Pancreatology xxx (2016) 1–7

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Original Article

Association between serum SPan-1 and lymph node metastasis in invasive intraductal papillary mucinous neoplasm of the pancreas

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ARTICLE INFO

Article history:
Received 28 July 2016
Received in revised form
27 October 2016
Accepted 8 December 2016
Available online xxx

Keywords:
Intraductal papillary mucinous neoplasm
Lymph node metastasis
Prognostic serum tumor marker

ABSTRACT

Background and aim: Lymph node metastasis predicts poorer prognoses in patients with invasive intraductal papillary mucinous neoplasms of the pancreas (IPMNs). Factors associated with lymph node metastasis of invasive IPMN remain unclear. Therefore, this study aimed to define factors associated with lymph node metastasis of invasive IPMN.

Methods: Between June 2000 to August 2015, 156 consecutive patients with IPMN underwent surgical resection at Kobe University Hospital, and were enrolled in this study. The relationship between lymph node metastasis and clinical characteristics, including imaging studies and serum tumor markers, was evaluated. A multivariate logistic regression analysis was performed to assess the relationship between serum tumor markers and the presence of lymph node metastasis of IPMN, adjusted for clinical characteristics.

Results: Lymph node metastasis was observed in 7.7% (12/156) of IPMNs via a pathological examination. The multivariate logistic regression analysis revealed that serum SPan-1 was associated with the presence of lymph node metastasis of IPMN (odds ratio [OR] = 7.32; 95% confidence interval [CI] = 1.10 to 56.0; $P = 0.04$). In addition, survival was poorer among serum SPan-1-positive patients than SPan-1 negative patients (Log-rank test; $P = 0.0002$). Lymph node enlargement was detected preoperatively on computed tomography scans in only 16.7% (2/12) of cases that were positive for lymph node metastasis.

Conclusions: Elevated serum SPan-1 was associated with lymph node metastasis in this cohort of patients who underwent resection for invasive IPMN.

1. Introduction

Intraductal papillary neoplasms (IPMNs) are mucin-producing cystic pancreatic tumors, some of which progress to invasive IPMN (IPMN with an associated invasive carcinoma) [1]. Previous studies reported that the prognosis of invasive IPMN is better than that of conventional pancreatic ductal adenocarcinoma (PDAC) [1–4]. Lymph node metastasis is one of the strongest predictors of survival in invasive IPMN. IPMN patients with lymph node involvement have a worse prognosis as do those with conventional

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; CI, confidence interval; CT, computed tomography; DM, diabetes mellitus; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; IPMN, intraductal papillary mucinous neoplasm; MD-CT, multi-detector computed tomography; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; OR, odds ratio; PDAC, pancreatic ductal adenocarcinoma.

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http://dx.doi.org/10.1016/j.pan.2016.12.002
1424-3903/

PDAC [4–6].

Factors associated with lymph node metastasis of invasive IPMN have not yet been clarified. Imaging studies, including computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasonography (EUS), are commonly performed to select the surgical indication for treating IPMN. However, difficulties are sometimes associated with making a precise preoperative diagnosis of lymph node metastasis using imaging studies alone. Previous studies demonstrated that the accuracy of diagnosing lymph node metastasis of IPMN via CT was between 25% and 75% [7–9], and reactive lymph nodes have occasionally been detected in patients with IPMN, leading to an overdiagnosis of lymph node metastasis [7].

Mural nodules in IPMN have been correlated with lymph node metastasis [10]. In that study, all IPMN patients with lymph node metastasis presented with mural nodules in cysts. However, only 12% (7/57) of patients with a mural nodule had lymph node metastasis.

Limited information is currently available on lymph node metastasis-related factors in invasive IPMN. Clarifying the tumor characteristics of invasive IPMN accompanying lymph node metastasis is an important clinical issue that is critical for making appropriate treatment decisions. Therefore, we utilized a database of 156 consecutive patients who underwent surgical resection for IPMN with or without lymph node involvement at Kobe University Hospital and examined the relationship between lymph node metastasis and clinical characteristics.

2. Methods

2.1. Study design

Between June 2000 to August 2015, 156 consecutive patients underwent surgical resection for IPMN at Kobe University Hospital and were enrolled in this study. Among these patients, 47 were pathologically diagnosed with invasive IPMN. In this retrospective study, clinical information had been prospectively collected using a preoperative questionnaire at the time of surgical resection. This questionnaire included age, body mass index (BMI), sex, abdominal symptoms (presence/absence), diabetes mellitus (presence/absence), history of pancreatitis (presence/absence), alcohol consumption (more than 50 g/day/less than 50 g/day), macroscopic type of IPMN (main duct, mixed, or branch duct type), location of IPMN (head, body to tail), diameter of the main pancreatic duct (less than 5 mm, 5 mm–10 mm, more than 10 mm), nodules in IPMN (presence/absence), diameter of IPMN (less than 30 mm, 30–40 mm, more than 40 mm), serum carcinoembryonic antigen (CEA, more than 5 ng/ml/less than 5 ng/ml), serum carbohydrate antigen 19-9 (CA19-9, more than 37 U/ml/less than 37 U/ml), serum DUPAN-2 (more than 150 U/ml/less than 150 U/ml), and serum SPan-1 (more than 30 U/ml/less than 30 U/ml). The macroscopic type of IPMN was classified as the main duct, mixed, or branch duct type based on the results of preoperative radiological imaging studies, mainly magnetic resonance cholangiopancreatography (MRCP) according to the 2012 international consensus guidelines [11]. The diameter of the main pancreatic duct and cyst (IPMN) size were measured using MRCP in most cases. Patients who did not undergo MRCP were examined using an alternative method, such as EUS, endoscopic retrograde cholangiopancreatography (ERCP), or CT. The presence of mural nodules was evaluated using EUS and MRI. EUS and ERCP were primarily performed by 3 endoscopists who have combined experience of more than 1000 EUS and ERCP. The pathological stage of invasive IPMN was classified according to the 4th edition of the UICC classification [12]. The mucin phenotype of IPMN was classified as intestinal, gastric, pancreatobiliary, or oncocytic based on histopathological results according to current guidelines [11]. Lymph node metastasis was pathologically diagnosed in resected specimens. The indication for lymph node dissection was based on the findings of preoperative imaging studies (invasive features or suspicion of lymph node metastasis on imaging studies) and intraoperative findings (surface exposure of solid tumor or regional lymph node swelling). Adjuvant chemotherapy was administered according to the pathological findings of resected specimens and the patient's condition. This study was conducted in accordance with the Declaration of Helsinki and its amendments (UMIN-CTR ID: 000021474). This study protocol was approved by the Kobe University School of Medicine Ethics Committee (No. 160124). All authors had access to the study data and have reviewed and approved the final manuscript.

2.2. Assessment of lymph node enlargement on CT

We evaluated lymph node enlargement via CT. A single radiologist reviewed contrast-enhanced CT from invasive IPMN patients and was blinded to clinical features. The diameter of a lymph node was measured on an axial image, and nodes $\geq$10 mm were considered to have positive lymph node enlargement.

2.3. Statistical analysis

All statistical analyses were conducted using JMP (version 11, SAS Institute, Cary, NC, USA) and all P values were two-tailed. In order to assess the relationships between categorical data, a chi-squared test (or Fisher's exact test, if appropriate) was performed. In order to compare mean age and body mass index (BMI), the Student's t-test or ANOVA (analysis of variance) assuming equal variance was performed. A multivariate logistic regression analysis was conducted to assess the relationship between serum SPan-1 and the presence of lymph node metastasis of invasive IPMN. The binary categorical variable (presence/absence) for the presence of lymph node metastasis of invasive IPMN was used as an outcome variable. A multivariate binary logistic regression analysis was performed to adjust for potential confounders. The odds ratio was adjusted for abdominal symptoms and serum tumor markers (serum CEA, CA19-9, DUPAN-2, and SPan-1), for which the P value was less than 0.05 via a univariate analysis (Table 1). A Kaplan-Meier estimation was used to assess patient prognosis according to lymph node metastasis and serum tumor markers (serum CEA, CA19-9, DUPAN-2, and SPan-1). Significance was estimated via a Log-rank test. Death from causes other than invasive IPMN was censored for cancer-specific mortality. We also used Cox's proportional hazard model to assess the relationship between serum SPan-1 and the cancer-specific mortality of invasive IPMN, adjusted by the UICC stage and serum DUPAN-2. In all analyses, $P < 0.05$ was considered to be significant.

3. Results

3.1. Patient characteristics according to lymph nodes metastasis of IPMN

All 156 patients underwent radical surgery and resected margins were clean (R0). Lymph node metastasis was observed in 7.7% (12/156) of patients with IPMN after the pathological examination. Radical lymph node dissection (D2 dissection) was performed in 51.3% (80/156) of patients. It was possible to evaluate regional lymph nodes near the pancreas (N1 lymph nodes) in all patients without radical lymph node dissection. Approximately 3.2% (the number of metastatic lymph nodes; 0.8 ± 2.2, the number of lymph nodes removed; 24.8 ± 12.0) were metastatic from the lymph

Please cite this article in press as: Yamanaka K, et al., Association between serum SPan-1 and lymph node metastasis in invasive intraductal papillary mucinous neoplasm of the pancreas, Pancreatology (2016), http://dx.doi.org/10.1016/j.pan.2016.12.002