Machine learning-based model for prediction and feature analysis of recurrence in pancreatic neuroendocrine tumors G1/G2

村上, 正俊

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Masatoshi Murakami[1], Nao Fujimori[1], Kohei Nakata[2], Masafumi Nakamura[2], Shinichi Hashimoto[3], Hiroshi Kurahara[4], Kazuyoshi Nishihara[5], Toshiya Abe[5], Shunpei Hashigo[6], Naotaka Kugiyama[6], Eisuke Ozawa[7], Kazuhisa Okamoto[8], Yusuke Ishida[9], Keiichi Okano[10], Ryo Takaki[11], Yutaka Shimamatsu[12], Tetsuhide Ito[13,14], Masami Miki[15], Noriko Oza[16], Daisuke Yamaguchi[17], Hirofumi Yamamoto[18], Hironobu Takedomi[19], Ken Kawabe[20], Tetsuro Akashi[21], Koichi Miyahara[22], Jiro Ohuchida[23], Yasuhiro Ogura[24], Yohei Nakashima[25], Toshiharu Ueki[26], Kousei Ishigami[27], Hironobu Umakoshi[1], Keijiro Ueda[1], Takamasa Oono[1], and Yoshihiro Ogawa[1]

[1]Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, 812-8582, Japan.
[2]Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.
[3]Digestive and Lifestyle Diseases, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan.
[4]Department of Digestive Surgery, Breast and Thyroid Surgery, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan.
[5]Department of Surgery, Kitakyushu Municipal Medical Center, Kitakyushu, Japan.
[6]Department of Gastroenterology and Hepatology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan.

[7]Department of Gastroenterology and Hepatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan.

[8]Department of Gastroenterology, Faculty of Medicine, Oita University, Oita, Japan.

[9]Department of Gastroenterology and Medicine, Faculty of Medicine, Fukuoka University, Fukuoka, Japan.

[10]Department of Gastroenterological Surgery, Faculty of Medicine, Kagawa University, Kita-gun, Japan.

[11]Department of Gastroenterology, Urasoe General Hospital, Urasoe, Japan.

[12]Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Kurume, Japan

[13]Neuroendocrine Tumor Centre, Fukuoka Sanno Hospital, Fukuoka, Japan.

[14]Department of Gastroenterology, Graduate School of Medical Sciences, International University of Health and Welfare, Fukuoka, Japan

[15]Department of Gastroenterology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan.

[16]Department of Hepato-Biliary-Pancreatology, Saga-ken Medical Centre Koseikan, Saga, Japan.

[17]Department of Gastroenterology, National Hospital Organization Ureshino Medical Center, Ureshino, Japan.

[18]Department of Surgery, Hamanomachi Hospital, Fukuoka, Japan.

[19]Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, Saga University, Saga, Japan.

[20]Department of Gastroenterology, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan.

[21]Department of Internal Medicine, Saiseikai Fukuoka General Hospital, Fukuoka, Japan.

[22]Department of Internal Medicine, Karatsu Red Cross Hospital, Karatsu, Japan.

[23]Department of Surgery, Miyazaki Prefectural Miyazaki Hospital, Miyazaki, Japan.

[24]Department of Surgery, Fukuoka Red Cross Hospital, Fukuoka, Japan.

[25]Department of Surgery, Japan Community Health Care Organization, Kyushu Hospital, Kitakyushu, Japan.

[26]Department of Gastroenterology, Fukuoka University Chikushi Hospital, Chikushino, Japan.

[27]Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

[*]**Corresponding author:** Nao Fujimori, MD, PhD

Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, 812-8582, Japan.

Telephone number: +81-92-642-5285

Fax number: +81-92-642-5287

Email: fujimori.nao.239@m.kyushu-u.ac.jp

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Abstract

Background

Pancreatic neuroendocrine neoplasms (PanNENs) are a heterogeneous group of tumors. Although the prognosis of resected PanNENs is generally considered to be good, a relatively high recurrence rate has been reported. Given the scarcity of large-scale reports about PanNEN recurrence due to their rarity, we aimed to identify the predictors for recurrence in patients with resected PanNENs to improve prognosis.

Methods

We established a multicenter database of 573 patients with PanNENs, who underwent resection between January 1987 and July 2020 at 22 Japanese centers, mainly in the Kyushu region. We evaluated the clinical characteristics of 371 patients with localized non-functioning pancreatic neuroendocrine tumors (G1/G2). We also constructed a machine learning-based prediction model to analyze the important features to determine recurrence.

Results

Fifty-two patients experienced recurrence (14.0%) during the follow-up period, with the median time of recurrence being 33.7 months. The random survival forest (RSF) model showed better predictive performance than the Cox proportional hazards regression model in terms of the Harrell's C-index (0.841 vs. 0.820). The Ki-67 index, residual tumor, WHO grade, tumor size, and lymph node metastasis were the top five predictors in the RSF model; tumor size above 20 mm was the watershed with increased recurrence probability, whereas the 5-year disease-free survival rate decreased linearly as the Ki-67 index increased.

Conclusions

Our study revealed the characteristics of resected PanNENs in real-world clinical practice. Machine learning techniques can be powerful analytical tools that provide new insights into the relationship between the Ki-67 index or tumor size and recurrence.

Keywords: pancreatic neuroendocrine tumor; recurrence; machine learning; prediction model; random survival forest

Introduction

Neuroendocrine neoplasms (NENs) are malignant neoplasms of neural crest origin. They occur throughout the body, with the pancreas and gastrointestinal tract being the most frequently affected sites [1, 2]. Although pancreatic NENs (PanNENs) are relatively rare, accounting for 1%–2% of primary pancreatic tumors, their incidence has been increasing worldwide due to the dissemination of the disease concept and advances in diagnostic modalities [3, 4].

PanNENs are a heterogeneous group of tumors, and their biological behavior varies among patients. According to the World Health Organization (WHO) 2019 classification [5], PanNENs have been divided into pancreatic neuroendocrine tumors (PanNETs) and pancreatic neuroendocrine carcinomas. PanNETs are subdivided by tumor proliferation rate into NET G1 (Ki-67 index of <3%), G2 (Ki-67 index of 3%–20%), and G3 (Ki-67 index of >20%). On the other hand, PanNETs are classified as functioning (F-) or non-functioning (NF-) tumors by the absence or presence of the specific hormonal hyperexpression symptoms. PanNETs are generally considered indolent and slow growing compared to pancreatic ductal adenocarcinomas. Given the favorable prognosis of curatively resected PanNETs [3, 4, 6], surgical resection is recommended for localized and sometimes even metastatic PanNETs [7]. However, a relatively high recurrence rate of 13.5%–30% with a median duration of 2–3.3 years until recurrence has been reported [8].

It is important to identify the predictors for recurrence among patients with PanNETs who require postoperative treatments and intensive follow-up. Tumor proliferation rates (Ki-67 index and mitotic rate) have been used as predictive factors for the recurrence of PanNETs [9, 10]; however, they are not always satisfactory in clinical

practice. Currently, many studies have aimed to define the predictors for recurrence, including functionality [9–11], tumor size [12], lymph node metastasis [9, 11, 13, 14], vascular invasion [11, 14], neural invasion [14, 15], and hypovascularity [12], using conventional analysis methods such as Cox proportional hazards regression (Cox) and logistic regression analysis. However, these reports examined patients with various types of PanNENs according to WHO tumor grade and functionality, thereby leading to inconsistent conclusions.

Recent advances in artificial intelligence research, including machine learning (ML) techniques, have facilitated the construction of highly accurate prediction models in the medical field [16, 17]. There are several studies in which artificial intelligence has been used within PanNET research. Zhou et al. employed biochemical and tumor markers using classical supervised ML models (logistic regression, support vector machine, linear discriminant analysis, and multi-layer perceptron) to predict PanNET grading [18], whereas Luo *et al.* used contrast-enhanced computed tomography (CT) images using a deep learning method [19]. Song *et al.* used clinicopathological features for ML (logistic regression, support vector machine, random forest, and deep learning) to predict survival [20]. However, to the best of our knowledge, no studies have constructed a prediction model and investigated the factors affecting the recurrence of PanNETs using ML algorithms for time-to-event analysis.

In this study, we established a multicenter database of resected PanNENs from real-world clinical practice at 22 Japanese centers, mainly in the Kyushu region. Considering the limited clinical benefit of identifying high-risk patients with NET G3 or NEC and/or distant metastasis, we evaluated the clinical characteristics of patients with localized NF-PanNET G1/G2, who underwent curative resection. We also constructed an ML-based

prediction model to analyze the important features that determine recurrence in patients with localized NF-PanNET G1/G2.

Methods

Kyushu pancreatic neuroendocrine tumor (Q-P-NET) registry

We collected the medical records of patients with PanNENs who underwent curative-intent surgery at 22 Japanese centers between January 1987 and July 2020. The data were collected and managed using the Research Electronic Data Capture (REDCap) electronic data capture tool hosted at Kyushu University ("Q-P-NET registry"). REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages, and 4) procedures for data integration and interoperability with external sources [21, 22].

Patients and data collection

After characterization of PanNENs in the Q-P-NET registry, we retrieved the medical records of patients with localized NF-PanNET G1/G2 from it for review. We also constructed prediction models for recurrence. This analysis was part of the Q-P-NET registry. Fig. 1 shows the flowchart of the patient selection process.

The clinicopathological factors used in this study are presented in Table 1. Blood tests were performed within 3 months of resection. F-PanNETs were defined according to the presence or absence of elevated serum hormone levels (at least higher than the upper normal limit) and/or positive target antigens on immunohistochemical staining, in addition to characteristic hormonal symptoms [23]. In cases of multiple tumors in the pancreas, hormone-secreting tumors or the largest tumor in the NF-PanNETs were evaluated. The contrast-enhanced CT/ magnetic resonance imaging (MRI) features of all

the PanNETs were retrospectively reviewed by experienced gastroenterologists, gastroenterological surgeons, and radiologists. Representative CT and MRI findings are shown in Supplementary Fig. 1. Lymph node metastases were assessed radiologically, and patients who underwent lymphadenectomy were also evaluated pathologically. When lymphatic and venous invasion were evaluated separately, a positive result for either was defined as positive for lymphovascular invasion. Although no central review of the imaging or pathological findings was conducted, previous cases were described in accordance with the WHO 2019 classification by reviewing pathology slides and/or reports from each institution. For cases that were difficult to determine, decisions were made through multiple web conferences with the data collection center. Follow-up plans were based on each facility's daily medical practice, and recurrence was assessed by radiological imaging and/or histological biopsy. Case registration was done in December 2021 using REDcap, and outcomes were determined at the time of the event or the last follow-up before registration.

This study was approved by the institutional review board of Kyushu University Hospital (#2020-509) and all participating institutions (Supplementary Table 1).

Constructing prediction models and feature analysis

We constructed two prediction models, the random survival forest (RSF) and Cox models, for predicting recurrence using 19 clinicopathological factors (17 categorical and 2 continuous variables; Supplementary Table 2) (the "randomForestSRC" and "survival" R packages [24] were used, respectively). Overall, 4.2% of the data were missing from the cohort. The missing data were imputed through a multiple imputation by chained equations using the "MICE" package. To evaluate the accuracy of the models, the data

were split randomly into two complementary parts: training (75%) and test (25%) datasets, under the same event/censoring proportions. Prediction models were constructed using the training dataset, and their predictive performances were evaluated using the test dataset. Discrimination was assessed using the Harrell's concordance index (C-index) [25] and the time-dependent area under the receiver operator curve (tAUC) [26]. Calibration was assessed using the integrated Brier score (IBS) [27] and the calibration plot. In the RSF model, variable importance (VIMP) was used as a general measure of feature relevance to confirm the relative ranking of spectral features. A larger VIMP value for variables indicates a more important predictor role, while zero or negative values indicate no predictive power.

Statistical analysis

All statistical analyses were performed using the R software (v4.0.2; http://r-project.org). Statistical significance was set at $p < 0.05$. The code that supports the findings of this study is tailored to the data and is thus not provided because it is of no use as a standalone without access to the data *per se*.

Results

The Q-P NET registry

After excluding duplicate or insufficient medical records, 573 patients with PanNENs who underwent curative-intent surgery were analyzed. PanNET G1/G2 was the most prevalent category, accounting for approximately 90% of cases in the Q-P-NET registry (Supplementary Fig. 2a). The recurrence rates of NET G1, NET G2, NET G3, and NEC were 7.6%, 33.7%, 77.8%, and 77.8%, respectively. Patients with NET G3 and NEC had early relapse (Supplementary Fig. 2c). The Kaplan-Meier survival curves of the Q-P-NET registry were markedly different among patients according to tumor grade, and the median survival time (MST) was significantly longer in patients with NET G1/G2 than in those with NET G3 or NEC for both overall survival (OS) and cancer-specific survival (CSS) (Supplementary Fig. 3). In contrast, one-fourth of the patients had F-PanNENs (NF-PanNENs: 436 and F-PanNENs: 137) with varying recurrence rates depending on the type of F-PanNENs (Supplementary Fig. 2b). The smaller number of patients with F-PanNENs other than insulinoma (n=35) showed a recurrence-free survival comparable to that of patients with NF-PanNENs (Supplementary Fig. 2d).

The Q-P-NET registry consists of a heterogeneous group of tumors with varying rates of recurrence. The recurrence rate was significantly different between the patients with and without distant metastases (82.1% and 14.6%, respectively). In addition, most of the patients with NET G3 and NEC had a relapse during the follow-up period in this registry. Therefore, we examined patients with localized NF-PanNET G1/G2 who underwent curative resections. The clinical characteristics of 371 patients were analyzed and used to construct prediction models for recurrence (Fig. 1).

Analysis of patients with localized NF-PanNET G1/G2 who received curative resection

Fig. 2 shows the results of the Kaplan-Meier survival analysis of patients with and without recurrence. In the analysis of OS, patients with recurrence had a significantly poor prognosis (MST: not reached (NR) and 202 months with and without recurrence, respectively; $p = 0.03$; Fig. 2a). Recurrence was negatively correlated with CSS (MST: NR and 202 months with and without recurrence, respectively; $p < 0.0001$; Fig. 2b).

Fifty-two out of 371 patients in this cohort had recurrence (recurrence rate: 14.0%) within an average observation period of 59.9 months (interquartile range (IQR) 20.7–84.4 months). The median disease-free survival (DFS) was 232.0 months (IQR 112.8–NR), with 5- and 10-year DFS rates of 82.9% and 73.4%, respectively (Fig. 3a). In contrast, the median time to recurrence was 33.7 months (IQR 12.2–53.9) in patients with recurrence. More than 80% of recurrences occurred within 5 years after surgery, and only two had a recurrence more than 10 years later. All initial recurrences were observed in the abdominal organs: liver only (34 patients), pancreas only (5 patients), lymph node only (4 patients), and multiple sites (9 patients) (Fig. 3b). Seven out of 9 patients with multiple sites experienced liver recurrence. Therefore, 41 of 52 patients with recurrence (78.8%) had liver metastases.

The clinical characteristics of the patients with localized NF-PanNET G1/G2 who underwent curative surgery are summarized in Table 1. In this cohort, 5.6% of the patients had inherited diseases and 76.6% were asymptomatic. Although approximately 30% of patients were investigated, preoperative neuron-specific enolase and pro-gastrin-releasing peptide levels were not high (positive rate: 8.8% and 5.1%, respectively). Atypical contrast patterns and main pancreatic duct (MPD) obstruction were observed in

39.4% and 12.4% of patients, respectively. In this study, more than 40% of patients underwent minimally invasive surgery, approximately 10% underwent enucleation, and the rest underwent pancreatic resections. In contrast, 47 patients had surgery-related adverse events ≥ grade 3 according to the Clavien-Dindo classification, with no surgery-related deaths. The pathological findings revealed that two-thirds of the patients had NET G1 and the rest had NET G2. A tumor size < 20 mm was found in more than 50% of the patients. Regional lymph node metastasis was observed in one-fourth of patients. According to the WHO tumor grade, lymph node metastasis was more frequent in patients with NET G2 than in those with NET G1 (20.9% and 4.8%, respectively; $p < 0.0001$; Fig. 3c). In contrast, only three patients with tumor size < 20 mm had lymph node metastasis, and no patients with tumor size < 10 mm had lymph node metastasis (Fig. 3d). Most patients (97.3%) underwent R0 resection with relatively high rates of lymphovascular and perineural invasion (24.0% and 15.9%, respectively).

Prediction models

After the missing data were imputed, the dataset was split randomly into training and test datasets (Supplementary Table 2). We constructed two prediction models, the RSF and Cox models, for recurrence in localized NF-PanNET G1/G2 using the training dataset and compared their performance using the test dataset (Fig. 1). The RSF model had a higher C-index (0.841) than that of the Cox model (0.820) (Table 2). Similarly, in the analysis of tAUC, the RSF model was superior to the Cox model at all time points (AUC at 1-year DFS: 0.937 and 0.936, 5-year DFS: 0.937 and 0.936, and 10-year DFS: 0.911 and 0.810, respectively) (Fig. 4 and Table 2). In the calibration plot, the predicted

DFS probability corresponded more closely to the observed DFS probability in the RSF model than in the Cox model (Supplementary Fig. 4).

Next, we analyzed the important features for recurrence obtained from the high-performance RSF model. In the VIMP plot, the top five variables for predicting recurrence were, in descending order, the Ki-67 index, residual tumor, WHO grade, tumor size, and lymph node metastasis (Fig. 5a). The partial dependence plots for 5-year DFS of the most influential variables of the RSF model are shown in Fig. 5b–f, showing the effect of the covariate when the other covariates were fixed. Regarding continuous variables, the partial dependence plots show the actual contribution of the measured value in a continuous manner. The 5-year predicted DFS rate decreased linearly from approximately 90% to 30% as the Ki-67 index increased (Fig. 5b). Similarly, the 5-year predicted DFS rate decreased from approximately 90% to 65% with every 1-mm increase in tumor size up to 40 mm. However, no significant change was observed when the tumor size exceeded 40 mm (Fig. 5e). On the other hand, for categorical variables such as residual tumor, patients without residual tumor had a higher 5-year predicted DFS (approximately 90%) than those with residual tumor (approximately 50%) (Fig. 5c).

Discussion

We established a large database and retrospectively reviewed the data of 573 patients with PanNENs who underwent curative resection in Japanese multicenter, mainly in the Kyushu region. There are racial differences in PanNET outcomes, although socioeconomic differences should be considered [28, 29]. There are a few large-scale reports on resected PanNETs [30, 31], especially from Japan, but the characteristic features of patients with resected PanNETs after curative surgery remain unclear. The quality of our study is guaranteed by REDCap, which contains data on many factors, some of which have never been addressed on a large scale, thus producing important clinical implications.

The prognosis of resected PanNENs in our study was clearly categorized according to WHO tumor grade. This study demonstrates that most patients with NET G3 and NEC relapsed, especially early in the follow-up period, with unfavorable outcomes even after curative resection, consistent with previous reports [32, 33]. Surgical intervention alone was not effective in this group, and multimodal treatments, including adjuvant therapy, should be considered. Taken together, these observations suggest that the clinical benefit of selecting a high-risk group of patients with NET G3 or NEC and/or distant metastasis is limited. In this study, the recurrence rate of F-PanNETs differed markedly according to the type of F-PanNET, suggesting that F- and NF-PanNETs should be analyzed separately. On the other hand, it is of great importance to identify the predictors for recurrence among patients with localized NF-PanNET G1/G2, considering the poor prognosis after recurrence. Therefore, we evaluated the clinical characteristics of patients with localized NF-PanNET G1/G2 who underwent curative resections.

Although radical resection is the first choice in patients with localized PanNETs, the “watch and wait” strategy has been recently advocated for asymptomatic small NF-PanNETs because of their indolent nature and high surgical invasiveness [34, 35]. In this study, among the 371 patients who underwent resection, there were few lymph node metastases in those with a tumor size <20 mm and no lymph node metastasis in those with a tumor size <10 mm. Accordingly, we propose that active surveillance and enucleation without lymphadenectomy should be allowed in NF-PanNETs <10 mm unless lymph node metastases are suspected, which is consistent with the guidelines of the Japanese Neuroendocrine Tumor Society [7]. Nevertheless, the prediction of aggressive PanNETs preoperatively remains elusive and should be addressed in future studies.

In this study, we developed an ML-based model using RSF to predict recurrence after curative resection, while also demonstrating its superiority compared to the Cox model in terms of predicting performance. The Cox model has generally been applied for data analysis of recurrent events. This is a simple analysis method but is restricted to the proportional hazards assumption and generally log-linearity. In contrast, RSF, an ML algorithm for time-to-event analysis, is based on the original random forest method [36] and has been proposed as an alternative to traditional survival methods [37]. RSF allows for less restrictive assumptions and can incorporate linear and non-linear effects even if the existence of various interactions is expected, whereas the Cox model cannot be useful in such situation. ML techniques, including RSF, are powerful analytical tools for this purpose.

High-performance RSF provides a fully nonparametric measure of variable importance, thus revealing new insights into the predictors of recurrence. Using RSF, we

analyzed relevant factors related to recurrence and identified residual tumor and lymph node metastasis as important predictors, consistent with previous reports [9, 11, 13, 14]. Moreover, the Ki-67 index is more important for predicting recurrence than the WHO grade. These observations suggest that the current cut-off values of 3% and 20% are insufficient to predict recurrence, whereas new cut-off values of 6% and 10% have been advocated as prognostic factors [6, 38, 39]. We also found a negative linear relationship between the Ki-67 index and 5-year DFS. This is consistent with a recent report by Gao et al., although they used a restricted cubic spline in their regression models [9]. More attention must be paid to recurrence in patients with a high Ki-67 index, even in the same PanNET G2. Furthermore, we showed a negative, nonlinear relationship between tumor size and 5-year DFS, with a tumor size 20 mm being the watershed with increased recurrence probability. This suggests that lesions larger than 20 mm harbor the possibility of increased malignancy; therefore, resection is strongly recommended.

This study has several limitations. First, as this was a retrospective multicenter study with varying follow-up periods, the registration period of the patients differed among the institutions. Although we used the RSF model, which considers the time axis (especially censoring) and can output the probability of event occurrence at any point in time, differences in follow-up periods may have affected the results of this study. Second, lymphadenectomy was not performed in all patients, and in those without lymphadenectomy, lymph node metastasis was evaluated based on imaging findings and the clinical course. Third, as this was a multicenter study across 22 institutions with a long study period, the imaging and pathological findings were not evaluated uniformly.

In conclusion, we established a large multicenter database of resected PanNENs in real-world clinical practice and evaluated the clinical characteristics of patients with

localized NF-PanNET G1/G2 who underwent curative resection. We also constructed an ML-based prediction model and identified important features to determine recurrence in patients with localized NF-PanNET G1/2. This study provides clues for the appropriate management of patients with localized NF-PanNET G1/G2 who underwent curative resection.

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Author contributions

All authors contributed to the study conception and design, and/or data collection. Data analyses were performed and the first draft of the manuscript was written by Masatoshi Murakami and Nao Fujimori, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figure captions

Fig. 1 Flowchart for patient inclusion and exclusion in the present study

Using the Q-P-NET registry, the medical records of patients with PanNENs who underwent curative-intent surgery at 22 Japanese centers between January 1987 and July 2020 were investigated. After characterizing PanNENs in the Q-P-NET registry, we evaluated the clinical characteristics of 371 patients with localized non-functioning pancreatic neuroendocrine tumor G1/G2. Moreover, we also constructed prediction models for recurrence using the random survival forest and Cox proportional hazards regression in this group

PanNENs, pancreatic neuroendocrine neoplasms; Q-P-NET registry, Kyushu pancreatic neuroendocrine tumor registry; PanNET, pancreatic neuroendocrine tumor.

*Overlapping

Fig. 2 Kaplan-Meier survival curves of patients with localized non-functioning PanNET G1/G2 who received curative resection surgery

(a) Overall and (b) cancer specific survival curves comparing patients with and without recurrence. (a, b) The significant differences were analyzed by log-rank tests between patients with (n=52) and without recurrence (n=319)

PanNET, pancreatic neuroendocrine tumor;MST, Median survival time; NR, not reached.

Fig. 3 (a) Disease-free survival curve and (b) initial recurrent location after curative resection in patients with localized NF-PanNET G1/G2. Relationship between lymph nodes status and (c) tumor grade and (d) tumor size in patients with localized NF-PanNET G1/G2 who received curative resection surgery

NF-PanNET, non-functioning pancreatic neuroendocrine tumor.

Fig. 4 Time-dependent ROC curves for comparison of the RSF and Cox models

(a) Time-dependent ROC curves and ROC analysis to predict (b) 1-year, (c) 5-year, and (d) 10-year DFS using the RSF and Cox models

ROC, receiver operating characteristic; RSF, random survival forest; Cox, Cox proportional hazards regression; DFS, disease-free survival.

Fig. 5 Out-of-bag variable importance of RSF and partial 5-year predicted DFS for the five most influential variables

(a) Out-of-bag variable importance of RSF for the log-rank splitting rule. (b–e) The values on the vertical axis represent the predicted DFS probability for a given predictor, after adjusting for all other predictors. (b, e) Continuous variables. (c, d, f) Discrete variables.

RSF, random survival forest; LN, lymph node; LVI, lymph vascular invasion; MPD, main pancreatic duct; PNI, perineural invasion; DFS, disease-free survival.

Figures

Fig.1

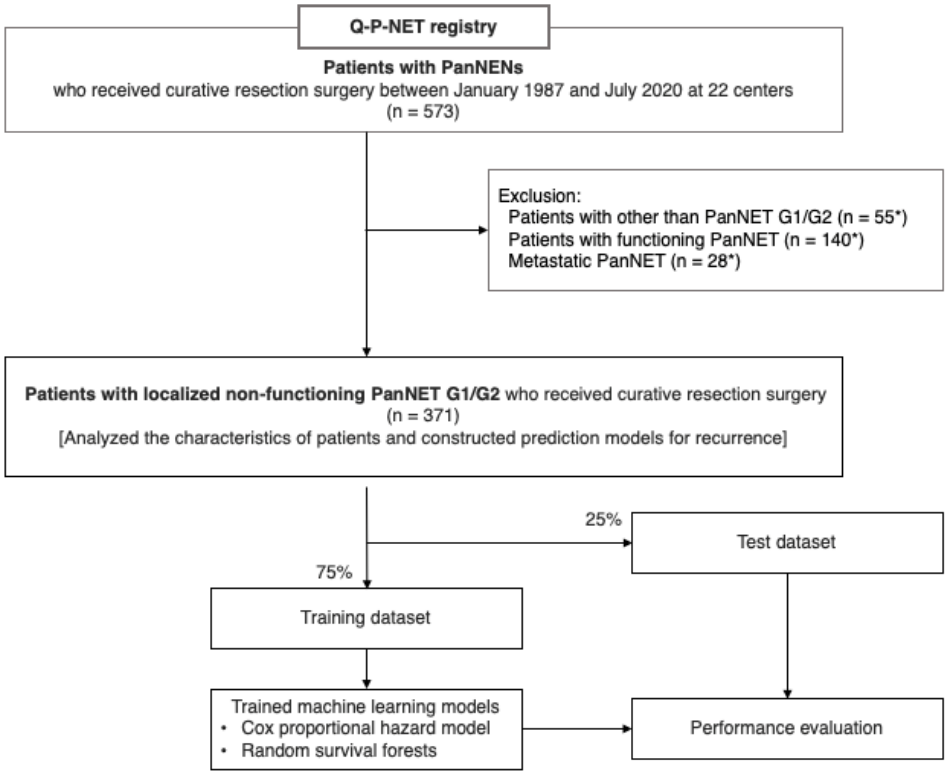
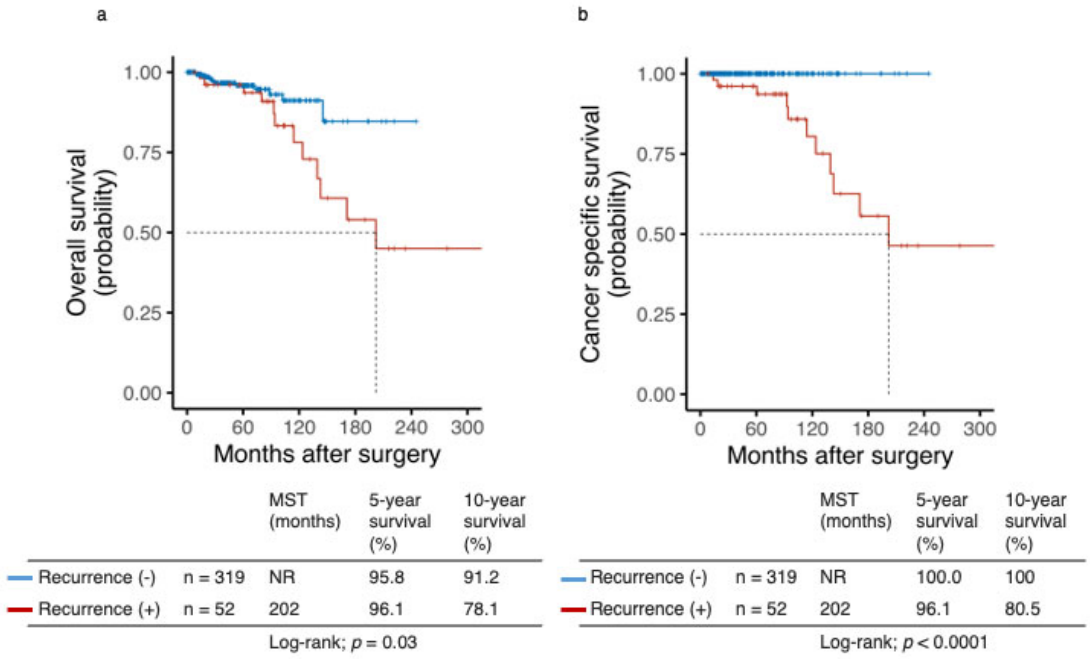


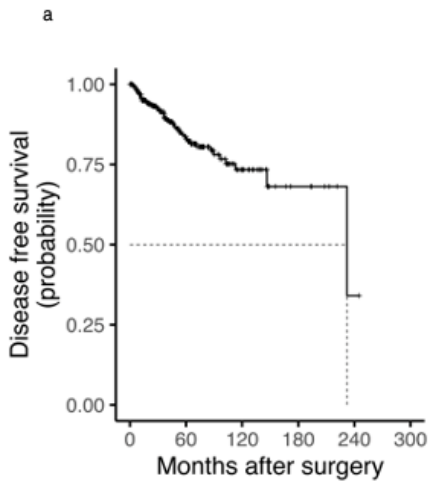
Fig.2

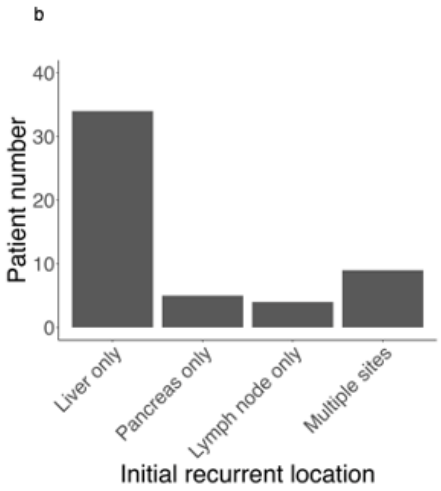


		MST (months)	5-year survival (%)	10-year survival (%)
Recurrence (-)	n = 319	NR	95.8	91.2
Recurrence (+)	n = 52	202	96.1	78.1
Log-rank; $p = 0.03$				

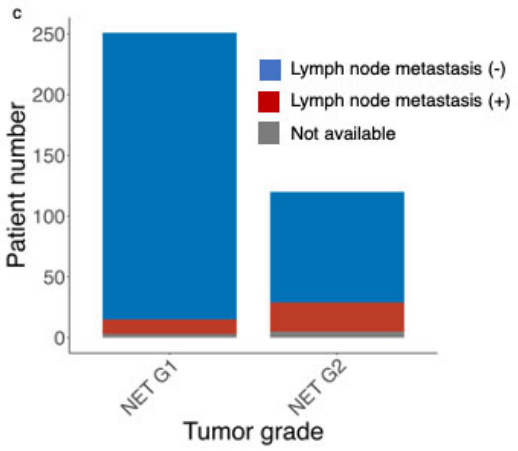
		MST (months)	5-year survival (%)	10-year survival (%)
Recurrence (-)	n = 319	NR	100.0	100
Recurrence (+)	n = 52	202	96.1	80.5
Log-rank; $p < 0.0001$				

Fig.3



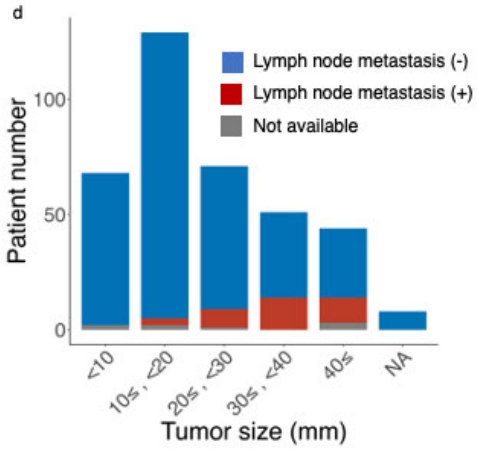


Initial recurrent location	n (%)
Liver only	34 (65.4)
Pancreas only	5 (9.6)
Lymph node only	4 (7.7)
Multiple sites	9 (17.3)



Tumor grade	Patient, n (%)	Lymph node metastasis (+), n (%)
NET G1	248	12 (4.8)
NET G2	115	24 (20.9)

excluded 8 patients whose lymph node status was unknown



Tumor size	Patient, n (%)	Lymph node metastasis (+), n (%)
<10mm	66	0 (0.0)
10mm≤, <20mm	127	3 (2.4)
20mm≤, <30mm	70	8 (11.4)
30mm≤, <40mm	51	14 (27.5)
40mm≤,	41	11 (26.8)
Not available	8	0 (0)

excluded 8 patients whose lymph node status was unknown

Fig.4

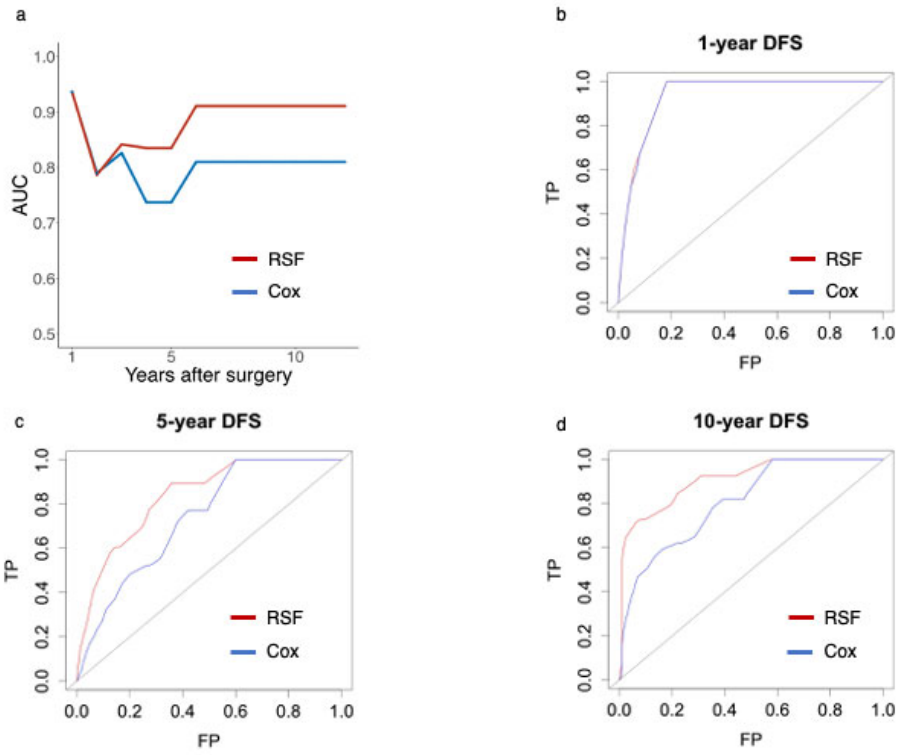
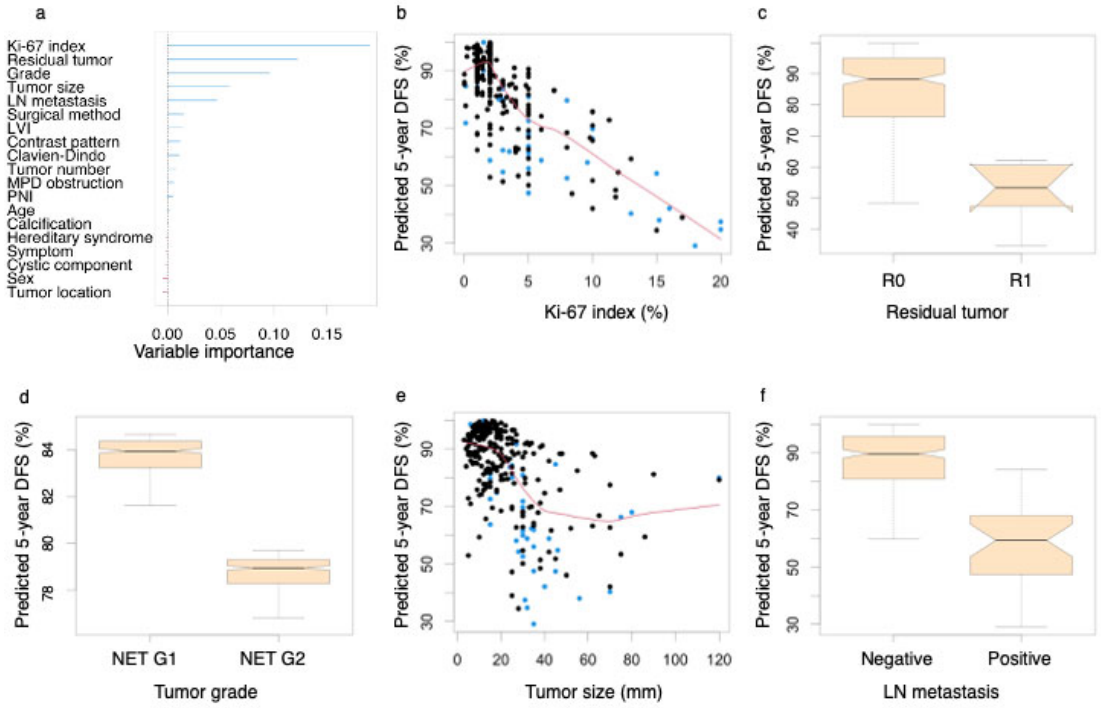

a
AUC
Years after surgery
RSF
Cox
b
1-year DFS
TP
FP
RSF
Cox
c
5-year DFS
TP
FP
RSF
Cox
d
10-year DFS
TP
FP
RSF
Cox

Fig.5


a
Ki-67 index
Residual tumor
Grade
Tumor size
LN metastasis
Surgical method
LVI
Contrast pattern
Clavien-Dindo
Tumor number
MPD obstruction
PNI
Age
Calcification
Hereditary syndrome
Symptom
Cystic component
Sex
Tumor location
0.00 0.05 0.10 0.15
Variable importance
b
Predicted 5-year DFS (%)
Ki-67 index (%)
c
Predicted 5-year DFS (%)
R0
R1
Residual tumor
d
Predicted 5-year DFS (%)
NET G1
NET G2
Tumor grade
e
Predicted 5-year DFS (%)
Tumor size (mm)
f
Predicted 5-year DFS (%)
Negative
Positive
LN metastasis

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Journal name: Journal of Gastroenterology

Author names:

Masatoshi Murakami[1], Nao Fujimori[1], Kohei Nakata[2], Masafumi Nakamura[2], Shinichi Hashimoto[3], Hiroshi Kurahara[4], Kazuyoshi Nishihara[5], Toshiya Abe[5], Shunpei Hashigo[6], Naotaka Kugiyama[6], Eisuke Ozawa[7], Kazuhisa Okamoto[8], Yusuke Ishida[9], Keiichi Okano[10], Ryo Takaki[11], Yutaka Shimamatsu[12], Tetsuhide Ito[13,14], Masami Miki[15], Noriko Oza[16], Daisuke Yamaguchi[17], Hirofumi Yamamoto[18], Hironobu Takedomi[19], Ken Kawabe[20], Tetsuro Akashi[21], Koichi Miyahara[22], Jiro Ohuchida[23], Eishi Nagai[24], Yohei Nakashima[25], Toshiharu Ueki[26], Kousei Ishigami[27], Hironobu Umakoshi[1], Keijiro Ueda[1], Takamasa Oono[1], and Yoshihiro Ogawa[1]

Affiliation:

[1]Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, 812-8582, Japan.

[2]Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

[3]Digestive and Lifestyle Diseases, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan.

[4]Department of Digestive Surgery, Breast and Thyroid Surgery, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan.

[5]Department of Surgery, Kitakyushu Municipal Medical Center, Kitakyushu, Japan.

[6]Department of Gastroenterology and Hepatology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan.

[7]Department of Gastroenterology and Hepatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan.

[8]Department of Gastroenterology, Faculty of Medicine, Oita University, Oita, Japan.

[9]Department of Gastroenterology and Medicine, Faculty of Medicine, Fukuoka University, Fukuoka, Japan.

[10]Department of Gastroenterological Surgery, Faculty of Medicine, Kagawa University, Kita-gun, Japan.

[11]Department of Gastroenterology, Urasoe General Hospital, Urasoe, Japan.

[12]Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Kurume, Japan

[13]Neuroendocrine Tumor Centre, Fukuoka Sanno Hospital, Fukuoka, Japan.

[14]Department of Gastroenterology, Graduate School of Medical Sciences, International University of Health and Welfare, Fukuoka, Japan

[15]Department of Gastroenterology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan.

[16]Department of Hepato-Biliary-Pancreatology, Saga-ken Medical Centre Koseikan, Saga, Japan.

[17]Department of Gastroenterology, National Hospital Organization Ureshino Medical Center, Ureshino, Japan.

[18]Department of Surgery, Hamanomachi Hospital, Fukuoka, Japan.

[19]Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, Saga University, Saga, Japan.

[20]Department of Gastroenterology, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan.

[21]Department of Internal Medicine, Saiseikai Fukuoka General Hospital, Fukuoka, Japan.

[22]Department of Internal Medicine, Karatsu Red Cross Hospital, Karatsu, Japan.

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[24]Department of Surgery, Fukuoka Red Cross Hospital, Fukuoka, Japan.

[25]Department of Surgery, Japan Community Health Care Organization, Kyushu Hospital, Kitakyushu, Japan.

[26]Department of Gastroenterology, Fukuoka University Chikushi Hospital, Chikushino, Japan.

[27]Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

[*]Corresponding author: Nao Fujimori, MD, PhD

Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, 812-8582, Japan.

Telephone number: +81-92-642-5285

Fax number: +81-92-642-5287

Email: fujimori.nao.239@m.kyushu-u.ac.jp

Captions to Supplementary Figures

Supplementary Fig. 1 The representative CT/MRI findings of PanNETs

The CT/MRI features of PanNETs were retrospectively reviewed for contrast patterns and the presence or absence of MPD obstruction, cystic component, and calcification. Contrast patterns were evaluated by contrast-enhanced CT/MRI in the arterial phase and classified as typical or atypical; hypervascular and homogenous internal contrast patterns were defined as typical, while iso-or hypovascular and/or heterogeneous internal contrast patterns were defined as atypical. Arrows represent tumors (a-d), and arrowheads represent dilated MPD (b)

CT, computed tomography; MRI, magnetic resonance imaging; PanNETs, pancreatic neuroendocrine tumors; MPD, main pancreatic duct.

Supplementary Fig. 2 Breakdown of the Q-P-NET registry

Breakdown of the Q-P-NET registry regarding tumor grade (a) and functionality (b) with and without recurrence, and disease-free survival comparing patients with each tumor grade (c) and functionality (d)

Q-P-NET registry, Kyushu pancreatic neuroendocrine tumor registry; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; DFS, disease-free survival; NF-PanNENs, non-functioning pancreatic neuroendocrine neoplasms; F-PanNENs, functioning pancreatic neuroendocrine neoplasms

Supplementary Fig. 3 Kaplan–Meier survival curves of patients in the Q-P-NET registry

(a) Overall and (b) cancer-specific survival comparing patients with each tumor grade (a, b). The significant differences were analyzed by log-rank tests between NET G1, G2 and G3, or NEC

Q-P-NET registry, Kyushu pancreatic neuroendocrine tumor registry; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm.

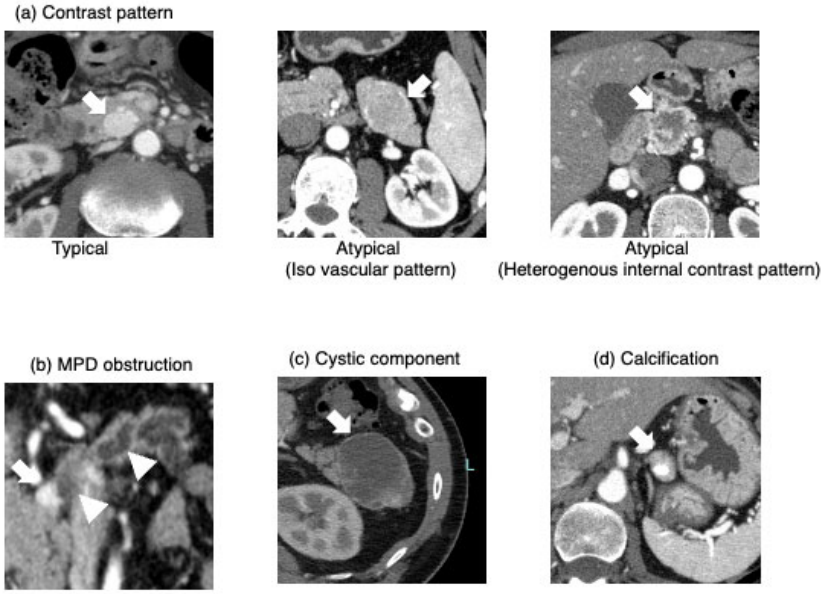
Supplementary Fig. 4 Calibration plots on the test dataset

Calibration plots on the test dataset using the RSF and Cox models for (a) 1-year, (b) 5-year, and (c) 10-year DFS

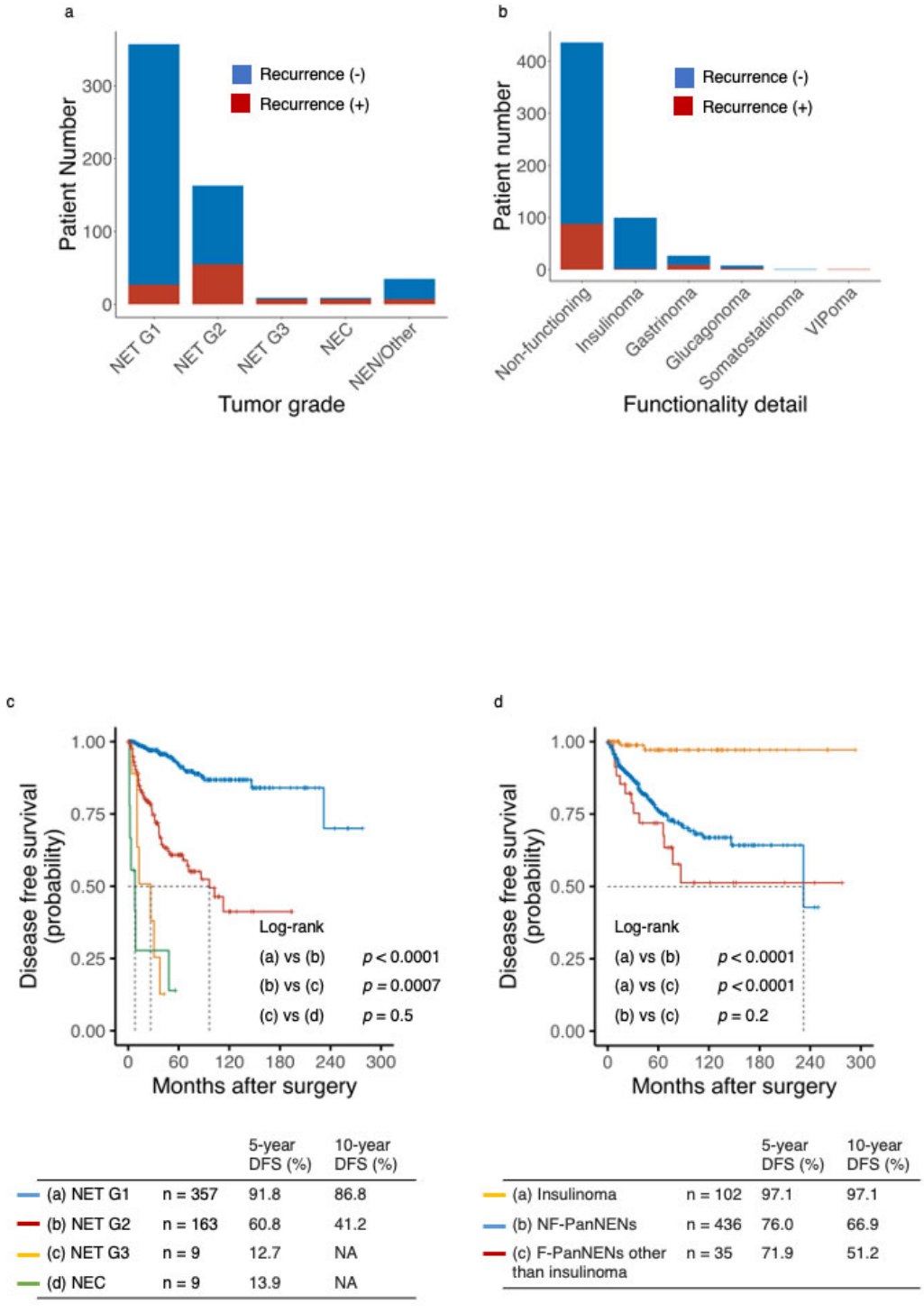
RSF, random survival forest; Cox, Cox proportional hazards regression; DFS, disease-free survival.

Supplementary figures

Supplementary Fig. 1



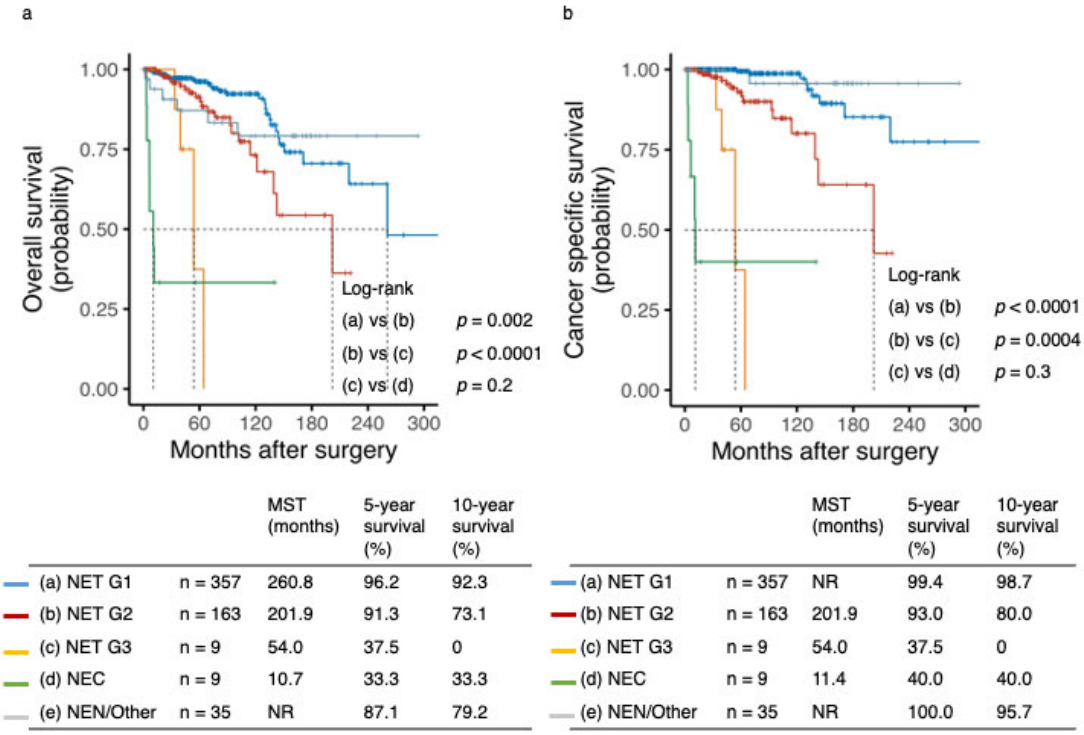
Supplementary Fig. 2



		5-year DFS (%)	10-year DFS (%)
(a) NET G1	n = 357	91.8	86.8
(b) NET G2	n = 163	60.8	41.2
(c) NET G3	n = 9	12.7	NA
(d) NEC	n = 9	13.9	NA

		5-year DFS (%)	10-year DFS (%)
(a) Insulinoma	n = 102	97.1	97.1
(b) NF-PanNENs	n = 436	76.0	66.9
(c) F-PanNENs other than insulinoma	n = 35	71.9	51.2

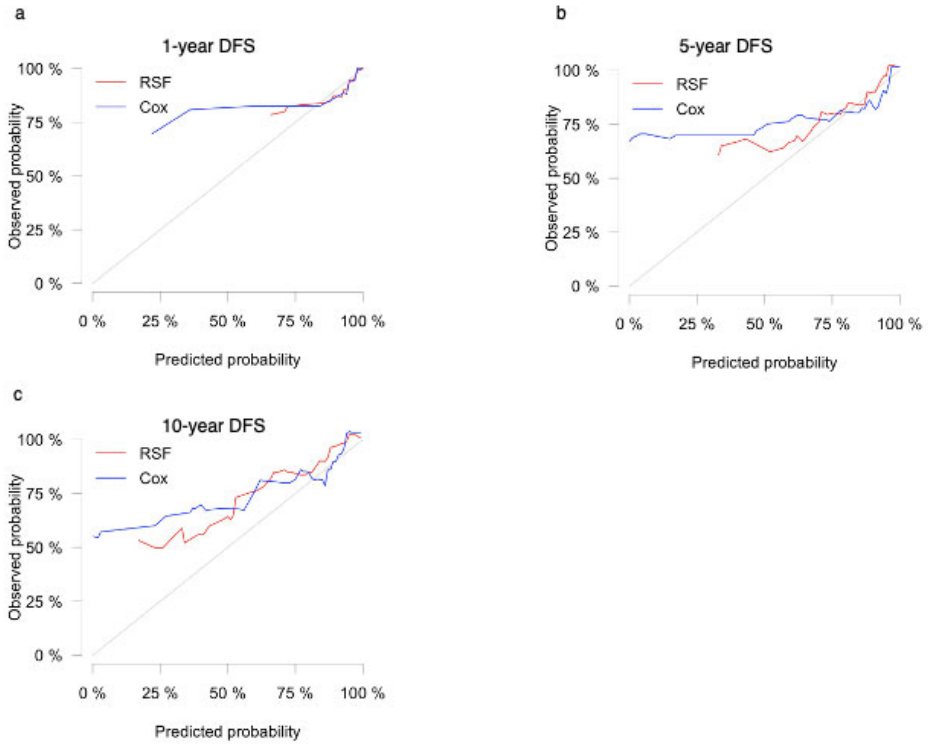
Supplementary Fig. 3



		MST (months)	5-year survival (%)	10-year survival (%)
(a) NET G1	n = 357	260.8	96.2	92.3
(b) NET G2	n = 163	201.9	91.3	73.1
(c) NET G3	n = 9	54.0	37.5	0
(d) NEC	n = 9	10.7	33.3	33.3
(e) NEN/Other	n = 35	NR	87.1	79.2

		MST (months)	5-year survival (%)	10-year survival (%)
(a) NET G1	n = 357	NR	99.4	98.7
(b) NET G2	n = 163	201.9	93.0	80.0
(c) NET G3	n = 9	54.0	37.5	0
(d) NEC	n = 9	11.4	40.0	40.0
(e) NEN/Other	n = 35	NR	100.0	95.7

Supplementary Fig. 4



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[26]Department of Gastroenterology, Fukuoka University Chikushi Hospital, Chikushino, Japan.

[27]Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

[*]Corresponding author: Nao Fujimori, MD, PhD

Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, 812-8582, Japan.

Telephone number: +81-92-642-5285

Fax number: +81-92-642-5287

Email: fujimori.nao.239@m.kyushu-u.ac.jp

Supplementary Table 1. Names and approval numbers of the participating facilities

No	Prefecture	Institution	Department	Approval number
1	Fukuoka	Kyushu University Hospital	Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences Department of Surgery and Oncology, Graduate School of Medical Sciences Department of Clinical Radiology, Graduate School of Medical Sciences	2020-509
2	Kagoshima	Kagoshima University Hospital	Digestive and Lifestyle Diseases, Graduate School of Medical and Dental Sciences Department of Digestive Surgery, Breast and Thyroid Surgery, Graduate School of Medical and Dental Sciences	200268
3	Fukuoka	Kitakyushu Municipal Medical Center	Department of Surgery	202011016
4	Kumamoto	Kumamoto University Hospital	Department of Gastroenterology and Hepatology, Graduate School of Medical Sciences	2204
5	Nagasaki	Nagasaki University Hospital	Department of Gastroenterology and Hepatology, Graduate School of Biomedical Sciences	21011806
6	Oita	Oita university Hospital	Department of Gastroenterology, Faculty of Medicine	2015
7	Fukuoka	Fukuoka University Hospital	Department of Gastroenterology and Medicine, Faculty of Medicine	H21-02-006
8	Kagawa	Kagawa University Hospital	Department of Gastroenterological Surgery, Faculty of Medicine	2020-185
9	Okinawa	Urasoe General Hospital	Department of Gastroenterology	2020-025
10	Fukuoka	Kurume University Hospital	Division of Gastroenterology, Department of Medicine	20235
11	Fukuoka	Fukuoka Sanno Hospital	Neuroendocrine Tumor Centre	21-FS-491
12	Fukuoka	National Hospital Organization Kyushu Cancer Center	Department of Gastroenterology	2020-73
13	Saga	Saga-ken Medical Centre Koseikan	Department of Hepato-Biliary-Pancreatology	21-01-01-02
14	Saga	National Hospital Organization Ureshino Medical Center	Department of Gastroenterology	20-66
15	Fukuoka	Federation of National Public Service Personnel Mutual Aid Associations Hamanomachi Hospital	Department of Surgery	2020-36
16	Saga	Saga University Hospital, Japanese Red Cross Karatsu Hospital	Department of Internal Medicine	540
17	Fukuoka	National Hospital Organization Kyushu Medical Center	Division of Gastroenterology	21C061
18	Fukuoka	Saiseikai Fukuoka General Hospital	Department of Internal Medicine	2020-23
19	Saga	Karatsu Red Cross Hospital	Department of Internal Medicine	9-1
20	Miyazaki	Miyazaki Prefectural Miyazaki Hospital	Department of Surgery	21-6
21	Fukuoka	Japanese Red Cross Fukuoka Hospital	Department of Surgery	540
22	Fukuoka	Japan Community Health Care Organization Kyushu Hospital	Department of Surgery	739

Supplementary Table 2. Baseline characteristics about the dataset using for the prediction models after imputating the missing data

Variable	Total (n=371)	Training dataset (n=279)	Test dataset (n=92)	P value
Age at surgical treatment, ≥65	137 (36.9)	105 (37.6)	32 (34.8)	0.6231
Sex, Male	178 (48.0)	130 (46.6)	48 (52.2)	0.353
Symptom, presence	81 (21.8)	61 (21.9)	20 (21.7)	0.98
Hereditary syndrome, presence	21 (5.7)	17 (6.1)	4 (4.3)	0.5298
Tumor location, head	154 (41.5)	120 (43.0)	34 (37.0)	0.3068
Tumor number, solitary	26 (7.0)	21 (7.5)	5 (5.4)	0.4955
Contrast pattern*, atypical	177 (47.7)	129 (46.2)	48 (52.2)	0.3228
CT; Main pancreatic duct obstruction, presence	54 (14.6)	38 (13.6)	16 (17.4)	0.3737
Cystic component, presence	99 (26.7)	69 (24.7)	30 (32.6)	0.1385
Calcification, presence	44 (11.9)	36 (12.9)	8 (8.7)	0.279
Surgical method, minimally surgery	164 (44.2)	119 (42.7)	45 (48.9)	0.2944
Clavien-Dindo classification, ≥Grade III	68 (18.3)	49 (17.6)	19 (20.7)	0.5066
Tumor size [median(CI)]	18.0 (10.0-30.0)	18.0 (11.0-30.0)	17.0 (10.0-28.3)	0.9157
Ki-67 index [median(CI)]	2.0 (1.0-4.0)	2.0 (1.0-4.0)	2.0 (1.0-4.0)	0.5857
Tumor grade, G2**	120 (32.3)	96 (34.4)	24 (26.1)	0.139
Lymph node metastasis, presence	39 (10.5)	32 (11.5)	7 (7.6)	0.2951
Residual tumor, R1	8 (2.2)	7 (2.5)	1 (1.1)	0.4155
Lymph-vascular invasion, presence	101 (27.2)	79 (28.3)	22 (23.9)	0.4107
Perineural invasion, presence	72 (19.4)	55 (19.7)	17 (18.5)	0.7951
Recurrence	52 (14.0)	40 (14.3)	12 (13.0)	0.7566
Recurrence free survival [median(CI)]	39.1 (17.8-70.1)	40.2 (17.7-70.1)	34.4 (17.8-69.7)	0.9245

Abbreviations: NF-PanNET, non-functioning pancreatic neuroendocrine tumor.

*non-hypervascular or heterogenous internal contrast pattern **WHO 2019 classification

Table 1. Patient and tumor characteristics about patients with localized NF-PanNET G1/2 who received curative-intent surgery

Variables	Number (n=371)
Age at surgical treatment, y (median [IQR])	61.0 [51.0-69.0]
Sex (n, %)	
Male	178 (48.0)
Female	193 (52.0)
Hereditary syndrome	
Absence	350 (94.3)
Multiple Endocrine Neoplasia type 1	15 (4.0)
Von Hippel-Lindau Syndrome	6 (1.6)
Symptom (n, %)	
Absence	288 (77.6)
Presence	74 (19.9)
Not available	9 (2.4)
Tumor location (n, %)	
Pancreatic head	153 (41.3)
Pancreatic body/ tail	216 (58.2)
Not available	2 (0.5)
Tumor number (n, %)	
Solitary	345 (93.0)
Multiple	26 (7.0)
NSE (median [IQR]) (Not avairable=235)	11.0 [9.2-12.8]
ProGRP (median [IQR]) (Not avairable=273)	33.3 [22.9-45.4]
Contrast pattern* (n, %)	
Typical	184 (49.6)
Atypical	146 (39.4)
Not available	41 (11.1)
Cystic component (n, %)	
Absence	258 (69.5)
Presence	90 (24.3)
Not available	23 (6.2)
Calcification (n, %)	
Absence	312 (84.1)
Presence	36 (9.7)
Not available	23 (6.2)
Main pancreatic duct obstruction (n, %)	
Absence	302 (81.4)
Presence	46 (12.4)
Not available	23 (6.2)
Surgical method (n, %)	
Open surgery	205 (55.3)
Laparoscopic or robotic assisted surgery	164 (44.2)
Not available	2 (0.5)
Surgical procedure (n, %)	
Pancreatoduodenectomy	126 (34.0)
Distal pancreatectomy	183 (49.3)
Segmental pancreatectomy	23 (6.2)
Enucleation	39 (10.5)
Lymphadenectomy (n, %)	
Absence	267 (72.0)
Presence	90 (24.3)
Not available	14 (3.8)
Clavien-Dindo classification (n, %)	
≤grade II	291 (78.4)
grade III	42 (11.3)
grade IV	5 (1.3)
Not available	33 (8.9)
Ki-67 index (median [IQR]) (Not available=15)	2.0 [1.0-4.0]
Tumor grade** (n, %)	
NET G1	251 (67.7)
NET G2	120 (32.3)
Tumor size (median [IQR]) (Not available=8)	18.0 [10.0-30.0]
Tumor size	
<10mm	68 (18.3)
10mm≤, <20mm	129 (34.8)
20mm≤, <30mm	71 (19.1)
30mm≤, <40mm	51 (13.7)
40mm≤,	44 (11.9)
Not available	8 (2.2)
Lymph node metastasis	
Absence	327 (88.1)
Presence	36 (9.7)
Not available	8 (2.2)
Stage*** (n, %)	
Stage I	201 (54.2)
Stage II	122 (32.9)
Stage III	39 (10.5)
Not available	9 (2.4)
Residual tumor (n, %)	
R0	361 (97.3)
R1	8 (2.2)
Not available	2 (0.5)
Lymphovascular invasion (n, %)	
Absence	255 (68.7)
Presence	89 (24.0)
Not available	27 (7.3)
Perineural invasion (n, %)	
Absence	278 (74.9)
Presence	59 (15.9)
Not available	34 (9.2)

Abbreviations: NF-PanNET, non-functioning pancreatic neuroendocrine tumor; NSE, neuron specific enolase; ProGRP, pro-gastrin releasing peptide.

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***Union for International Cancer Control staging (8th edition)

Table 2. Comparison of the RSF and Cox model on the test dataset

	RSF	Cox
C-index	0.841	0.820
IBS	0.108	0.151
AUC		
1-year DFS	0.937	0.936
5-year DFS	0.835	0.737
10-year DFS	0.911	0.810

Abbreviations: RSF, random survival forest; Cox, Cox proportional hazards; C-index, Harrell's concordance index; IBS, integrated Brier score; AUC, area under the receiver operator curve; DFS, disease free survival.