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ORIGINAL ARTICLE

# Prediction of Tumor Prognosis of Pancreatic Neuroendocrine Tumors Using Image, Surgical and Pathologic Findings

**Feifan Chen[1*], Yinshi Huang[1*], Congying Chen[1], Yajing Zhang[1], Yiyi Zhang[1], Rong Wan[1], Min Xu[1]**

1 Department of Gastroenterology, Shanghai General Hospital, Shanghai Jiaotong University, 200080, Shanghai, P.R. China

*These authors contribute equally to this work.

*Correspondence to:* Min Xu MD
Department of Gastroenterology, Shanghai General Hospital, Shanghai Jiaotong University, No. 100 Haining Road, Shanghai, P.R. China, 200080
tel: 13386259716, e-mail: xumin73@126.com

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## Abstrac

**OBJECTIVES:** To evaluate the magnetic resonance imaging (MRI) and computed tomography (CT) findings along with other surgical and pathologic features as prognosis predictors in pancreatic neuroendocrine tumors (PNETs).
**METHODS:** In this study, we retrospectively analyzed a clinical data pool of patients with pathologically confirmed PNETs. CT and MRI findings were evaluated as potential prediction parameters of tumor-nodes-metastases (TNM) stage and grade, using Fisher's exact test. Univariate and multivariate logistic regression models were used to estimate the risk factors associated with tumor recurrence after surgery. The Kaplan-Meier method and Cox proportional hazards model were used for recurrence-free survival analysis.
**RESULTS:** The predictors of higher TNM stages were tumor diameter, tumor boundary, distant metastases, and lymphadenopathy on CT scan. From MRI images, tumor diameter, T2-weighted image, tumor enhancement, and pancreatic duct dilatation showed statistically significant differences among TNM stages. Univariate analysis showed that American Joint Committee on Cancer (AJCC) TNM stage, World Health Organization (WHO) tumor grade, sex, smoking, and drinking were associated with tumor recurrence and disease-free survival (DFS); while tumor and metastasis also affected DFS. Multivariate survival analysis confirmed that AJCC TNM was an independent predictor after adjusting other covariates. Peripancreatic invasion and lymph node metastases as well as blurred boundary detected by CT or MRI may be independent risk factors for TNM stage and clinical outcome of PNETs.
**CONCLUSION:** TNM stage is a valuable predictor of prognosis in PNETs. Information from CT and MRI imaging can be used to determine the TNM stage, and to estimate the tumor prognosis, guide the follow-up, and avoid ineffective treatments.

**Abbreviations:**

| | |
|---|---|
| AJCC | - American Joint Committee on Cancer |
| ADC | - Apparent diffusion coefficient |
| CT | - Computed Tomography |
| DWI | - Diffusion weighted imaging |
| DFS | - Disease-free survival |
| EUS | - Endoscopic ultrasonography |
| HR | - Hazard ratio |
| MRI | - Magnetic Resonance Imaging |
| MEN-I | - Multiple endocrine neoplasia-I type |
| PNETs | - Pancreatic neuroendocrine tumors |
| SD | - Standard deviation |
| TNM | - Tumor-nodes-metastases |
| WHO | - World Health Organization |

## INTRODUCTION

Pancreatic neuroendocrine tumors (PNETs), originated from pancreatic neuroendocrine, account for about 2% of all pancreatic tumors, with an annual incidence rate of about 20-30 per million (Reid *et al.* 2014; Sun *et al.* 2019). Although relatively rare, the incidence of PNETs has increased significantly over the past few decades (Dasari *et al.* 2017; Luo *et al.* 2017; Wu *et al.* 2019; Liu *et al.* 2022). As heterogeneous neoplasm, PNETs may arise anywhere in the pancreas, from mature pancreatic endocrine cells to pluripotent stem cells of the pancreas, and are associated with von Hippel–Lindau, MEN1, and other syndromes. PNETs have a fairly wide range of morphologic features, including oncocytic, pleomorphic, ductulo-insular, sclerosing, and lipid-rich variants (Reid *et al.* 2014; Mihalache *et al.* 2019), and require appropriate treatment strategy (Lim *et al.* 2023). Although the overall 10-year survival rate reaches 60–70% (Watzka *et al.* 2020), all PNETs are malignant with a protracted clinical course, so even low-stage, low-grade patients may relapse or metastasize during long-term follow-up (Yang *et al.* 2017; Lim *et al.* 2023). Therefore, accurate estimation of the recurrence probability will help for judging prognosis, guiding follow-up, and avoiding futile treatment.

The main adverse prognostic factor is histopathological grade according to the World Health Organization (WHO) 2010 classification, which mainly depends on proliferative activity and the stage at diagnosis (Reid *et al.* 2014; Rindi *et al.* 2010). Recently, several studies have demonstrated that higher tumor grade and more advanced tumor-nodes-metastases (TNM) stage are effective predictors of worse clinical outcomes and shorter survival periods after surgical resection (You *et al.* 2019; Yang *et al.* 2019; Yang *et al.* 2015b). The new American Joint Committee on Cancer (AJCC) TNM staging system for PNETs adopted in clinical practice has prognostic implication (You *et al.* 2019; Heng *et al.* 2023), and the tumor grade confirmed by postoperative histopathology affects treatment strategies (Rindi *et al.* 2010). Computed tomography (CT) and magnetic resonance imaging (MRI) have become the main imaging methods for evaluating pancreatic tumors (Choi *et al.* 2018; De Robertis *et al.* 2017; Guo *et al.* 2019; Kim *et al.* 2015; Kim *et al.* 2016; Li *et al.* 2021; Salahshour *et al.* 2020; Sun *et al.* 2019; Zhao *et al.* 2020), particularly in TNM staging, and are of great value in the qualitative diagnosis of tumors. The non-invasive imaging findings can be used not only for estimating the TNM stage and grade of PNETs, but also for formulating therapeutic strategies and predicting prognosis prior to surgery (Sun *et al.* 2019; Zhao *et al.* 2020). Here, we performed a retrospective cohort study from a clinical dataset containing patients with confirmed PNETs to assess potential determinants of postoperative tumor prognosis, including tumor recurrence risk and disease-free survival time.

## MATERIALS & METHODS

### *Study design*

A clinical dataset containing 59 patients with pathologically confirmed PNETs admitted to our Hospital from March 2012 to April 2019 was retrospectively analyzed. CT and MRI findings were evaluated as potential predictors of TNM stage and grade, using Fisher's exact test. Univariate and multivariate survival analysis were performed using Kaplan-Meier method and Cox proportional hazards model.

### *Patients' enrollment criteria*

Patients with PNETs were pathologically confirmed by surgical biopsy or fine needle aspiration, according to 2017 AJCC eighth-edition cancer staging manual (Amin *et al.* 2017). All enrolled patients underwent imaging examinations within 2 months prior to surgery. Patients with other malignant tumors, including those with a few diffused neuroendocrine cells in the pancreas, were excluded. In addition, patients showing suspicious clinical symptoms without pathological confirmation were also excluded. All patients who received preoperative radical surgical resection without distant metastasis were included in the analysis of disease-free survival (DFS).

### *Pathological assessment*

Patients were diagnosed with PNETs at different stages, based on AJCC cancer staging manual (Amin *et al.* 2017). Tumor characteristics, including diameter, location, invasion and metastasis status (peripancreatic invasion, main pancreatic duct dilatation, vascular cancer embolus, perineural invasion, surgical margin status, lymph node and distant metastases) were evaluated based on pathological findings. Histopathological tumor grading was carried out postoperatively with the standard of the 2010 WHO grading classifications (Rindi *et al.* 2010).

### *Imaging analysis*

Imaging examinations including B-ultrasound, contrast-enhanced CT, MRI, endoscopic ultrasonography (EUS), as well as $^{18F\text{-}FDG}$PET-CT, were

conducted. CT and MRI images were blindly reviewed independently by two experienced radiologists with at least 8 years of experience. When discrepancy existed, the final conclusion was reached after discussion with a senior radiologist with 15 years of experience in abdominal imaging. The following findings from CT and MRI were analyzed:

1) tumor diameter, location (head, neck, body, and tail), component (cystic, solid, mixed), tumor boundaries (clear or blurred), and pancreatic duct dilatation (absent, present).
2) enhancement (none, homo-, heterogeneous), calcification (absent, present), distant metastases, and lymphadenopathy from CT only.
3) enhancement (hypo-, hyper-, similar or ring-enhancement), T1WI (hypo-, isointense, mixed), and T2WI (hypo-, iso-, hyperintense, mixed) from MRI only.

*Outcome*

The disease outcome was defined as death, tumor recurrence, or metastasis after radical surgical resection as assessed by CT or MRI during follow-up. Overall survival time was defined as the time from the radical surgical resection to either death, tumor recurrence, or disease-free last contact. Patients were followed up with outpatient visit and, in some cases, telephone interviews. The follow-up ranged from 0.5 to 70 months.

*Covariates*

In addition to TNM stage and WHO grade, other clinical information such as patients' sex, age, past medical history, treatment method, surgical data (tumor size, peripancreatic invasion, main pancreatic duct dilatation, vascular cancer embolus, perineural invasion, surgical margin status, lymph node and distant metastases), and postoperative complication were included in the analysis.

*Statistical analysis*

Numeric variables were showed as means ± standard deviation (SD). Categorical variables were reported as percentage (%). Imaging findings were grouped into different subtypes, and their association with TNM stage and grade was tested by Fisher's exact test. The association between tumor recurrence and each category variables were tested using Fisher's exact test and univariate logistic linear regression model. For all risk factors with $p < 0.05$ in univariate analysis, multivariate logistic linear regression model was applied. The univariate analysis of the risk factors affecting disease-free survival was conducted using the Kaplan-Meier method with log-rank (Mantel-Cox) test and Mantel-Haenszel hazard ratio (HR). Cox regression proportional hazards model and likelihood ratio test were employed for univariate and multivariate analyses, in which only factors with $p < 0.05$ in univariate analysis were enrolled. Hazard ratios (HRs) and 95% confidence interval were calculated. All statistical analyses were performed in either SPSS25.0 for Mac software (IBM, Armonk, NY, USA), R for Mac OS X, or SAS Studio University Edition. $p < 0.05$ was considered significant.

**Tab. 1.** Summary of Clinical characteristics of enrolled patients

| | **Total (N=59)** |
|---|---|
| **Sex** | |
| male | 23 |
| female | 36 |
| **Age** | |
| median | 58 |
| mean | 57 |
| **PNETs** | |
| functional | 8 (13.6%) |
| insulinomas | 5 |
| gastrinoma | 1 |
| MEM-I | 1 |
| non-functional | 51 (86.4%) |
| **Main Symptoms** | |
| abdominal pain | 19 |
| epigastric bloating | 8 |
| weight loss | 5 |
| hypoglycemia | 5 |
| nausea and vomiting | 4 |
| diarrhea | 3 |
| **Complications** | |
| hypertension | 16 |
| diabetes | 7 |
| peptic ulcers | 3 |
| **Surgical treatment** | |
| radical surgical resection | 40 |
| Palliative resection | 2 |
| somatostatin analogs | 2 |
| **Postoperative complications** | |
| Surgical site infection | 6 |
| Wound bleeding | 1 |
| anastomotic bleeding | 1 |
| incisional hernia | 1 |
| pancreatic leakage | 1 |

## RESULTS

*Clinical characteristics of enrolled patients*

This study included 59 patients, 23 males and 36 females (Table 1). The age range was between 19-83 years old, with the median age at 58 and mean

**Tab. 2.** Computed Tomography (CT) scan with tumor-nodes-metastases (TNM) stage and World Health Organization (WHO) 2010 Grade

| | TNM stage | | | | | WHO 2010 Grade | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **I** | **II** | **III** | **IV** | ***p*-value** | **G1** | **G2** | **G3** | ***p*-value** |
| Tumor diameter[1] | 3.23±1.27 | 3.84±0.44 | 5.16±2.14 | 8.00 | 0.071 | 2.92±0.81 | 5.08±0.80 | 3.80±0.54 | 0.019 |
| Location | | | | | 0.141 | | | | 0.842 |
| Head | 4(40.0%) | 4(22.2%) | 3(60.0%) | 0(0.0%) | | 5(33.3%) | 5(33.3%) | 1(25.0%) | |
| Neck | 3(30.0%) | 1(5.6%) | 0(0.0%) | 0(0.0%) | | 3(20.0%) | 1(6.7%) | 0(0.0%) | |
| Body and tail | 3(30.0%) | 13(72.2%) | 2(40.0%) | 1(100.0%) | | 7(46.7%) | 9(60.0%) | 3(75.0%) | |
| Component | | | | | 0.055 | | | | 0.837 |
| Cystic | 2(20.0%) | 4(22.2%) | 4(80.0%) | 0(0.0%) | | 5(33.3%) | 3(20.0%) | 2(50.0%) | |
| Solid | 8(80.0%) | 9(50.0%) | 1(20.0%) | 1(100.0%) | | 8(53.3%) | 9(60.0%) | 2(50.0%) | |
| Mixed | 0(0.0%) | 5(27.8%) | 0(0.0%) | 0(0.0%) | | 2(13.3%) | 3(20.0%) | 0(0.0%) | |
| Enhancement | | | | | 0.159 | | | | 0.703 |
| None | 2(20.0%) | 4(22.2%) | 1(20.0%) | 0(0.0%) | | 3(20.0%) | 3(20.0%) | 1(25.0%) | |
| Homogeneous | 8(80.0%) | 12(66.7%) | 2(40.0%) | 0(0.0%) | | 11(73.3%) | 9(60.0%) | 2(50.0%) | |
| Heterogeneous | 0(0.0%) | 2(11.1%) | 2(40.0%) | 1(100.0%) | | 1(6.7%) | 3(20.0%) | 1(25.0%) | |
| Tumor boundary | | | | | 0.000 | | | | 0.035 |
| Clear | 10(100.0%) | 13(72.2%) | 0(0.0%) | 0(0.0%) | | 13(86.7%) | 9(60.0%) | 1(25.0%) | |
| Blurred | 0(0.0%) | 5(27.8%) | 5(100.0%) | 1(100.0%) | | 2(13.3%) | 6(40.0%) | 3(75.0%) | |
| Calcification | | | | | 0.598 | | | | 0.302 |
| Absent | 9(90.0%) | 14(77.8%) | 5(100.0%) | 1(100.0%) | | 14(93.3%) | 11(73.3%) | 4(100.0%) | |
| Present | 1(10.0%) | 4(22.2%) | 0(0.0%) | 0(0.0%) | | 1(6.7%) | 4(26.7%) | 0(0.0%) | |
| Distant metastases | | | | | 0.029 | | | | 1.000 |
| Absent | 10(100.0%) | 18(100.0%) | 5(100.0%) | 0(0.0%) | | 15(100.0%) | 14(93.3%) | 4(100.0%) | |
| Present | 0(0.0%) | 0(0.0%) | 0(0.0%) | 1(100.0%) | | 0(0.0%) | 1(6.7%) | 0(0.0%) | |
| Lymphadenopathy | | | | | 0.034 | | | | 0.474 |
| Absent | 10(100.0%) | 17(94.4%) | 4(80.0%) | 0(0.0%) | | 14(93.3%) | 14(93.3%) | 3(75.0%) | |
| Present | 0(0.0%) | 1(5.6%) | 1(20.0%) | 1(100.0%) | | 1(6.7%) | 1(6.7%) | 1(25.0%) | |
| Pancreatic duct dilatation | | | | | 0.630 | | | | 0.615 |
| Absent | 8(80.0%) | 15(83.3%) | 3(60.0%) | 1(100.0%) | | 11(73.3%) | 13(86.7%) | 3(75.0%) | |
| Present | 2(20.0%) | 3(16.7%) | 2(40.0%) | 0(0.0%) | | 4(26.7%) | 2(13.3%) | 1(25.0%) | |

age at 57. Among them, 51 cases (86.4%) had non-functional PNETs, and 8 cases (13.6%) had functional PNETs, including 5 insulinomas, 1 gastrinoma, and 1 multiple endocrine neoplasia-I type (MEN-I). There were 21 cases of asymptomatic, 19 cases of abdominal pain, 8 cases of epigastric bloating, 5 cases of weight loss, 5 cases of hypoglycemia with dizziness and palpitation, 4 cases of nausea and vomiting, and 3 cases of diarrhea as the main symptom. The patients with gastrinoma had refractory gastric ulcers and suffered from severe upper gastrointestinal bleeding 40 years ago. Of the 59 patients, 16 patients had hypertension, 7 patients had diabetes, and 3 patients had peptic ulcers.

*Surgical treatment*

Fifty patients (92.6%) underwent radical surgical resection, 2 patients (3.7%) underwent palliative resection due to severe abdominal cavity adhesion, and 2 patients (3.7%) received somatostatin analogs after pancreas fine-needle aspiration biopsy under B ultrasound. Among the 50 patients with surgery, 41 of them (82.0%) underwent laparotomy and 9 (18.0%) received laparoscopic surgery. The surgical methods were distal pancreatectomy in 27 cases (54.0%), pancreaticoduodenectomy in 19 cases (38.0%), and local pancreatic tumors resection in 4 cases (8.0 %). After surgery, there were 6 cases of surgical site infection, 1 case of wound bleeding, 1 case of anastomotic bleeding,

**Tab. 3.** Magnetic Resonance Imaging (MRI) findings with tumor-nodes-metastases (TNM) stage and World Health Organization (WHO) 2010 Grade

| | TNM stage | | | | | Grade | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **I** | **II** | **III** | **IV** | ***p*-value** | **G1** | **G2** | **G3** | ***p*-value** |
| Tumor diameter[1] | 1.38±0.18 | 2.98±0.41 | 4.91±1.79 | 5.5 | 0.001 | 1.91±0.26 | 3.18±0.78 | 4.92±0.94 | 0.021 |
| Location | | | | | 0.101 | | | | 0.641 |
| Head | 6(42.9%) | 3(17.6%) | 4(66.7%) | 0(0.0%) | | 6(33.3%) | 6(37.5%) | 1(25.0%) | |
| Neck | 2(14.3%) | 2(11.8%) | 0(0.0%) | 1(100.0%) | | 1(5.6%) | 3(18.8%) | 1(25.0%) | |
| Body and tail | 6(42.9%) | 12(70.6%) | 2(33.3%) | 0(0.0%) | | 11(61.1%) | 7(43.8%) | 2(50.0%) | |
| Component | | | | | 0.563 | | | | 1.000 |
| Cystic | 1(7.1%) | 1(5.9%) | 0(0.0%) | 0(0.0%) | | 1(5.6%) | 1(6.3%) | 0(0.0%) | |
| Mixed | 0(0.0%) | 3(17.6%) | 1(16.7%) | 0(0.0%) | | 2(11.1%) | 2(12.5%) | 0(0.0%) | |
| Solid | 13(92.9%) | 13(76.5%) | 5(83.3%) | 1(100.0%) | | 15(83.3%) | 13(81.3%) | 4(100.0%) | |
| Tumor boundary | | | | | 0.120 | | | | 0.004 |
| Clear | 10(71.4%) | 13(76.5%) | 2(33.3%) | 0(0.0%) | | 11(61.1%) | 14(87.5%) | 0(0.0%) | |
| Blurred | 4(28.6%) | 4(23.5%) | 4(66.7%) | 1(100.0%) | | 7(38.9%) | 2(12.5%) | 4(100.0%) | |
| Ring-enhancement | | | | | 0.018 | | | | 0.283 |
| Hypo | 2(14.3%) | 5(31.3%) | 3(50.0%) | 0(0.0%) | | 6(33.3%) | 2(12.5%) | 2(66.7%) | |
| Similar | 1(7.1%) | 2(12.5%) | 3(50.0%) | 0(0.0%) | | 2(11.1%) | 4(25.0%) | 0(0.0%) | |
| Hyper | 11(78.6%) | 9(56.3%) | 0(0.0%) | 1(100.0%) | | 10(55.6%) | 10(62.5%) | 1(33.3%) | |
| MRI(T1) | | | | | 0.759 | | | | 1.000 |
| Hypointense | 13(92.9%) | 15(88.2%) | 5(83.3%) | 1 | | 16(88.9%) | 14(87.5%) | 4(100.0%) | |
| Isointense | 1(7.1%) | 1(5.9%) | 0(0.0%) | 0(0.0%) | | 1(5.6%) | 1(6.3%) | 0(0.0%) | |
| Mixed | 0(0.0%) | 1(5.9%) | 1(16.7%) | 0(0.0%) | | 1(5.6%) | 1(6.3%) | 0(0.0%) | |
| MRI(T2) | | | | | 0.010 | | | | 0.756 |
| Hypointense | 2(14.3%) | 0(0.0%) | 0(0.0%) | 0(0.0%) | | 2(11.1%) | 0(0.0%) | 0(0.0%) | |
| Isointense | 4(28.6%) | 0(0.0%) | 0(0.0%) | 0(0.0%) | | 2(11.1%) | 2(12.5%) | 0(0.0%) | |
| Hyperintense | 8(57.1%) | 15(88.2%) | 5(83.3%) | 0(0.0%) | | 13(72.2%) | 12(75.0%) | 3(75.0%) | |
| Mixed | 0(0.0%) | 2(11.8%) | 1(16.7%) | 1(100.0%) | | 1(5.6%) | 2(12.5%) | 1(25.0%) | |
| Pancreatic duct dilatation | | | | | 0.000 | | | | 0.438 |
| Absent | 14(100.0%) | 17(100.0%) | 2(33.3%) | 1(100.0%) | | 16(88.9%) | 15(93.8%) | 3(75.0%) | |
| Present | 0(0.0%) | 0(0.0%) | 4(66.7%) | 0(0.0%) | | 2(11.1%) | 1(6.3%) | 1(25.0%) | |

1 case of incisional hernia, and 1 case of with pancreatic leakage (Table 1).

*Pathological feature*

Among 59 patients, 35(59.3%), 10(16.9%), 8(13.6%), and 6(10.2%) were diagnosed as stage I~IV respectively; and 26 (44.1%), 27(46.8%), and 8(13.6%) were classified as WHO2010 G1-G3 grades respectively. The tumor size in patients ranged from 0.2 cm to 13.5 cm diameter, with a median of 2.5 cm and mean of 2.97 cm. Twenty-three cases (39.0%) had tumors smaller than 2 cm, and 36 cases (61.0%) had equal or larger than 2 cm. In term of tumor location, 19 cases (35.2%) were located in pancreatic head, 3 cases (5.6%) in the neck, 28 cases (51.8%) in the body and tail, and 4 cases (7.4%) in multiple parts of the pancreas.

Moreover, 17 cases (31.5%) were positive with peripancreatic invasion, and 37 cases (68.5%) were negative. Eight cases (14.8%) exhibited main pancreatic duct dilatation and vascular cancer embolus. Eleven cases (20.4%) had perineural invasion. Three cases (5.6%) were positive with surgical margins and 51 (94.4%) were negative. In term of metastasis, 7 cases (13.0%) had lymph node metastases and 2 cases (3.7%) had distant metastases.

*Imaging findings*

Forty-nine patients received CT scans with detection rate of 93.9% (46/49), and 41 underwent MRI with

**Tab. 4.** Baseline characteristic with tumor recurrence

| Covariates | | non-recurrence (n=51) | Recurrence (n=8) | *p* value* |
|---|---|---|---|---|
| sex | male | 17 (33.3%) | 6 (75.0%) | 0.05 |
| | female | 34 (66.7%) | 2 (25.0%) | |
| age | mean = 57.12 | 57.5 | 54.6 | 0.5 |
| Clinic symptom | No | 22 (43.1%) | 2 (25.0%) | 0.5 |
| | Yes | 29 (56.9%) | 6 (75.0%) | |
| Combined tumor | 0 | 35 (68.6%) | 5 (62.5%) | 0.5 |
| | 1 | 10 (19.6%) | 1 (12.5%) | |
| | 2 | 6 (11.8%) | 2 (25.0%) | |
| Medical history | | 30 (58.8%) | 4 (50.0%) | 0.7 |
| smoking | | 4 (7.8%) | 3 (37.5%) | 0.05 |
| drinking | | 3 (5.9%) | 3 (37.5%) | 0.03 |
| OPR | others | 5 (9.8%) | 1 (12.5%) | 1 |
| | radical surgery | 46 (90.2%) | 7 (87.5%) | |
| tumor size | mean = 2.97 | 2.73 | 4.88 | 0.0009 |
| tumor size class | < 2cm | 22 (43.1%) | 1 (12.5%) | 0.1 |
| | ⩾2 cm | 29 (56.9%) | 7 (87.5%) | |
| Metastasis | | 17 (33.3%) | 8 (100.0%) | 0.0005 |
| TNM | 1 | 35 (68.6%) | 0 (0.0%) | 0.00003 |
| | 2 | 9 (17.6%) | 1 (12.5%) | |
| | 3 | 5 (9.8%) | 3 (37.5%) | |
| | 4 | 2 (3.9%) | 4 (50.0%) | |
| WHO 2010 | G1 | 24 (47.1%) | 2 (25.0%) | 0.1 |
| | G2 | 22 (43.1%) | 3 (37.5%) | |
| | G3 | 5 (9.8%) | 3 (37.5%) | |
| tumor | functional | 7 (13.7%) | 1 (12.5%) | 1 |
| complication | | 14(27.5%) | 0 ( 0.0%) | 0.2 |
| Ultrosonic Diagnosis | space-occupying | 21 (41.2%) | 5 (62.5%) | 0.3 |
| Ultrosonic boundaries | no data | 42 (84.3%) | 7 (87.5%) | 0.8 |
| | clear | 4 (7.8%) | 0 (0.0%) | |
| | blurred | 4 (7.8%) | 1 (12.5%) | |
| CT Diagnosis | space-occupying | 44 (86.3%) | 5 (62.5%) | 0.1 |
| CT boundaries | no data | 17 (33.3%) | 5 (62.5%) | 0.01 |
| | clear | 26 (51.0%) | 0 (0.0%) | |
| | blurred | 8 (15.7%) | 3 (37.5%) | |
| CTA Diagnosis | space-occupying | 14 (27.5%) | 3 (37.5%) | 0.7 |
| MRI Diagnosis | space-occupying | 35 (68.6%) | 7 (87.5%) | 0.4 |
| MRI boundaries | no data | 25 (49.0%) | 6 (75.0%) | 0.05 |
| | clear | 20 (39.2%) | 0 (0.0%) | |
| | blurred | 6 (11.8%) | 2 (25.0%) | |

* Fisher's exact test, except for Age and Tumor Size with Student's t-test after log transformation.

detection rate of 100% (41/41). The minimum diameter of the lesion was 0.67 cm and 0.8 cm respectively. Thirty-three patients received B-ultrasound examination, with detection rate of 69.7% (23/33), and the minimum diameter of the lesion was 1.3 cm. The typical sonographic appearances were hypoechoic mass lesions. Nine patients accepted endoscopic ultrasonography (EUS) and four patients underwent $^{18F\text{-}FDG}$PET-CT examination, all of which were detected.

The TNM stage was strongly associated with blurred tumor boundary (stage I: 0.0% vs stage II: 28.7% vs stage III: 100.0% vs stage IV: 100%, $p = 0.000$), present of distant metastases (stages I~II 0.0% vs stage IV: 100.0%, $p = 0.029$) and lymphadenopathy (stage I: 0.0% vs stage II: 5.6% vs stage III: 20.0% vs stage IV: 100.0%, $p = 0.043$) (n = 34) from CT scans (Table 2). From MRI analysis (n = 38), TNM stage was associated with tumor enhancement ($p = 0.018$), pancreatic duct dilatation ($p = 0.000$) and T2-weighted image ($p = 0.010$) (Table 3). WHO grades were associated with tumors diameter (CT: $p = 0.019$; MRI: $p = 0.021$) and boundary (CT: $p = 0.035$; MRI: $p = 0.004$) in both CT scan (Table 2) and MRI analysis (Table 3).

*Risk of Tumor recurrence or death*

After surgery, patients were followed up from 0.5 to 70 months until the last clinical visit or death. There were four deaths (7.4%), 3 cases of tumor progression, 1 case of postoperative complication; 6 cases (11.1%) of tumor recurrence or metastasis, and 3 cases (5.6%) of withdrawal in follow-up. Fisher's exact test revealed that AJCC TNM stage ($p = 0.00003$), lymph node metastasis ($p = 0.0005$), drinking ($p = 0.03$), and CT boundaries ($p = 0.01$) were strongly associated with the risk of tumor recurrence/death, while the association of MRI boundaries ($p = 0.05$), sex ($p = 0.05$), and smoking were marginal ($p = 0.05$). The mean tumor sizes were significantly different ($p = 0.0009$, Student's t-test) between patients with or without tumor recurrence (Table 4).

Univariate logistic linear regression analysis confirmed that the risk of tumor recurrence was strongly associated with sex ($p = 0.039$), smoking ($p = 0.029$), drinking ($p = 0.016$), WHO grade ($p = 0.00073$), TNM stage ($p = 0.00079$), and marginally with tumor size ($p = 0.074$) (Table 5). These factors were included in the multivariate analysis. As expected, TNM stage remained the sole significant factor ($p < 0.05$), after adjusting for other variables (Table 5). It suggested that TNM stage is strongly associated with the risk of tumor recurrence; thus, it is most likely to be the predictor of tumor prognosis.

*Disease-free survival (DFS) analysis*

Because the observed follow-up time differed for each patient, the simple binomial variable "risk" may not correctly reflect the likelihood of tumor recurrence (Ricci *et al.* 2020). Therefore, we further performed a survival analysis regarding the disease-free period. The K-M survival curve of all participants was drawn (Figure 1), revealing that the DFS time ranged from 1 to 71 months, with a median survival time larger than 59 months. Divided by TNM stage, there were significant differences among groups ($p < 0.0001$), with the median survival time of 36 and 25 months for stage III and IV respectively.

A Cox proportional hazard ratio test was performed to further confirm whether there were significant different survival rates for each categorical variable. The likelihood ratio test concluded a significant association with smoking ($p = 0.007$), drinking ($p = 0.005$), tumor size ($p = 0.03$), metastasis ($p = 0.0003$), TNM stage ($p = 0.00004$), and WHO grade (p = 0.01) and a marginal significance with sex ($p = 0.05$) (Table 6). No significance was found for all other variables (data not shown). A full model including sex, smoking, drinking, tumor size, metastasis, TNM stage, and WHO grade, was constructed (Table 6, Model I). Backward stepwise selection from the full model eliminated the metastasis, tumor size, smoking and drinking respectively, without significant contribution to the model ($p > 0.1$). The truncated model (Model II) including TNM stage

**Tab. 5.** Logistic regression analysis

| **Univariate** | | | **Estimate** | **SE** | ***p* values** |
|---|---|---|---|---|---|
| tumor size | | | 0.244 | 0.136 | 0.074 |
| sex | | | 1.792 | 0.869 | 0.039 * |
| smoking | | | 1.953 | 0.897 | 0.029 * |
| drinking | | | 2.262 | 0.942 | 0.016 * |
| | overall | | | | 0.1344 |
| WHO | G2 | 0.492 | 0.959 | 0.5388 | |
| | G3 | 1.974 | 1.037 | 0.048 | |
| Metastasis | | | -19.812 | 3040.733 | 0.995 |
| TNM | | | 1.85 | 0.55 | 0.00079 *** |
| CT | | | -1.327 | 0.836 | 0.11 |
| MRI | | | 1.16 | 1.11 | 0.295 |
| MRI boundaries | | | -0.265 | 0.566 | 0.63983 |
| | | | | | |
| Multivariate | | | | | |
| (Intercept) | | | -10.885 | 5.026 | 0.030 * |
| Tumor size | | | -0.149 | 0.301 | 0.621 |
| sex | | | 3.126 | 2.208 | 0.157 |
| TNM | | | 2.755 | 1.384 | 0.047 * |
| smoking | | | -13.878 | 3956.181 | 0.997 |
| drinking | | | 13.131 | 3956.181 | 0.997 |
| WHO | G2 | | 1.643 | 2.314 | 0.478 |
| | G3 | | 0.824 | 1.982 | 0.678 |

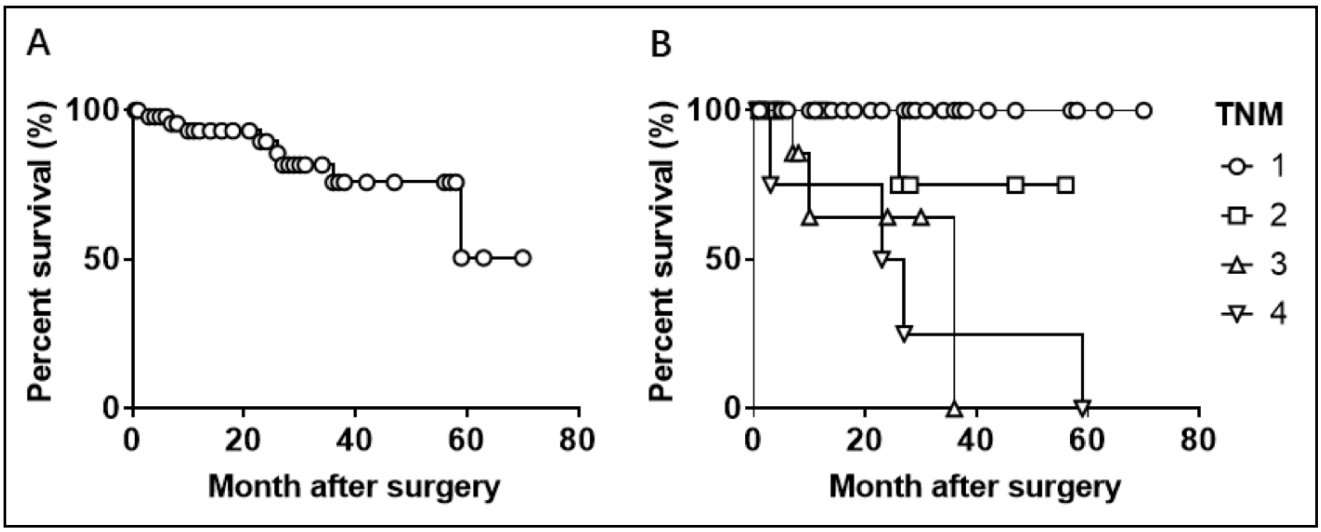


**Fig. 1.** Kaplan-Meier survival analysis of disease-free survival (DFS) (A) total participants, (B) divided according to Tumor-nodes-metastases (TNM) category of American Joint Committee on Cancer (AJCC) 7th edition.

(p = 0.01), WHO grade (p = 0.02 vs G3), and sex (p = 0.1) or model III with TNM stage (p = 0.003) and sex (p = 0.697) revealed that sex was insignificant for the survival in these models (Table 6).

Because the TNM stage was associated with blurred tumor boundary in CT and MRI images (Table 2&3), we further analyzed whether the DFS was associated with tumor boundary and estimated the hazard ratio (HR) between groups. From the K-M curves, there was a significant difference between patients with blurred and clear tumor boundary from CT ($p$ = 0.011, HR = 23.95 [2.09, 273.9]) or MRI ($p$ = 0.035, HR = 25.17 [1.26, 503.9]) analysis (Figure 2). Therefore, tumor boundary status is likely to be a predictor of tumor prognosis.

## DISCUSSION

Our study found that the predictors of higher TNM stages were tumor boundary, distant metastases and lymphadenopathy on CT or tumor enhancement and pancreatic duct dilatation on MRI. In univariate analysis, AJCC TNM stage, WHO tumor grade, sex, smoking, and drinking were associated with tumor recurrence and DFS, while tumor size and metastasis also affected DFS. Multivariate survival analysis confirmed that AJCC TNM stage was an independent predictor after adjusting other covariates. Blurred tumor boundary on CT and MRI imaging predicted a higher risk of recurrence or death.

Previous studies have shown that some imaging findings can predict the pathological grade of PNETs. Choi *et al.* (Choi *et al.* 2018) reported that CT texture variables such as lower sphericity, higher skewness, and lower kurtosis were useful for predicting grade 2/3 PNETs. Kim *et al.* (Kim *et al.* 2015) found that portal enhancement ratio (< 1.1), size (>3 cm), bile duct dilatation, and vascular invasion showed high sensitivity and specificity in distinguishing grade 3 from grade 1/2. Recently, Yang *et al.* reported that dynamic contrast-enhanced ultrasound analysis predicted the WHO2019 grades of PNETs (Yang *et al.* 2023). Similar results were also exhibited in MRI. Compared with G1, G2/G3 tumors exhibited a higher frequency of predominantly solid tumor type, local invasion or metastases, arterial phase hypoenhancement, and restricted diffusion (Guo *et al.* 2019). In our study, larger tumor diameter and metastases on CT and MRI imaging indicated higher tumor grade and TNM stage. Tumor boundary was a valuable predictor of PNET grade and stage on CT and MRI, which had been reported in many studies (De Robertis *et al.* 2017; Guo *et al.* 2019; Kim *et al.* 2015; Kim *et al.* 2016; Li *et al.* 2021; Salahshour *et al.* 2020; Zhao *et al.* 2020). Similar conclusions were also drawn in our study.

Surgery is the main therapy for PNETs, however, its strategy remains a controversial issue and object of research (Mauriello *et al.* 2015; Assi *et al.* 2020; Jeune *et al.* 2020; Najafi *et al.* 2020). Patients who underwent pancreaticoduodenectomy had significantly lower long-term survival than patients who underwent other types of pancreatectomy (Bilimoria *et al.* 2008; Postlewait *et al.* 2016). Cherif *et al.* (Cherif *et al.* 2012) reported that parenchyma-sparing pancreatectomy was associated with increased postoperative morbidity despite excellent postoperative pancreatic function. Given the potential morbidity of postoperative complications and surgery (Lim *et al.* 2023), it is important to know the risk factors of this disease.

We observed that AJCC TNM stage, tumor grade, and tumor metastases were associated with the tumor recurrence risk and DFS by univariate analysis, which was consistent with previous studies (Shen *et al.* 2019; Yang *et al.* 2015a; Zhang *et al.* 2019; Yang *et al.* 2019;

Murakami *et al.* 2023). Some imaging biomarkers associated with tumor recurrence or death have already been reported. In multivariable analysis, enhancement pattern and apparent diffusion coefficient (ADC) were significant independent predictors of DFS (Sun *et al.* 2019; Guo *et al.* 2019; Oleinikov *et al.* 2020). Canellas *et al.* (Canellas *et al.* 2018) showed that "nonbright lesions" larger than 2.0 cm on T2-weighted images of pancreatic duct dilatation were associated with shorter progression-free survival curves. Zhou *et al.* (Zhou *et al.* 2019) found that tumors sized > 2.5 cm and perineural invasion were associated with poorer DFS. In another study, Sun *et al.* (Sun *et al.* 2019) demonstrated that tumor size larger than 2.0 cm was a significant factor in assessing DFS after curative surgery for PNETs. Consistently, we observed a higher risk of tumor recurrence and shorter DFS in patients with large tumor size (>2 cm) or blurred tumor boundary on CT and MRI imaging, in compare to the others.

One factor that should be carefully considered is lymph node metastasis (Sadowski *et al.* 2020; Lopez-Aguiar *et al.* 2019; Guo *et al.* 2019; Milanetto *et al.* 2023, Ren *et al.* 2023). We found that the presence of lymph node metastasis may shorten DFS time in univariate but not in multivariate survival analysis including TNM stage. Part of the reason may be that it is strongly associated with TNM stage. Nevertheless, lymph node status is an important predictor of patient outcomes, and lymphadenectomy should be strongly recommended when resecting PNETs (Postlewait *et al.* 2016; Dong *et al.* 2019). Controversy remains as to the surgical margin status for prognosis of PNETs. Karl and colleagues found that surgical margin status was

**Tab. 6.** Cox proportional hazard ratio estimation

| **Covariates** | | **coef** | **exp(coef)** | **se(coef)** | **z** | **Pr(>\|z\|)** | **Likelyhood ratio test** |
|---|---|---|---|---|---|---|---|
| sex | | 1.471 | 4.352 | 0.824 | 1.78 | 0.074 | p=0.05 |
| smoking | | 2.520 | 12.424 | 0.855 | 2.95 | 0.0032 | p=0.007 |
| drinking | | 2.638 | 13.981 | 0.843 | 3.13 | 0.0018 | p=0.005 |
| Tumor size | | 1.870 | 6.510 | 1.080 | 1.74 | 0.082 | p=0.03 |
| Metastasis | | -21.479 | 0.000 | 1.45E+04 | 0 | 1.000 | p=0.0003 |
| TNM | | 1.270 | 3.570 | 0.370 | 3.44 | 0.00059 | p=0.00004 |
| WHO | G1 | -2.958 | 0.052 | 1.014 | -2.92 | 0.0035 | p=0.01 |
| | G2 | -2.287 | 0.102 | 0.896 | -2.55 | 0.0107 | |
| | | | | | | | |
| Model I | | coef | exp(coef) | se(coef) | z | Pr(>\|z\|) | |
| sex | | 5.950 | 383.574 | 0.881 | 7 | 1.44E-11 | |
| smoking | | -6.539 | 0.001 | 0.860 | -8 | 3E-14 | |
| drinking | | 2.576 | 13.151 | 0.860 | 3 | 0.003 | |
| Tumor size class | | 4.817 | 123.550 | 2.630 | 2 | 0.067 | |
| Metastasis | | -16.953 | 0.000 | 3380.593 | 0 | 0.996 | |
| TNM | | 2.027 | 7.592 | 0.505 | 4 | 5.97E-05 | |
| WHO | G1 | -7.378 | 0.001 | 1.999 | -4 | 2.23E-04 | |
| | G2 | -2.638 | 0.072 | 0.895 | -3 | 0.003 | |
| | | | | | | | |
| Model II | | coef | exp(coef) | se(coef) | z | Pr(>\|z\|) | |
| sex | | 1.730 | 5.650 | 1.040 | 2.000 | 0.100 | |
| TNM | | 1.130 | 3.110 | 0.440 | 3.000 | 0.010 | |
| WHO | G1 | -3.800 | 0.020 | 1.690 | -2.000 | 0.020 | |
| | G2 | -1.730 | 0.180 | 1.110 | -2.000 | 0.120 | |
| | | | | | | | |
| Model III | | coef | exp(coef) | se(coef) | z | Pr(>\|z\|) | |
| sex | | 0.400 | 1.400 | 0.900 | 0.400 | 0.697 | |
| TNM | | 1.200 | 3.300 | 0.400 | 3.000 | 0.003 | |

**Tab. 7.** Subgroup analysis with tumor boundary defined by Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)

| covariates | coef | exp(coef) | se(coef) | z | Pr(>\|z\|) | Likelyhood ratio test |
|---|---|---|---|---|---|---|
| CT (n=37) | 2.231e+01 | 4.912e+09 | 2.741e+04 | 0.001 | 0.999 | 0.008459 |
| MRI (n=28) | 2.236e+01 | 5.142e+09 | 3.398e+04 | 0.001 | 0.999 | 0.03044 |

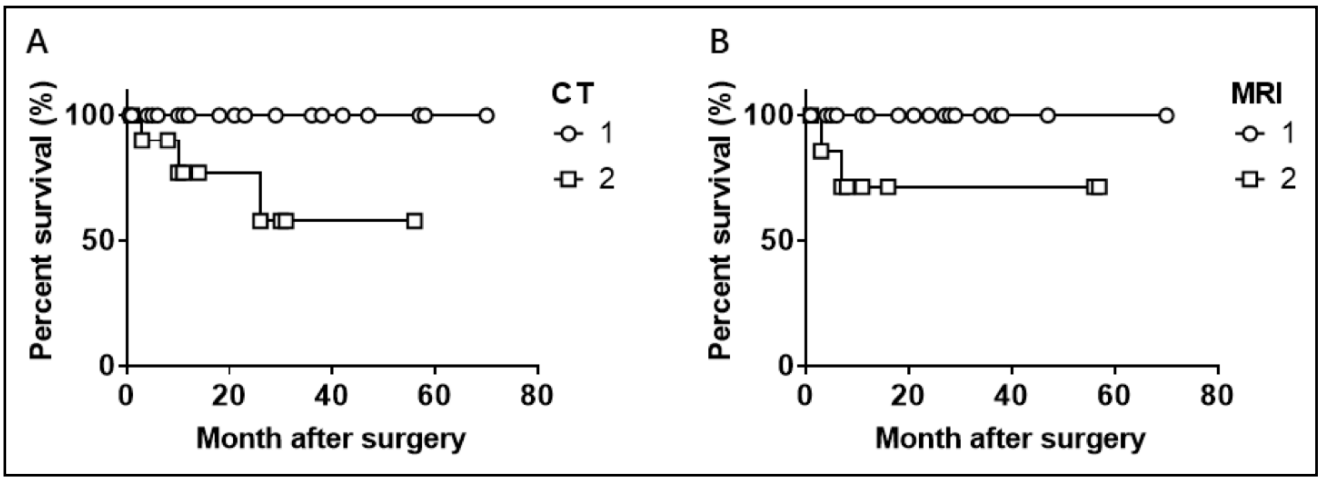


**Fig. 2.** Kaplan-Meier survival analysis of Disease-free survival (DFS) divided according to tumor boundary determined by (A) Computed Tomography (CT) and (B) Magnetic Resonance Imaging (MRI) imaging.

not independently associated with survival (Karl *et al.* 2020; Karl *et al.* 2015). However, other studies noted that in univariate analysis, positive resection margins predicted worse DFS (Zhang *et al.* 2019; Ballian *et al.* 2009) and poorer overall survival (Hashim *et al.* 2014; Yang *et al.* 2019; Zhang *et al.* 2019). Further research is needed to clarify the controversy.

Our study provides a non-invasive approach to evaluate the grade of PNETs. It can be combined with other strategies, such as machine learning (Li *et al.* 2023, Jiang *et al.* 2023, Murakami *et al.* 2023; Mori *et al.* 2023), to identify the optimal treatment strategy and predict the prognosis. Our study has a number of limitations. First, it is retrospective and inherently subject to selection and information bias. The analysis was limited to available information, with potential selection bias due to missing values. Patients with PNETs and other tumors were excluded from our study, which prevented us from obtaining information on the compounding of PNETs with other tumors. Second, the analyzed sample size was small due to the low incidence of PNETs and limited data from one medical center, which reduced the statistical power. Third, the observed follow-up time varied among patients and was short in many cases. Because patients with tumor recurrence were more likely to return to the hospital and be identified, there may be a recall bias and an underestimation of DFS time. Fourth, the imaging analysis was limited, as CT enhancement was simply divided and only T1WI and T2WI sequences in MRI were analyzed. Further studies, such as enhance patterns of CT (anterior, arterial, venous) and other sequences of MRI (diffusion weighted imaging (DWI), ADC) may help to distinguish the detail differences. In addition, inter-observer variability in qualitative imaging results can be eliminated when radiologists agree during image analysis. In summary, it is necessary to further validate the prognosis model through prospective studies with longer follow-up time and larger sample size, such as a multi-centers study.

In conclusion, TNM stage remains a valuable predictor of prognosis in PNETs. In addition, the non-invasive imaging information of CT and MRI can not only be used to determine the TNM stage, but also may help to estimate the tumor prognosis, guide the follow-up, and avoid ineffective treatments.

## DECLARATION

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None.

*Conflict of interest*

All of the authors in this manuscript have no financial interests and no affiliations (relationships) to be disclosed.

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*Ethical approval and informed consent*

All procedures performed in studies involving human participants complied with the ethical standards of the Shanghai General Hospital, Shanghai Jiaotong University and the 1964 Helsinki declaration and its subsequent amendments or similar ethical standards. All patients provided written inform consent.

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