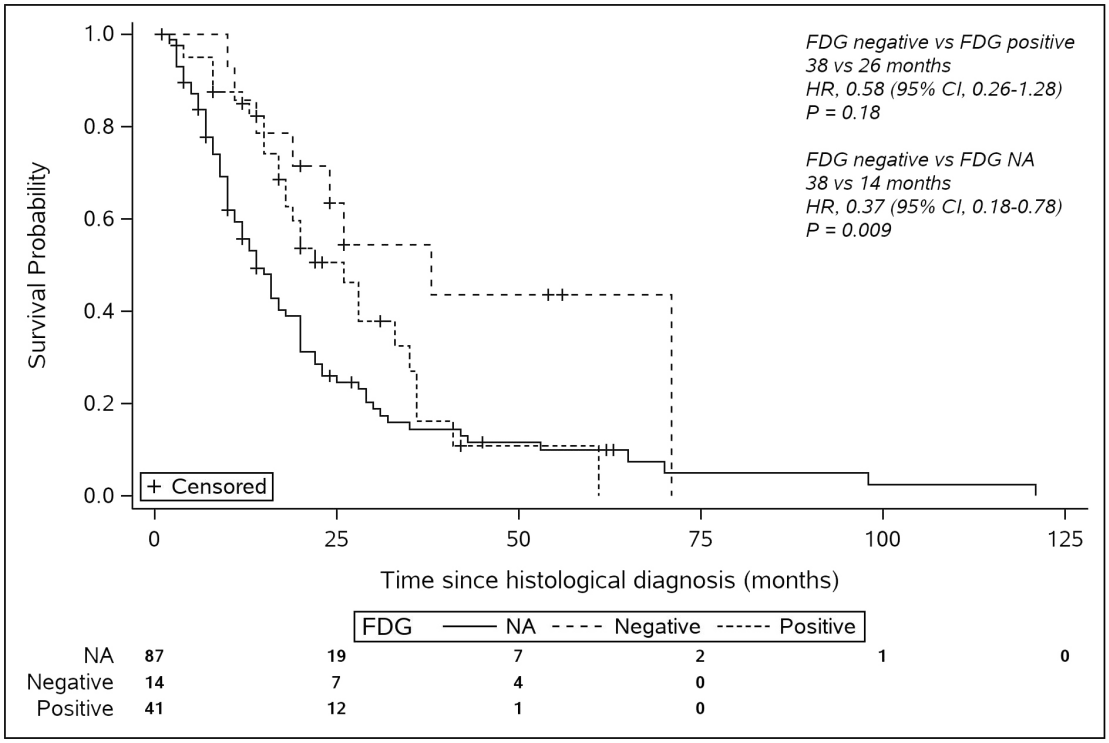
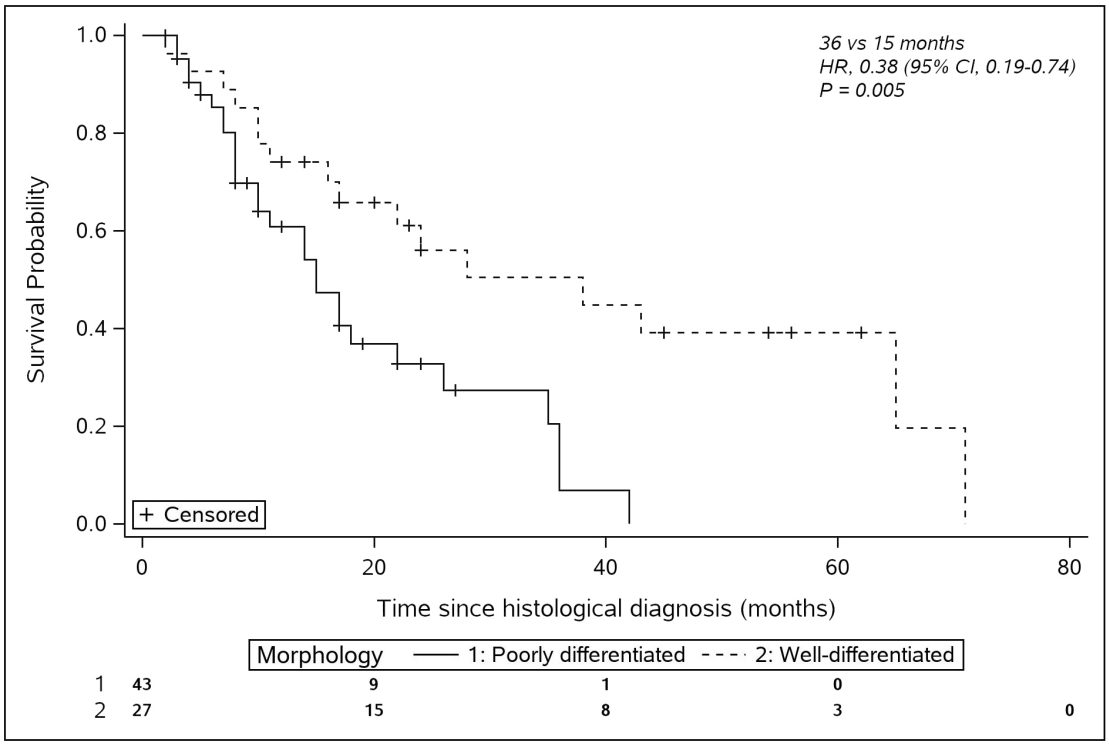

FDG negative vs FDG positive
38 vs 26 months
HR, 0.58 (95% CI, 0.26-1.28)
P = 0.18
FDG negative vs FDG NA
38 vs 14 months
HR, 0.37 (95% CI, 0.18-0.78)
P = 0.009
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
+ Censored
0
25
50
75
100
125
Time since histological diagnosis (months)
FDG NA Negative Positive
NA 87 19 7 2 1 0
Negative 14 7 4 0
Positive 41 12 1 0

Figure 2.

A


36 vs 15 months
HR, 0.38 (95% CI, 0.19-0.74)
P = 0.005
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
+ Censored
0
20
40
60
80
Time since histological diagnosis (months)
Morphology
1: Poorly differentiated
2: Well-differentiated
1 43 9 1 0
2 27 15 8 3 0

B

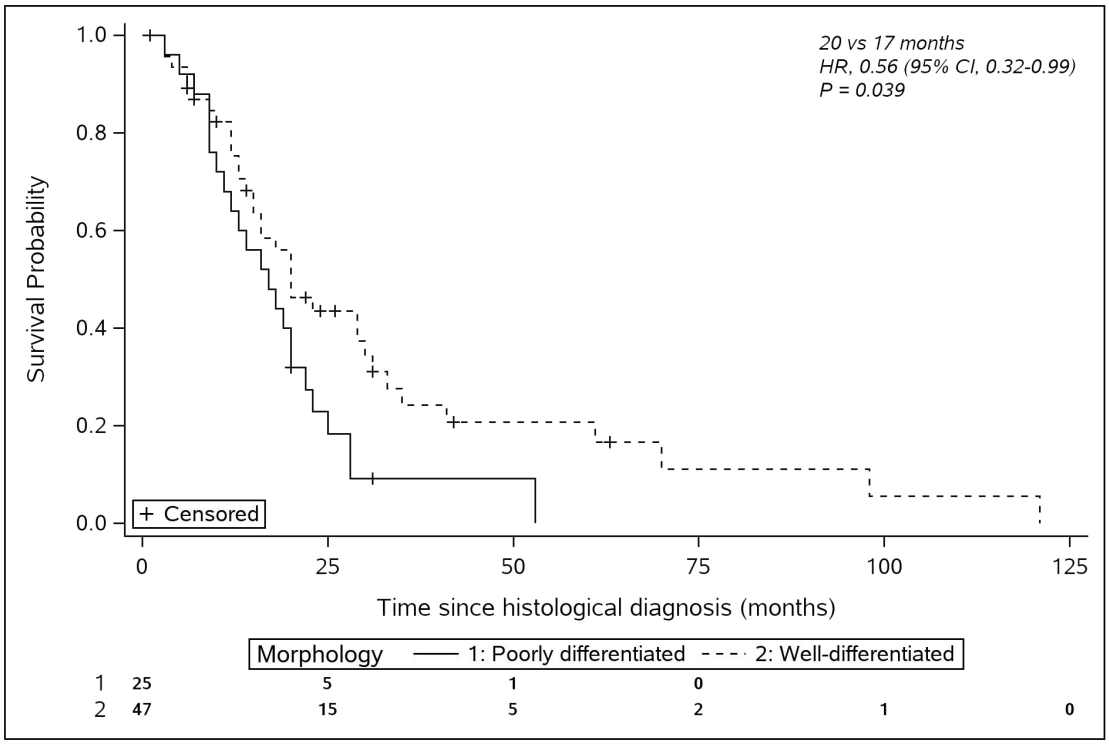
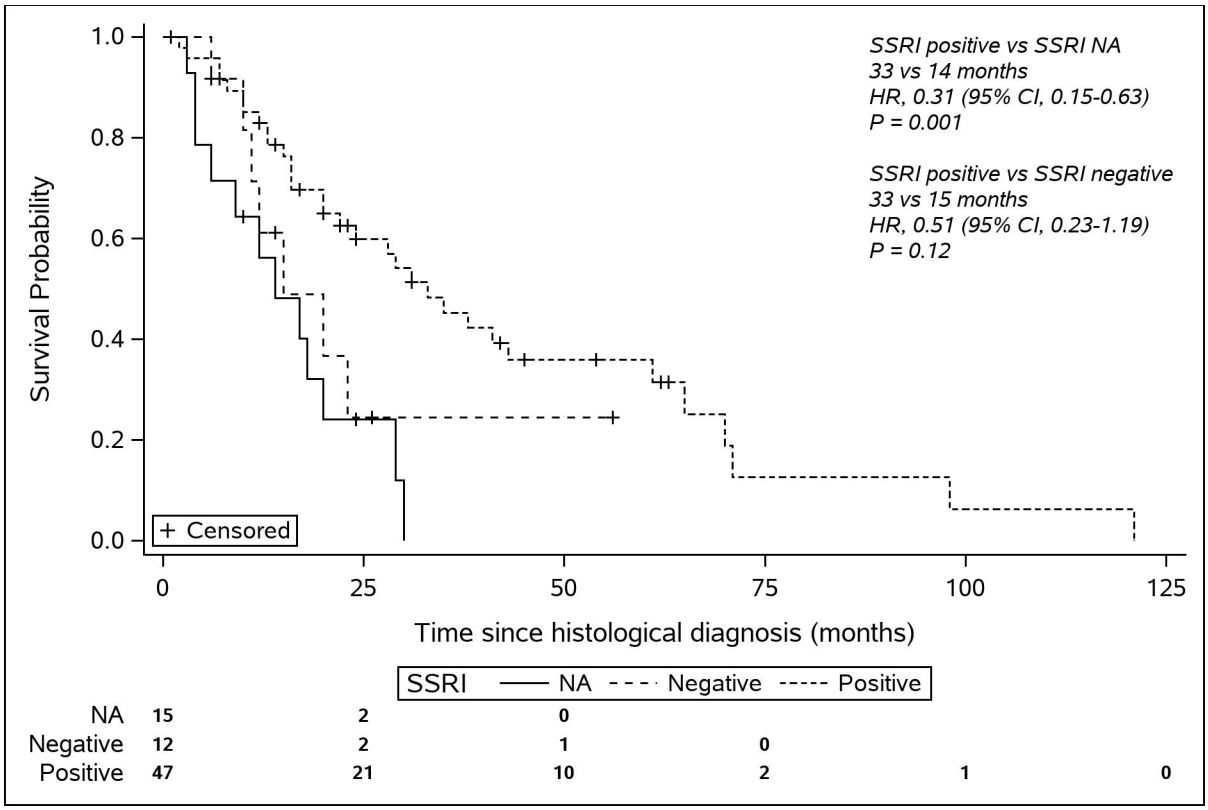

20 vs 17 months
HR, 0.56 (95% CI, 0.32-0.99)
P = 0.039
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
+ Censored
0
25
50
75
100
125
Time since histological diagnosis (months)
Morphology
1: Poorly differentiated
2: Well-differentiated
1 25 5 1 0
2 47 15 5 2 1 0

Figure 3.


1.0
0.8
0.6
0.4
0.2
0.0
Survival Probability
SSRI positive vs SSRI NA
33 vs 14 months
HR, 0.31 (95% CI, 0.15-0.63)
P = 0.001
SSRI positive vs SSRI negative
33 vs 15 months
HR, 0.51 (95% CI, 0.23-1.19)
P = 0.12
+ Censored
0
25
50
75
100
125
Time since histological diagnosis (months)
SSRI NA Negative Positive
NA 15 2 0
Negative 12 2 1 0
Positive 47 21 10 2 1 0