ORIGINAL ARTICLE

Pancreatic cancer metastatic to a limited number of lymph nodes has no impact on outcome

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Abstract

Background: The purpose of this study was to determine the association of the extent of metastatic lymph node involvement with survival in pancreatic cancer.

Methods: This is a retrospective review of a prospectively maintained database of patients who underwent resection for pancreatic adenocarcinoma, 1999–2011.

Results: 165 patients were identified and divided into 3 groups based on the number of positive lymph nodes – 0 (group A), 1–2 (B), >3 (C). Each group had 55 patients. Those in group C were more likely to have a higher T stage, poorly differentiated grade, lymphovascular invasion (LVI), higher mean intra-operative blood loss, positive margins, tumor location involving the uncinate process, and a higher likelihood of undergoing a pancreaticoduodenectomy. Median overall survival (OS) for group A, B and C was 25.5 months (mo), 21 mo and 12.3 mo, respectively ($p < 0.001$). No survival difference was noted for survival between groups A and B ($p = 0.86$). The ratio of involved lymph nodes <0.2 was predictive of improved survival ($p < 0.001$).

Conclusions: Resected pancreatic cancer patients with only 1–2 positive lymph nodes or less than 20% involvement have a similar prognosis to patients without nodal disease. Current staging should consider stratification based on the extent of nodal involvement.

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Introduction

Over the past several years there has been much debate with regards to the prognostic and clinical significance of pancreatic cancer that is metastatic to lymph nodes. In 1973, Fortner first described the regional pancreatectomy in an attempt to clear a larger area including lymphatic channels and their associated lymph nodes.[1] This approach has not been embraced due to the failure to produce significantly better results over standard pancreatectomy, though some studies have reported modest benefit to extending the lymph node dissection.[2]

The current staging system for pancreatic cancer currently divides nodal status into a binary system, namely positive (N1) or negative nodes (N0). This is based upon multiple studies showing that any degree of lymph node positivity leads to equally adverse outcomes.[3–5] More recently, there has been interest in the metastatic lymph node ratio as a prognostic indicator in pancreatic cancer.[6–9] It has been proposed that an increasing positive lymph node ratio provides superior prognostic information over the current staging system. Along with an increasing node ratio, an increasing absolute number of removed lymph nodes has also been reported to be associated with an improved outcome. It is unclear whether this is due to stage migration or to additional clearance of tumor bearing tissue.[10,11]

The prognostic significance of positive lymph nodes and the extent to which lymph nodes should be removed during pancreatectomy needs clarification. To this end, we reviewed our experience of pancreatectomies to further delineate this issue and define the prognostic significance of metastatic lymph node involvement in pancreatic cancer.

Methods

Study population

A prospectively maintained database was reviewed for all patients who underwent pancreatectomy from 1999 to 2011 for curative intent for adenocarcinoma of the pancreas. Approval was

obtained from the institutional review board (IRB) prior to data collection. Patients who were found to have a diagnosis other than adenocarcinoma, who underwent surgery for reasons other than curative intent (diagnostic or palliative reasons), or had carcinoma arising from outside of the pancreas were excluded. The charts and pre-operative imaging were reviewed for all of these patients to confirm collected data and to provide additional data not originally collected. Data variables included patient age, gender, tumor location (head, body, tail), tumor size, grade, morphology, type of surgery performed, estimated blood loss (EBL), vein resection and repair, number of lymph nodes removed and positive lymph nodes, margin status, T stage, N stage, perineural invasion (PNI), lymphovascular invasion (LVI), neoadjuvant or adjuvant therapies, recurrence-free survival (RFS) and overall survival (OS).

The technical aspects of each surgery, including whether to perform a conventional pancreaticoduodenectomy (PD) or a pylorus-preserving pancreaticoduodenectomy (PPPD), were determined by each surgeon at the time of surgery. Vascular resection of the portal vein (PV) or superior mesenteric vein (SMV) was not routinely performed, but was done in select cases when required for complete resection of the tumor. Frozen section was routinely done on the pancreatic and bile duct margins. Extended regional lymphadenectomy was not performed in any of the reviewed cases.

Adjuvant chemotherapy and/or radiation therapy was considered for all patients with T2 or greater tumors. Treatment was considered to be adjuvant if there was no evidence of disease after surgical resection. Treatment was considered palliative if started when radiographic evidence of residual or recurrent pancreatic cancer was demonstrated. This included residual, recurrent, or metastatic disease found on post-surgical imaging. Treatment decisions were based upon individual patient considerations including performance status, patient desire for adjuvant treatment, and the ability to tolerate treatment based on the judgment of the treating physicians. Treatment regimens and dosing were left to the discretion of the treating physician. Tumors that were considered borderline resectable at time of presentation based on location of the tumor to the PV, SMV, or superior mesenteric artery (SMA) were considered for neoadjuvant treatment.

For the purposes of discriminating between head and body/tail lesions, patients who underwent pancreaticoduodenectomy were confirmed to have head lesions while patients who underwent distal pancreatectomy were considered to have body/tail lesions. The uncinate process was defined to be the area of the head of the pancreas to the right of the line between the SMV and inferior vena cava (IVC) as has traditionally been described. Tumors were then grouped into those involving the uncinate process or those confined to the head of the pancreas only based upon pre-operative CT scans, which were done with IV contrast in both arterial and portal venous phases. For charts without pre-operative imaging available for review, operative and/or pathology reports were used to determine the location of the tumor within the specimen.

Statistical methods

Patient characteristics were reported for the overall sample and by lymph node involvement using means and standard deviations for continuous variables; and frequencies and relative frequencies for categorical variables. Comparisons were made using the Kruskal Wallis and Pearson's chi-square test for continuous and categorical variables, respectively. The survival outcomes included overall survival (OS) and recurrence-free survival (RFS) and were summarized using standard Kaplan–Meier methods. Estimates of median survival and 1- and 3-year survival rates were obtained with corresponding 95% confidence intervals. Comparisons were made using the log-rank test. Continuous variables were categorized such that the Kaplan–Meier methods could be applied. All analyses were conducted in SAS v9.3 (Cary, NC) at a significance level of 0.05.

Results

Patient characteristics

Between January 1999 and October 2011, a total of 165 patients who underwent pancreatectomy for adenocarcinoma were identified. Table 1 summarizes patient demographics, tumor characteristics and treatments. Median age was 65 years; 91 (55.2%) of patients were female. Seven (4.2%) patients underwent total pancreatectomy due to inability to obtain a negative margin during resection. Vascular resection and repair was required for removal of the tumor in 21 (12.7%) of resections; 6 (28.6%) of these ultimately had positive margin resections. T4 tumors were defined post-resection by positive margins with involvement of unresectable vessels.

Absolute lymph node involvement

For the purposes of this analysis, metastatic pancreatic cancer to lymph nodes was stratified into three distinct categories: group A – no lymph node involvement (n = 55, 33.3%), group B – one or two positive lymph nodes (n = 55, 33.3%), and group C – three or more positive lymph nodes, (n = 55, 33.3%). The rationale for this grouping was derived from previous studies showing that patients with 1–2 positive nodes have similar outcomes compared to patients with no nodal involvement.[12,13] Interestingly, the distribution among the three groups was identical during the study time period. There were no statistical differences between these groups for age, gender, tumor size, pre-operative Ca 19-9 level, PNI, vein resection, or administration of neoadjuvant or adjuvant therapy (Table 2).

As the T stage of the tumor increased, the number of positive lymph nodes also increased. 54 (98.2%) of patients with three or more lymph nodes had T3 or T4 tumors, compared to 48 (87%) of those with one or two positive lymph nodes, and 37 (67.3%) without positive lymph nodes ($p < 0.001$). Tumors located