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Distinct clinicopathological and prognostic features of insulinoma with synchronous distant metastasis

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ABSTRACT

Background: The clinicopathological and prognostic features of insulinoma with synchronous metastases are unclear. This study aimed to verify the distinct clinicopathological and prognostic features of insulinoma with synchronous distant metastasis.

Methods: Patients with pancreatic neuroendocrine tumor (PanNET) were retrospectively enrolled and divided into cohort 1 (Fudan University Shanghai Cancer Center) and cohort 2 (Surveillance, Epidemiology, and End Results Program database). Both cohorts were further divided into three subgroups: insulinoma, nonfunctioning pancreatic neuroendocrine tumor (NF-PanNET), and non-insulinoma functioning pancreatic neuroendocrine tumor (NiF-PanNET).

Results: Cohorts 1 and 2 comprised 505 and 2761 patients (1566 M0 patients and 1195 M1 patients), respectively. In cohort 1 and cohort 2 M0 subgroup, insulinoma showed longer disease-free survival, overall survival (OS), and disease-specific survival (DSS) than NiF-PanNET and NF-PanNET (not reached vs. 48 and 60months, $p < 0.001$; 183months vs. 87 and 109months, $p < 0.001$; 247months vs. 121 and 140months, $p = 0.002$). However, in cohort 2 M1, the mDSS for metastatic insulinoma was shorter than that for NiF-PanNET (31months vs. 61months, $p = 0.045$), while the mDSS and mOS were similar to those for NF-PanNET. The percentage of T1 and N0 patients was similar between the metastatic insulinoma subgroup and NiF-PanNET and NF-PanNET subgroups. The Ki-67 index and recurrence had a positive linear relationship only for NiF-PanNET and NF-PanNET ($p = 0.009$).

Conclusions: Insulinoma with synchronous metastasis showed clinicopathological and prognostic characteristics similar to those of NF-PanNET. Metastatic insulinoma had worse prognosis than non-insulinoma F-PanNET. These findings may help in the clinical management of metastatic insulinoma.

Introduction

Pancreatic neuroendocrine tumors (PanNETs) are classified as functioning (F-PanNETs) and nonfunctioning (NF-PanNETs) according to hormone secretion and clinical symptoms. Previous studies have shown that F-PanNET has better prognosis than NF-PanNET (5-year survival rates: 97% for insulinoma vs. 30% for metastatic NF-PanNET) [1,2]. The primary type of F-PanNET is insulinoma, which accounts for more than 50% of all cases of F-PanNET [3]. Approximately 95% of insulinomas are solitary, and over 80% are characteristically small (<2 cm); thus, insulinoma commonly occurs as a nonmetastatic lesion with better prognosis [4,5].

Metastatic insulinoma is extremely rare; only 10% of all insulinomas have lymph node metastasis or remote metastasis [6]. Yu et al. analyzed nine patients with metastatic insulinoma and found that metastatic insulinoma rarely occurs as a progressed form of

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benign insulinoma but instead arises independently and behaves like an NF-PanNET [7]. Another study on nine malignant cases of insulinoma reported that the5-year survival of patients with malignant insulinoma was shorter than that of patients with benign insulinoma (16% vs.100%) [8]. However, because of the rarity of the disease, the prognosis of malignant insulinoma is yet to be clearly understood.

Our previous study [9] showed that insulinoma in stage I-III PanNET has better prognosis than non-insulinoma F-PanNET (NiF-PanNET) and NF-PanNET. However, the clinical features of insulinoma with synchronous distant metastasis remain unclear. In this study, we aimed to compare the clinicopathological and prognostic features of stage IV insulinoma with those of NF-PanNET and NiF-PanNET and verify the distinct clinicopathological and prognostic features of insulinoma with synchronous distant metastasis.

Methods

Patient selection

This is a retrospective review of two cohorts with PanNET. Cohort 1 comprised PanNET patients who underwent R0 resection at the Pancreatic Cancer Institute, Fudan University Shanghai Cancer Center, between January 2004 and May 2015. The inclusion criteria were as described previously [9].

Cohort 2 comprised PanNET cases registered in the Surveillance, Epidemiology, and End Results Program (SEER) database, as identifiedinthe "Incidence—SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2015 Sub (1973—2013 varying)." The following International Classification of Diseases for Oncology (ICD-O-3) codes were used to identify PanNETs: islet cell carcinoma (8150), insulinoma (8151), glucagonoma (8152), gastrinoma (8153), vipoma (8155), somatostatinoma (8156), carcinoid tumor (8240), argentaffin carcinoid tumor (8241), and neuroendocrine carcinoid (8246). Site Recode ICD-O-3/WHO 2008 data were used to filter results according to tumor location in the pancreas. Tumor-node-metastasis (TNM) staging data were retrieved based on the following codes: derived American Joint Committee on Cancer (AJCC) TNM stage group, 7th edition (2010+); derived AJCC TNM stage group, 6th edition (2004+); CS tumor size (2004+); CS lymph nodes (2004+); and CS mets at diagnosis (2004+). Information on survival was retrieved using the terms"-SEER cause-specific death classification," "SEER other cause of death classification," "vital status recode," and "survival months."

This research was approved by the hospital ethics committee of Fudan University Shanghai Cancer Center, and we were permitted to access patient information to be used for research purposes.

Patient characteristics

Data on the patients' characteristics included patient demographics (age and sex), functionality (insulinoma, NiF-PanNET, and NF-PanNET), pathological report (T stage, N stage, tumor grade, and differentiation), and M stage (without metastasis [M0] and with metastasis [M1]). All patients in cohort 1 had no metastasis.

Follow-ups and survival rates

Cohort 1 patients were followed up via outpatient visits or telephone calls between September 2016 and October 2016. As cohort 1 underwent R0 resection, disease-free survival (DFS) was calculated from the date of primary tumor resection to the date of the first outcome, in the following order: local recurrence, development of distant metastases, and death from cancer-related cause or the date of the last follow-up (censor date). Meanwhile, overall survival (OS) and disease-specific survival (DSS) were calculated in cohort 2. OS was computed as the time from diagnosis to death from any cause using the phrase "vital status recode," while DSS was calculated as the time from diagnosis to death from cancer-related cause using the phrase "SEER cause-specific death classification." The median follow-up time was calculated based on censored observations only.

Statistical analyses

Data were expressed as means±standard deviations for continuous variables and as numbers and percentages for categorical variables. Subgroup comparisons were performed using the chi-squared test or Fisher's exact test for categorical variables. For survival analysis, the Cox proportional model (with hazard ratios [HRs] and 95% confidence intervals [CIs]) and the Kaplan—Meier curve with the log-rank test were used to verify significant differences in survival curve, including DFS, OS, and DSS. Restricted cubic spline (RCS) functions were applied to all data points and used to estimate the dose—response association between continuous independent variables [10]. RCS analyses were performed using R (version 2.12.2; http://r-project.org), while other statistical tests were performed using SPSS (version 22.0; IBM Analytics, Armonk, NY, USA). All tests were two-sided and significance was set at a p-value of <0.05.

Results

Clinicopathological characteristics

The overall study population was 3266 patients (cohorts 1 and 2 comprised 505 patients and 2761 patients, respectively [1,566 M0 patients and 1195 M1 patients]). The baseline characteristics of cohort 1 are listed in Supplementary Table 1. Of the 505 patients in cohort 1,113 (22.4%), 37 (7.3%), and 355 (70.3%) had insulinomas, NiF-PanNETs (25 gastrinomas, 10 glucagonomas, and 2 vipomas), and NF-PanNETs, respectively. Regarding the distribution of clinicopathological features, the percentage of patients with T1, N0, and G1 was similar between the NiF-PanNET and NF-PanNET subgroups (T1: 18.9% and 21.4%; N0: 73% and 79.2%; and G1: 41.2% and 50.1%, respectively). Meanwhile, the percentage of patients with T1 (64.6%), N0 (95.6%), and G1 (73.7%) in the insulinoma subgroup was significantly higher than that in the NiF-PanNET and NF-PanNET subgroups ($p < 0.001$ for each, Fig. 1).

The baseline characteristics of cohort 2 are presented in Supplementary Table 2. Cohort 2 included 109 (3.9%) patients with insulinomas, 212 (7.7%) with NiF-PanNETs (128 gastrinomas, 56 glucagonomas, 26 vipomas, and 2 somatostatinomas), and 2440 (88.4%) with NF-PanNETs. Cohort 2 was divided into two subgroups: M0 PanNET (n = 1566 patients) and M1 PanNET (n = 1195 patients). In cohort 2 M0 subgroup, the number of patients with T1 (64.6% vs. 48.4% and 49.5%, $p = 0.011$) and N0 (95.3% vs. 52.2% and 80.8%, $p = 0.022$) was significantly higher in those with insulinoma than in those with NiF-PanNET and NF-PanNET. Meanwhile, in cohort 2 M1 subgroup, there was no significant difference in the percentage of patients with T1 and N0 between those with metastatic insulinoma and those with NiF-PanNET and NF-PanNET (Fig. 1).

Prognostic difference between insulinoma, NiF-PanNET, and NF-PanNET

The median follow-up time in cohort 1 was 71 months (range, 12—143months). The median DFS (mDFS) of the insulinoma

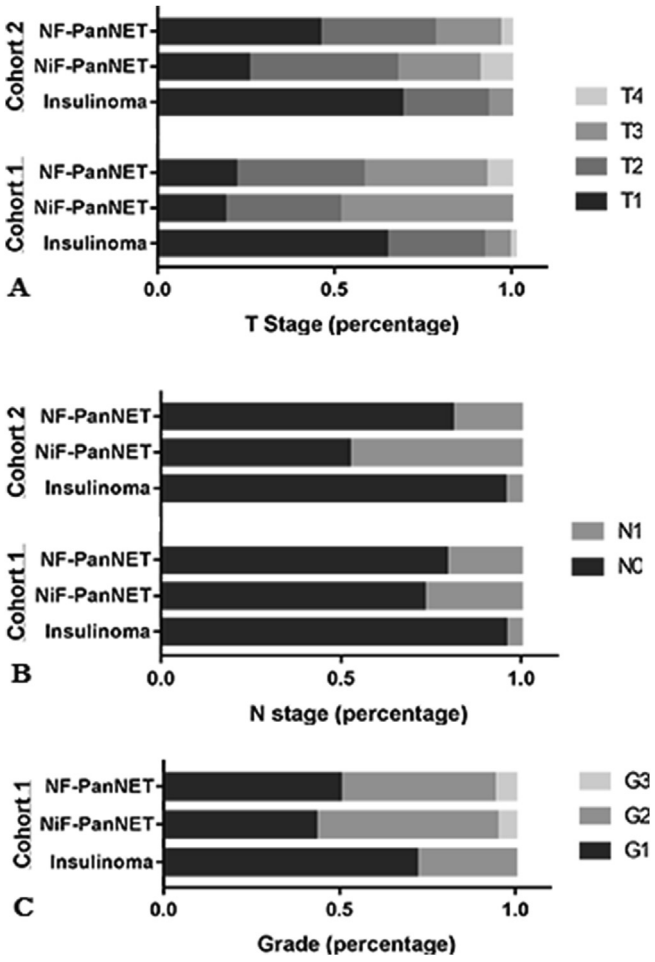

Fig. 1. Clinicopathological features of insulinoma compared with NiF-PanNET and NF-PanNET. (A) T stage, (B) N stage, and (C) grade.

subgroup was not reached (NR) and was significantly longer than that of the NiF-PanNET and NF-PanNET subgroups (48 and 60 months, respectively; HR, 1.734; 95%CI, 1.331–2.26; $p < 0.001$; Fig. 2). In cohort 2 M0 subgroup, the median OS (mOS) of the insulinoma, NiF-PanNET, and NF-PanNET subgroups were 183, 87, and 109 months, respectively; those with insulinoma had a significantly longer mOS than those with NiF-PanNET and NF-PanNET (HR, 1.209; 95%CI, 1.034–1.411; $p = 0.016$). The median DSS (mDSS) of patients with insulinoma was also longer than that of patients with NiF-PanNET and NF-PanNET (247 months vs. 121 and 140 months; HR, 1.197; 95%CI, 1.003–1.43; $p = 0.04$; Fig. 2).

However, in cohort 2 M1 subgroup, the mDSS of patients with insulinoma was significantly shorter than that of patients with NiF-PanNET (31 vs. 61 months; HR, 0.493; 95%CI, 0.228–0.995, $p = 0.045$).The mOS of the insulinoma subgroup was also shorter than that of the NiF-PanNET subgroup, but the difference was not statistically significant (31 vs. 51 months; HR, 0.571; 95%CI, 0.278–1.107, $p = 0.082$). The mDSS and mOS of the NF-PanNET subgroup (43 and 40 months, respectively) were not significantly different compared with those of the insulinoma subgroup ($p > 0.05$; Fig. 3).

Univariate analysis of functionality as a prognostic factor in nonmetastatic and metastatic PanNET

Functionality as a prognostic factor affecting DFS was evaluated via univariate analysis. In cohort 1 and cohort 2 M0 subgroup, insulinoma showed favorable prognosis compared with non-insulinoma PanNET with respect to DFS (HR, 2.243; 95%CI, 1.593–3.158; $p < 0.001$) and DSS (HR, 1.58; 95% CI, 1.245–2.007; $p < 0.001$).The insulinoma subgroup tended to have better OS than the non-insulinoma PanNET subgroup, but the difference was not statistically significant (HR, 2.501; 95%CI, 0.935–6.693; $p = 0.06$). The F-PanNET subgroup had better prognosis than the NF-PanNET subgroup (HR, 1.376; 95%CI, 1.114–1.699; $p = 0.003$; Fig. 4). However, the F-PanNET/NF-PanNET classification did not have any prognostic relevance in terms of OS or DSS ($p > 0.05$).

In cohort 2 M1 subgroup, both F-PanNET/NF-PanNET and insulinoma/non-insulinoma classifications did not show any prognostic relevance in terms of OS and DSS (Fig. 4).

Relationship between Ki-67 index and recurrence

In our previous study on the risk stratification of recurrence, we considered that grade should be a continuous rather than a categorical variable [9]. Thus, we analyzed the relationship between Ki-67 index and recurrence in the three groups in cohort 1. RCS analysis showed a linear association between Ki-67 index and recurrence for NiF-PanNET ($p = 0.08$) and NF-PanNET ($p = 0.001$) and exhibited a relatively steep and constant positive relationship with the log-hazard of recurrence (Fig. 5). However, no linear relationship between the Ki-67 index and recurrence was noted for insulinoma ($p = 0.287$; Fig. 5).

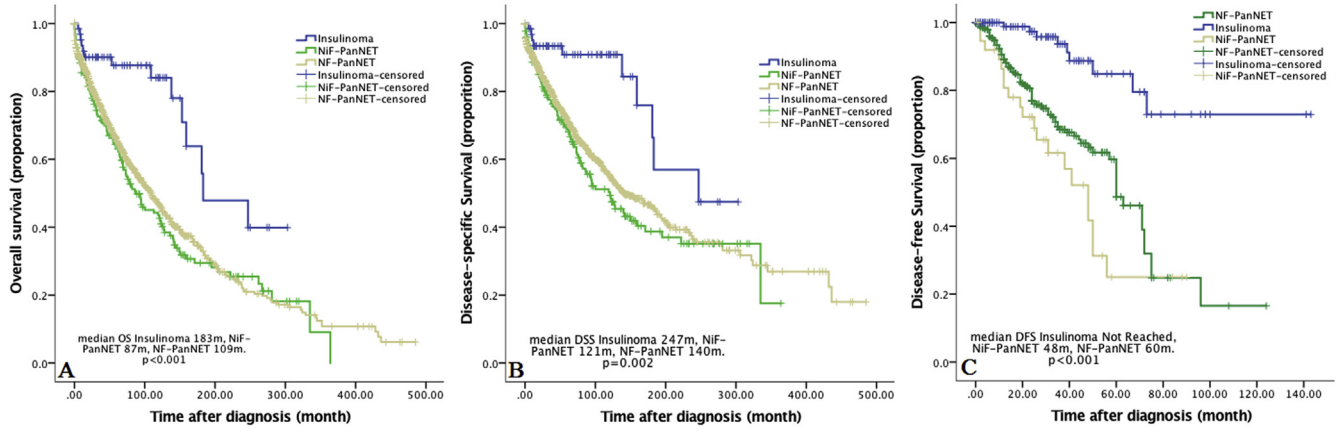

Fig. 2. Prognosis of nonmetastatic insulinoma, non-insulinoma functioning pancreatic neuroendocrine tumor (NiF-PanNET), and nonfunctioning pancreatic neuroendocrine tumor (NF-PanNET). (A) Overall survival (OS) and (B) disease-specific survival (DSS) in cohort 2 M0 PanNET subgroup. (C) Disease-free survival (DFS) in cohort 1.

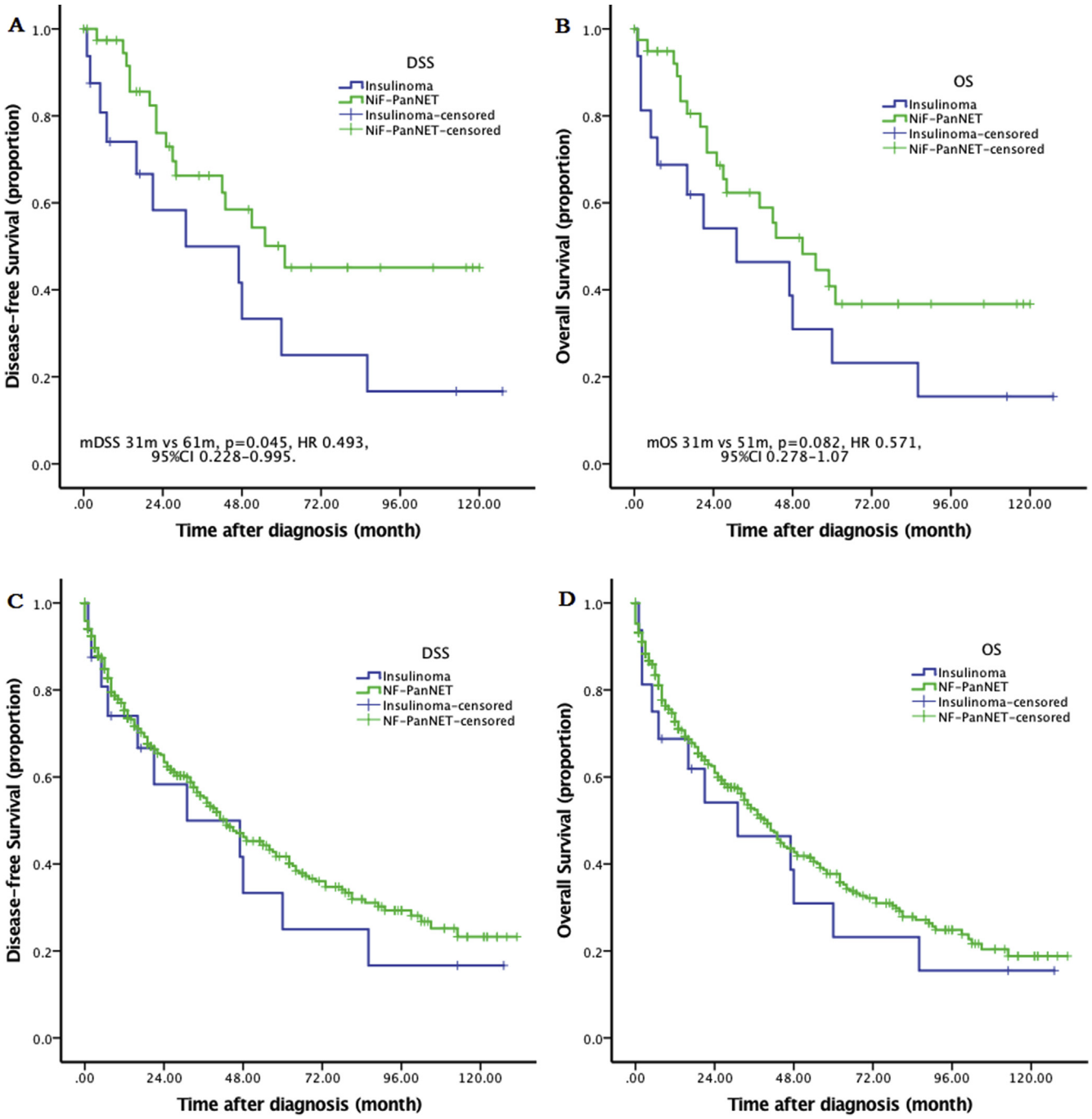

Fig. 3. Prognosisof stage IV insulinoma, non-insulinoma functioning pancreatic neuroendocrine tumor (NiF-PanNET), and nonfunctioning pancreatic neuroendocrine tumor (NF-PanNET)in cohort 2 M1 PanNET subgroup. (A) Overall survival (OS) and (B) disease-specific survival (DSS) ininsulinoma and NiF-PanNET.(C) OS and (D) DSS in insulinoma and NF-PanNET.

Discussion

In this study, we used two cohorts to analyze the distinct clinicopathological and prognostic characteristics of insulinoma with synchronousmetastasis. Our results showed that insulinoma with synchronous metastasis had worse prognosis than NiF-PanNET. Meanwhile, insulinoma with synchronous metastasis showed clinicopathological and prognostic features similar to those of NF-PanNET. Moreover, we found that the Ki-67 index and recurrence had no linear relationship in insulinoma.

The unusual features of nonmetastatic insulinoma are widely known [11], but studies focused on insulinoma with synchronous metastasis are limited. Insulinoma rarely recurs after pancreatectomy. In a previous study [12], only 3.5% of 198 insulinoma patients had lymph node/liver metastases, and only 6 patients developed tumor recurrence. In cohort 1 of our study, only 9(8%) insulinoma patients developed recurrence, and the DFS, OS, and DSS of patients with nonmetastatic insulinoma were longer than those of patients with NiF-PanNET and NF-PanNET. Meanwhile, nonmetastatic NiF-PanNET and NF-PanNET had similar prognosis in terms of DFS, OS, and DSS.

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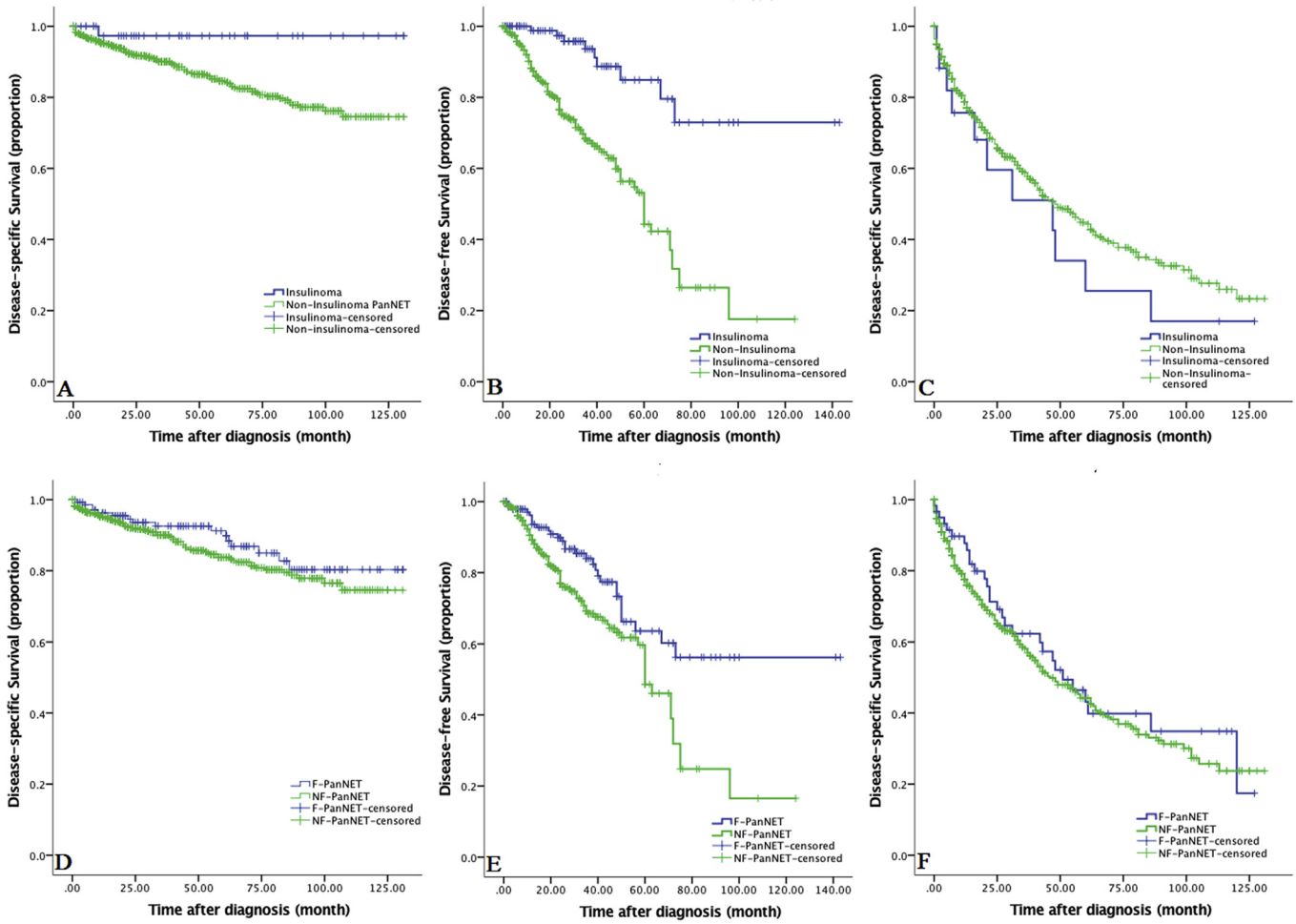

Fig. 4. Univariate analysis of functionality in prognosis. (A–C) Insulinoma/non-insulinoma. (D–F) Functioning pancreatic neuroendocrine tumor (F-PanNET)/nonfunctioning pancreatic neuroendocrine tumor (NF-PanNET). (A,D) Disease-specific survival (DSS) in cohort 2 M0 PanNET subgroup. (B, E) Disease-free survival (DFS) in cohort 1 (R0-resected PanNET). (C, F) DSS in cohort 2 metastatic (M1) PanNET subgroup.

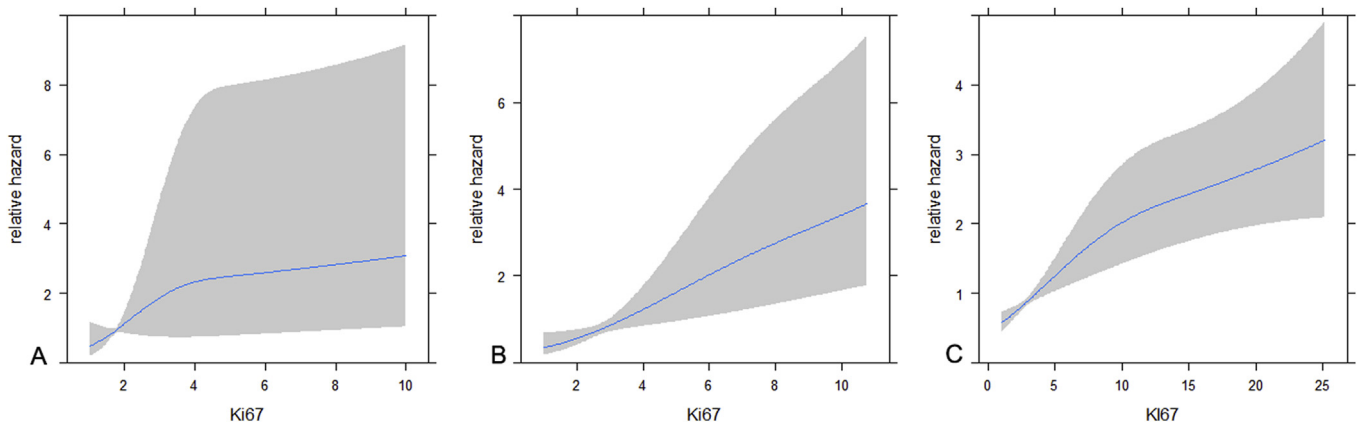

Fig. 5. Relationship between Ki-67 index and recurrence risk of resected pancreatic neuroendocrine tumor (PanNET) in cohort 1. The *y*-axis represents the hazard ratio for recurrence risk. (A) Insulinoma, (B) non-insulinoma functioning PanNET (NiF-PanNET), and (C) nonfunctioning PanNET (NF-PanNET).

metastatic insulinoma patients, and this is the first study to directly compare the prognosis and clinicopathologic features between insulinoma, NiF-PanNET, and NF-PanNET. We found that the percentage of T1 and N0 was lower in metastatic insulinoma than in NF-PanNET and NiF-PanNET, and the prognosis of insulinoma with synchronous metastasis was not superior to that of NF-PanNET and was even worse than that of metastatic NiF-PanNET with respect to DSS. The mOS was also shorter in metastatic insulinoma than in metastatic NiF-PanNET; however, the difference was not significant probably because of the limited number of patients. In the World

Health Organization (WHO) classification, neuroendocrine tumors are always considered as potentially malignant [13]. Some studies showed that metastatic insulinoma does not simply arise from "benign" insulinoma. Yu et al. analyzed nine metastatic insulinoma cases and found that none of the patients had a history of benign insulinoma, and only a small portion of malignant insulinoma cells expressed proinsulin and insulin [7]. The metastatic insulinoma was unlikely to have developed from benign insulinoma, which may partly explain the poor prognosis of metastatic insulinoma. However, the mechanism needs to be explored further.

Moreover, this study analyzed for the first time a new insulinoma/non-insulinoma classification based on favorable prognosis and the characteristics of nonmetastatic insulinoma, which maybe more suitable than the F-PanNET/NF-PanNET classification. Other studies had attempted to categorize insulinoma from F-PanNET. La Rosa proposed the idea of NiF-PanNET in 2008, and the associated clinical syndrome (insulinoma vs.NFT vs.NIFT) was significantly predictive of OS [14]. Other biomedical behaviors of insulinoma were also markedly different from those of NiF-PanNET. The serum chromogranin A level was lower in insulinoma than in non-insulinoma PanNET [15], and the rate of positive octreotide scintigraphy and ^{68}Ga-DOTANOC positron emission tomography/computed tomography was also lower in insulinoma than in non-insulinoma PanNET [16,17]. However, the prognosis according to functionality for metastatic PanNET (both insulinoma/non-insulinoma and NF-PanNET/F-PanNET) was not assessed in our study because metastatic insulinoma had even worse prognosis than NiF-PanNET.

The Ki-67 index is an important prognostic factor of PanNET, and Ellison et al. showed that tumor grade has a significantly higher prognostic power when used as a continuous variable [18]. In our study, RCS functions showed apositive linear relationship between the Ki-67 index and recurrencein NF-PanNET and NiF-PanNET. However, nonlinear association was noted in insulinoma. Because the SEER database did not contain data on the Ki-67 index, we were unable to analyze the relationship between Ki-67 index and prognosis in metastatic PanNET.

This retrospective study also had limitations. First, NiF-PanNET cases in our data were limited. Second, certain PanNET features, such as the rate of T3-4, were not included in the analysis. Moreover, the number of patients with N1 was also limited, and thus we did not analyze these groups.

In conclusion, by directly comparing insulinoma with NiF-PanNET and NF-PanNET in two separate cohorts, we showed that the clinicopathological features and prognosis of insulinoma with synchronous metastasis were similar to those of NF-PanNET, whereas they were worse than those of NiF-PanNET. These findings may help in further understanding the pathogenesis of metastatic insulinoma and improving its clinical management.

Conflicts of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2019.02.011.

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