Pancreatology xxx (2017) 1–6

Contents lists available at ScienceDirect

Pancreatology

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

Prognostic impact of nodal statuses in patients with pancreatic ductal adenocarcinoma

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ARTICLE INFO

Article history:
Received 3 July 2016
Received in revised form
9 December 2016
Accepted 14 January 2017
Available online xxx

Keywords:
Pancreatic ductal carcinoma
Lymph node
Survival analysis

ABSTRACT

Background: The present study aimed to clarify the prognostic impact of nodal statuses in pancreatic ductal adenocarcinoma (PDAC) after potentially curative pancreatectomy.
Methods: In 110 patients with >10 examined lymph nodes (ELNs), we investigated how nodal statuses were associated with postoperative survival. Nodal statuses included the number of positive LNs (PLNs); the ratio of PLNs to ELNs (lymph node ratio; LNR); and the location of regional LN metastases, classified as group one (peripancreatic area) and group 2 (outside the peripancreatic area). The maximum χ^2 value, provided by a Cox proportional hazards model, was used to determine the optimal cutoff value for the number of PLNs and the LNR.
Results: The median numbers of ELNs and metastatic LNs were 33 and 2, respectively. Median survival was longer in patients with ≤3 PLNs (37.5 months), LNR <0.11 (36.1 months), and group 1 LN metastases (37.5 months) compared to in patients with ≥4 PLNs (23.7 months), LNR ≥0.11 (23.9 months), and group 2 LN metastases (22.8 months), respectively. Multivariate analyses revealed that all three investigated nodal statuses were independent factors associated with survival: HR of 2.38 and $p = 0.0006$ for the location of LN metastases, HR of 1.92 and $p = 0.0071$ for the number of PLNs, and HR of 1.89 and $p = 0.010$ for the LNR.
Conclusions: Three nodal statuses—the number of PLNs, the LNR, and the location of LN metastases—could stratify postoperative survival among PDAC patients with an adequate number of examined LNs after pancreatectomy.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a treatment-refractory neoplasm with a 5-year survival rate below 10%. It is presently the fourth leading cause of cancer-related death, and its prevalence is increasing in Japan [1]. Despite drastic advances in chemo-radiotherapy over the last decade [2,3], resection is indisputably still the most reliable curative treatment.

Several investigations have identified survival indicators after potentially curative pancreatic resection, including resection margin status [4–11], tumor size [4,5,11–13], tumor differentiation [5,7–12,14–17], elevation of tumor/inflammatory markers [10,18–21], adjuvant chemotherapy [4,5,10,16,17,22,23], and nodal status [7–17,21,24–27]. Of these indicators, nodal status has most relevant prognostic implications in PDAC, and represents the main constituent of cancer staging. The 7th edition of the Union for International Cancer Control (UICC) TNM classification system for PDAC [28] states that N category is determined by the presence or absence of regional lymph node (LN) metastasis for any T category. On the other hand, the General Rules for the Study of Pancreatic Cancer by the Japan Pancreas Society (JPS) state that the N category is determined by the location of regional LN metastases [29]. The determination of nodal staging remains controversial since there are fewer resected cases of PDAC compared to gastric or colorectal carcinoma.

Previous reports have intensively discussed the predictive capacities of three types of node-based data: the total number of

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http://dx.doi.org/10.1016/j.pan.2017.01.003
1424-3903/

examined LNs (ELNs) [11,13–15,17], the number of positive LNs (PLNs) [7,16,17,25–27], and the ratio of metastatic to examined LNs (lymph node ratio; LNR) [7–12,15,21,24–27]. Three large sample cohort studies [13,15,17] demonstrated an association between ≤10 ELNs and impaired survival in node-negative cases, as well as in node-positive cases [17]. However, prior studies often included subjects with an insufficient number of ELNs, leading to scattering of results in their analyses. With regards to PLN number and LNR, it remains controversial which is superior, and the optimal cutoff points for these parameters differ across studies. Moreover, while regional LN classification in accordance with JPS recommendations [29] has been widely accepted [30], few studies have yet fully investigated the prognostic importance of the location of regional LN metastases compared to that of LNR and PLN number.

Our present study aimed to investigate the impact of three types of nodal information—the number of PLNs, the LNR, and the location of regional LNs—on postoperative survival among PDAC patients with adequate numbers of ELNs following potentially curative pancreatectomy.

2. Methods

2.1. Objective patients

This single-center retrospective observational study included 162 consecutive patients who received potentially curative (R0 or 1) pancreatic resection for PDAC between February 2003 and January 2014 at Osaka National Hospital. Patients were excluded if they showed distant metastases, including paraaortic LN metastases, or positive peritoneal lavage cytology (39 patients). Patients were also excluded if they received neoadjuvant chemotherapy and/or radiotherapy (4 patients). An additional 2 patients were excluded due to operation-related mortality, and 7 patients were excluded because fewer than 10 LNs were retrieved based on results of the previous studies [13,15,17]. Ultimately, a total of 110 patients were included in this analysis.

2.2. Surgical procedure

All pancreatic resections were performed by the same experienced surgical team. Subtotal stomach-preserving pancreaticoduodenectomy was performed for lesions of the pancreatic head, while distal pancreatectomy with splenectomy was performed for pancreatic lesions of the distal half. Total pancreatectomy was considered for tumor invasion of the whole pancreas. In cases with suspected vascular involvements, we performed portal vein resection with reconstruction (33 patients), or distal pancreatectomy with en bloc celiac axis resection (2 patients). Most operations included sampling or dissection of paraaortic LNs in the diaphragmatic hiatus, and between the upper margin of the celiac artery origin and the lower border of the left renal vein, together with standard regional LN dissection [29,30]. Patients with positive findings for paraaortic LNs were excluded from this analysis as distant metastases. We routinely performed intraoperative evaluation of the resection margins of the main pancreatic duct, and additional resection was performed in cases with a PanIN-2 or higher score [31].

2.3. Pathological assessment

Resected specimens were evaluated and diagnosed by expert pathologists at our institute, and only patients with histologically confirmed PDAC were eligible for analysis. T factor was categorized based on the 7th edition of the UICC TNM classification system [28]. Tumor invasions to adjacent great vessels (portal or splenic vein, celiac or splenic artery) and/or the extrapancreatic nerve plexus were evaluated as possible prognostic factors. For heterogeneous tumors that included various degrees of differentiation, we recorded the highest degree. R0 resection was defined as having at least 1 mm of the resection margin clearance. The LNR was calculated by dividing the number of PLNs by the number of ELNs. Regional LNs were anatomically categorized into two groups based on the JPS classification [29]: group 1 included peripancreatic LNs, and group 2 included LNs outside the peripancreatic area (Table 1). We then evaluated correlations among the number of PLNs, the LNR, the locations of regional LNs, and postoperative survival.

2.4. Postoperative management

All patients underwent postoperative follow-up that included assays of the biochemical tumor markers CA19-9 and DUPAN-2 performed monthly for the first year, every 3 months for the following 2 years, and every 6 months thereafter. Chest X-ray and abdominal computed tomography were performed every 3 months for the first 3 years, every 6 months for the following 2 years, and annually thereafter for the first 5 years after surgery. Complete post-surgical prognostic surveys were available for each included patient. Adjuvant chemotherapy with either gemcitabine or S-1 was administered for six months if possible since each medication has covered by insurance in Japan.

2.5. Statistical analyses

Statistical analyses were performed using JMP® software (SAS, Inc., Cary, NC, USA). Continuous variables were expressed as median (range). After comparing χ^2 values of each cutoff point, provided by a Cox proportional hazards model, maximum χ^2 value was used to determine the optimal cutoff values for the number of PLNs and the LNR according to the previous study [32]. The Kappa coefficient was used to evaluate the degree of concordance between two nodal examinations. Survival curves were estimated using the Kaplan-Meier method, and compared using the log-rank test. The Cox proportional hazards model was used to assess factors associated with survival. A p value of <0.05 was considered to indicate statistical significance.

3. Results

3.1. Patient characteristics

Table 2 summarizes the demographics and clinicopathological findings of our entire cohort, which included 60 males and 50 females with a median age of 70 years (range, 50–86 years). R0 resection was achieved in 90 patients (81.8%), and the majority of patients were categorized as stage pT3 (84.5%). Overall, the median number of ELNs was 33 (range, 14–92), the median number of PLNs was 2 (range, 0–16), and the median LNR was 0.06 (range, 0.0–0.55). Among the 75 patients with positive LNs, 35 showed metastases extending beyond the peripancreatic area (group 2).

3.2. Establishing optimal cutoff values for the number of PLNs and the LNR

Table 3 shows the changes of χ^2 values with statistically significant differences ($p < 0.05$) for the number of PLNs and the LNR, corresponding to each cutoff value, in all patients. For the number of PLNs, the optimal cutoff value was 4 ($\chi^2 = 8.82$; HR 2.04; 95%CI 1.23–3.22; $p = 0.0030$). LNR was stratified every 0.01, and the optimal cutoff value was 0.11 ($\chi^2 = 9.95$; Hazard ratio (HR) 2.08; 95% confidence interval (CI) 1.30–3.31; $p = 0.0016$). These optimal

Please cite this article in press as: Fukuda Y, et al., Prognostic impact of nodal statuses in patients with pancreatic ductal adenocarcinoma, Pancreatology (2017), http://dx.doi.org/10.1016/j.pan.2017.01.003