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Original Research

The number of positive lymph node is a better predictor of survival than the lymph node metastasis status for pancreatic neuroendocrine neoplasms: A retrospective cohort study

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ABSTRACT

Background: The recently released AJCC TNM staging system of pancreatic adenocarcinoma has endorsed the number of positive lymph node(NPLN) as the criterion of N staging. However, the prognostic role of NPLN is still unclear for pancreatic neuroendocrine neoplasms (pNENs).

Methods: Patients underwent resection and at least one lymph node examined were identified from the Surveillance, Epidemiology, and End Results database. The overall survival (OS) and disease specific survival (DSS) were estimated using Kaplan-Meier analysis and compared by log-rank test. The prognostic factors were determined by cox proportional regression model.

Results: Totally, 1,269 pNENs were included in the present study. The increasing NPLN (NPLN > 3) was corresponding significantly ($P < 0.05$) shorter OS and DSS in both entire cohort (OS: NPLN ≤ 3 vs. NPLN > 3, 93.624 ± 1.765 months vs. 75.075 ± 4.005 months; DSS: NPLN ≤ 3 vs. NPLN > 3, 104.829 ± 1.455 months vs. 85.443 ± 3.938 months, respectively) and cohort with the number of examined lymph node more than 11 (OS: NPLN ≤ 3 vs. NPLN > 3, 88.759 ± 2.756 months vs. 73.664 ± 4.700 months; DSS: NPLN ≤ 3 vs. NPLN > 3, 99.021 ± 2.212 months vs. 85.139 ± 4.686 months, respectively). Furthermore, the multivariate analysis showed the NPLN > 3 rather than lymph node status was the independent prognostic factors for OS and DSS in these two cohorts.

Conclusions: The NPLN seems more meaningful than the lymph node metastasis status as prognostic factor for survival. Taking into account the prognostic value of NPLN for pNENs might improve the current TNM staging systems. However, prospective study is needed to demonstrate our findings.

1. Introduction

Pancreatic neuroendocrine neoplasms (pNENs) are considered a rare group of neoplasms with relatively indolent tumor biology. However, recent epidemiological studies showed their incidence have increased significantly [1,2]; and the median overall survival (OS) of patients with pNENs is only 3.6 years [2]. It means the natural history of pNENs is more aggressive than commonly assumed. Therefore, identification of patients at higher risk and making better therapeutic decisions for these patients is needed.

Currently, the TNM staging system for pNENs is endorsed by the European Neuroendocrine Tumor Society (ENETS) [3] and American Joint Committee on Cancer (AJCC) [4]. Although the staging classifications are greatly different between these two systems, both of them considered lymphatic metastasis is an important prognostic indicator of advanced stage and worse outcome; and the lymph nodal staging is defined as either N0 (no regional lymph node metastasis) or N1(regional lymph node metastasis).

Unfortunately, several studies demonstrated that the lymphatic metastasis was not associated with survival for pNENs [5–7]. Recently, the number of positive lymph node (NPLN) has been shown to be a powerful prognostic factor for survival in PDAC [8] and other gastrointestinal cancers [9–11]. Furthermore, the recently released AJCC TNM staging system (eighth edition) of PDAC has revised the N staging

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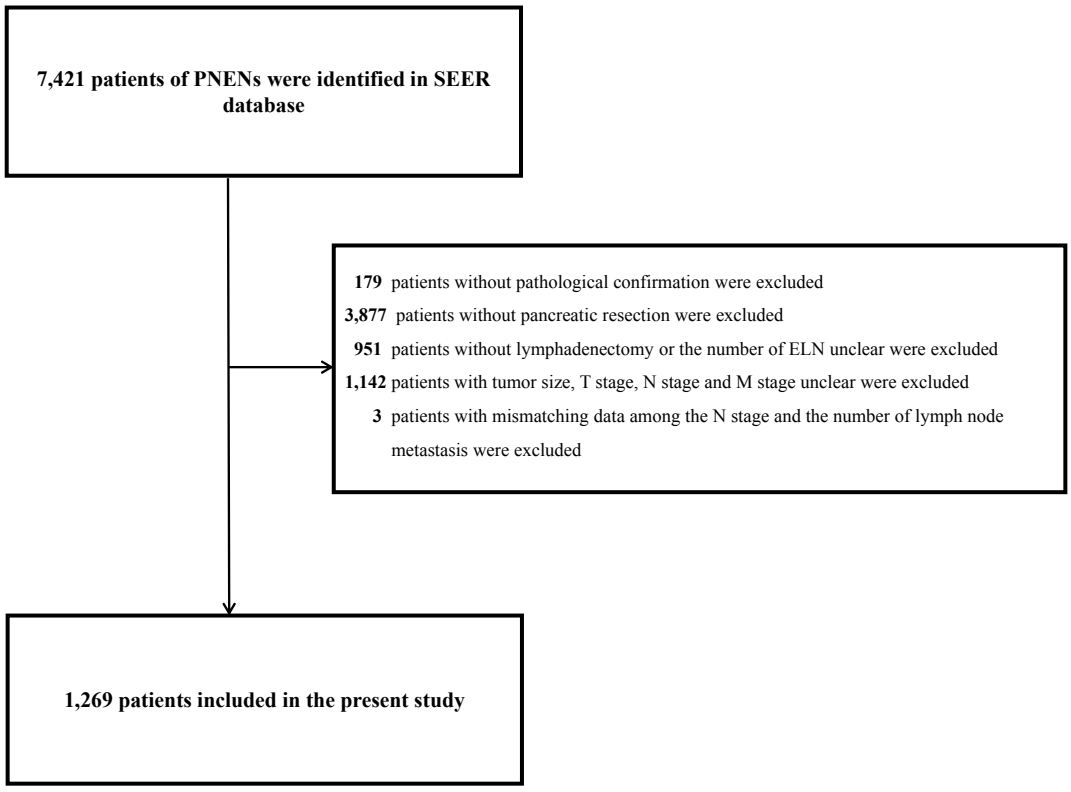

Fig. 1. Flowchart of patient selection.

based on the number of lymph node metastasis, N0 (no regional lymph node metastasis), N1 (1–3 regional lymph node metastases) and N2 (≥ 4 regional lymph node metastases) [12]. However, the prognostic role of NPLN in pNENs is still conflicting and no accepted threshold has been established [13–15].

Thus, we hypothesize the increasing NPLN is an adverse prognosis factor of survival for pNENs; and we aimed to use a large population to determine the threshold of NPLN for accurate prognostication.

2. Material and methods

2.1. Study cohort

The Surveillance, Epidemiology, and End Results (SEER) database was established in 1973 and encompassed approximately 28% of the USA population. A pancreatic tumor data set was created through structured querying to the SEER database, using the International Classification of Diseases for Oncology, third edition (ICD-*O*-3) for tumors located in pancreas: C25.0 to C25.9. The following histology ICD-*O*-3 codes were used to identify patients with pNENs: 8150 islet cell carcinoma, 8151 malignant beta cell tumor, 8152 malignant alpha cell tumor, 8153 malignant gastrinoma, 8154 mixed islet-cell/exocrine adenocarcinoma, 8155 vipoma, 8156 somatostatin cell tumor, 8157 malignant enteroglucagonoma, 8240 carcinoid, 8241 argentaffin carcinoid tumor, 8242 enterochromaffin cell tumor, 8243 mucocarcinoid tumor, 8244 composite carcinoid, 8245 adenocarcinoid tumor, 8246 neuroendocrine carcinoid and 8249 atypical carcinoid tumor [1].

2.2. Inclusion and exclusion criteria

Patient underwent pancreatic resection and at least one lymph node examined was included in our study. We excluded patients with incomplete data, such as: tumor size, AJCC T stage (seventh edition), AJCC N stage (seventh edition), AJCC M stage (seventh edition) and the number of examined lymph node (NELN). Patients with mismatched data among N stage and NPLN were also excluded. In addition, small-cell or large-cell neuroendocrine carcinomas were mostly originated from lung; thus, these patients were also excluded.

2.3. Outcome and variables

Survival time of SEER database was defined as the time from diagnosis until last contact, the date of death, or the date used as a cut-off [16]. The primary measured outcome for our study was OS, as time from diagnosis to death of any cause. The secondary measured outcome was disease specific survival (DSS), as time from diagnosis to death attributed to the pNENs.

The following variables were analyzed in our study: age, gender (male, female), race (white, black, others), primary tumor site (head, body, tail, others), histologic differentiation grade, T stage (defined as T1-T4 based on AJCC TNM staging, seventh edition [4]), N stage (defined as N1 and N0 according to lymph node metastasis or not), M stage (defined as M1 and M0 according to distant metastasis or not), NELN (NELN ≤ 11 vs. NELN > 11) and NPLN (NPLN ≤ 3 vs. NPLN > 3). To identify the prognostic factors in survival, all continuity variables were defined as category variables; and the cut-off values were determined as previous study for age [17] and the Youden's index [18] for NELN, NPLN.

Moreover, the 8th AJCC TNM staging system suggests examining at least 12 lymph nodes to accurately classify N staging for PDAC [12]; and according to the Youden's index, the most appropriate cut-off value of NELN was 11 in the present cohort. Thus we invested the prognostic role of NPLN in entire cohort and patients with NELN > 11.

The SEER database did not report tumor grade according to the WHO 2010 classification. The tumors were classified into four grades based on the basis of morphological description of ICD-*O*-3: grade I, well differentiated; grade II modreately differentiated; grade III poorly differentiated; and grade IV undifferentiated or anaplastic [19].