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ORIGINAL ARTICLE

Nodal sampling in pancreaticoduodenectomy: does it change our management?

ROOZBEH RASSADI[1], PAUL R. TARNASKY[2], JEFFREY D. LINDER[2], A. JOE SAAD[3] &
D. ROHAN JEYARAJAH[1,3]

Departments of [1]Surgery, [2]Gastroenterology and [3]Pathology, Methodist Dallas Medical Center, Dallas, TX, USA

Abstract

Background. Lymph node involvement in periampullary malignancy is the single most important factor in predicting survival in pancreaticoduodenectomy (PD). The role of nodal sampling in PD has not been well evaluated. This study evaluates the utility of nodal sampling of nodal stations 8 and 12, which are easily dissected early in PD, in overall final nodal status. *Patients and methods.* Fifty patients underwent PD at a single institution by a one surgeon over a 15 month period. Nodal stations 8 and 12 were sent separately for pathologic evaluation. Twenty-eight patients had a final diagnosis of periampullary malignancy. Demographic and pathologic data were collected retrospectively from patient charts. Positive and negative predictive values of nodes 8 and 12 were evaluated. *Results.* Eighteen of 28 patients with a diagnosis of periampullary malignancy had pathologically negative nodes 8 and 12, and a final nodal status (all peripancreatic lymph nodes) negative for nodal involvement. Nine of 28 patients had a negative nodal sampling result, but a positive final nodal status for metastatic tumor. The remaining four patients had both positive nodal sampling and final nodal status for metastatic tumor. The negative predictive value of negative nodes 8 and 12 was 0.625. *Conclusion.* The negative predictive of a negative node 8 and 12 of 0.625 suggests that the decision to proceed with or abort PD should not be based on intraoperative evaluation of these nodes. Performance of PD should be undertaken if technically feasible, and not based on intraoperative nodal assessment.

Key Words: *Pancreaticoduodenectomy, lymph nodes, Whipple*

Introduction

Pancreaticoduodenectomy (PD) remains the surgical procedure of choice in patients with a diagnosis of periampullary malignancy. In recent years, several high volume centers with significant expertise have reported an operative mortality of < 5% for PD [1–7], which has been linked to many factors including the hospital volume [8]. Indeed, our center is one such high volume center, and we have previously reported a mortality rate of 2.2% [9].

Although perioperative mortality has decreased significantly, the long-term survival of patients undergoing PD for malignant periampullary tumors remains poor. Lymph node involvement has consistently been considered one of the poor prognostic factors in long-term survival [10–12], although it has not been used as a definitive indicator for

selection of treatment. From a technical standpoint, the initial step in PD is evaluation of resectability. In past decades, peripancreatic lymph node involvement has been considered an absolute sign of unresectability [13] and surgeons have used this criterion as a reason to abandon the procedure. Intraoperative assessment of easily accessible lymph nodes is used by some surgeons to assess the extent of disease and decide on whether to proceed with PD.

The aim of this study was to evaluate the predictive value of nodal sampling of easily accessible nodes (stations 8 and 12 in the Japanese staging system [14]) on final nodal status in patients with a diagnosis of periampullary malignancy. The hypothesis is that nodal sampling is not predictive of final nodal status in PD and therefore should not dictate the decision to proceed with or abandon the resection.

Patients and methods

Patients who underwent a PD and had a confirmed histologic diagnosis of periampullary malignancy were included in this study. Of the 50 consecutive patients who underwent PD by a single surgeon between September 2005 and November 2006, 31 patients qualified for this study. Six patients with a final diagnosis of chronic pancreatitis, 3 with duodenal/ampullary adenoma, and 10 with a diagnosis of intraductal papillary mucinous neoplasm of the pancreas (IPMN) were excluded. Nodes were sent to pathology separately in a prospective manner. However, clinical and pathologic characteristics of patients were obtained by retrospective review of electronic medical records and paper charts. The protocol was approved by the Institutional Review Board at the Methodist Dallas Medical Center.

All patients underwent a pylorus-preserving PD unless there was concern regarding margin status of the specimen or duodenal ischemia. Routine duodeno- or gastro-jejunostomy, duct-to-mucosa pancreatic and biliary drainage were performed in all patients. During the portal nodal dissection, nodal group 8 (common hepatic artery nodal group) and 12 (hepatoduodenal nodal group) according to the Japan Pancreas Society classification of peripancreatic lymph node groups, were routinely sent to pathology (see Figure 1). These nodes were reported separately from the other nodes obtained en bloc with the specimen in the final pathology report as positive or negative for metastatic carcinoma.

The following data were analyzed: (1) demographics and preoperative data including co-morbidities, (2) final pathologic diagnosis, and (3) tumor characteristics including the margin status and lymphatic, vascular, and perineural invasion.

To evaluate the predictive value, patients were divided into three groups based on the results of nodal sampling and final nodal status for metastatic carcinoma. Group 1 had negative nodal sampling and also final nodal status for carcinoma. Group 2 had negative nodal sampling but positive nodal status for metastatic carcinoma. Group 3 had positive results for both nodal sampling and final nodal status.

Negative and positive predictive value of nodal sampling and prediction of final nodal status was calculated for negative and positive nodal sampling results, respectively. Statistical analysis was performed using the Fisher's exact test comparing the overall node positive group to the regional node (nodes 8 and 12) positive group.

Results

Patient demographics are shown in Table I. There were a total of 31 consecutive patients with a diagnosis of periampullary malignancy who underwent PD. The median age was 68 years with a range of 27–85 years. There were twenty (64%) females. Eighteen (58%) patients had a diagnosis of hypertension preoperatively. Nine (29%) patients had diabetes, seven (22.5%) had coronary artery disease, and three (9.6%) had a history of myocardial infarction. Three (9.6%) patients had chronic obstructive pulmonary disease (COPD) and one patient each had a diagnosis of congestive heart failure (CHF), peripheral vascular disease, and peptic ulcer disease.

Pathologic diagnoses of all patients who underwent PD and were included in this study are shown in Table II. There were a total of 27 (87%) patients with a diagnosis of periampullary malignancy. Of these, 17 (62.9%) had pancreatic adenocarcinoma as the final pathologic diagnosis and 5 (18.5%) had a diagnosis of ampullary adenocarcinoma. There were two (4.5%) patients with a diagnosis of distal bile duct adenocarcinoma and three (11.1%) with a diagnosis of
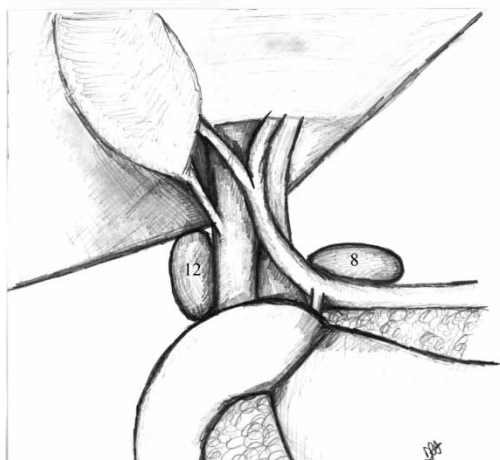

Figure 1. Illustration of nodes 8 and 12 in the Japanese classification system. This illustration shows node 8 (above the hepatic artery) and node 12 (lateral to the common bile duct) in relation to the portal structures.

Table I. Demographics of patients undergoing PD for malignant periampullary tumors.

Parameter	Value
Age (years), median (range)	68 (27–85)
Gender	
Male	11 (36)
Female	21 (64)
Past medical history	
Hypertension	18 (58)
Asthma	1 (3.2)
Congestive heart failure (CHF)	1 (3.3)
Diabetes mellitus	9 (29)
Coronary artery disease (CAD)	7 (22.5)
Myocardial infarction (MI)	3 (9.6)
Peripheral vascular disease	1 (3.2)
Chronic obstructive pulmonary disease (COPD)	3 (9.6)
Peptic ulcer disease	1 (3.2)

The table shows demographic data for patients undergoing PD at our tertiary care community hospital. Values are *n* (%) unless otherwise specified.

Table II. Pathologic diagnosis of 31 consecutive patients undergoing PD for malignant periampullary tumors.

Diagnosis	Value
Periampullary cancer	27 (87)
Pancreas	17 (62.9)
Ampulla	5 (18.5)
Distal bile duct	2 (7.4)
Duodenum	3 (11.1)
Neuroendocrine tumor	1 (3.2)
Cystadenoma/cystadenocarcinoma	2 (6.4)
Solid pseudopapillary tumor	1 (3.2)

The table shows the pathologic diagnosis code for which patients underwent PD in our series. Values in table are *n* (%) unless otherwise specified.

Table IV. Predictive value of nodal sampling.

Patients	Nodal sampling	Regional nodal	Predictive value
15	Negative	Negative	0.625 (NPV)
9	Negative	Positive	
4	Positive	Positive	1 (PPV)

The table shows positive and negative predictive values of group 8 and 12 nodes on final nodal status in 28 consecutive patients undergoing PD for a malignant periampullary tumor. NPV, negative predictive value; PPV, positive predictive value.

duodenal adenocarcinoma. We also included one (3.2%) patient with a neuroendocrine cancer, two (6.4%) patients with a cystadenoma/cystadenocarcinoma, and one patient with a solid pseudopapillary tumor.

Tumor characteristics and nodal status of patients included in this study are shown in Table III. There were 20 (64.5%) with a negative margin and 11 (35.5%) with a positive margin. The SMA margin was the most frequently positive margin. It is interesting that SMA positivity has increased since the operating surgeon orients and inks this margin specifically for the pathologist. Specific sections are submitted from the inked margin. Eighteen (58%) patients had a negative final nodal status and 13 (41.9%) had a positive nodal status in the final pathology. Lymphatic invasion was seen in 12 (38.7%) and 19 (61.2%) had no evidence of lymphatic invasion. Perineural invasion was seen in 15 patients (48.3%) and was absent in 16 (51.6%). Microscopic vascular invasion was identified in four patients (12.9%).

The predictive value of nodal groups 8 and 12 in prediction of overall nodal status of patients is shown in Table IV. Patients with borderline tumors ($n = 3$) were excluded from this analysis. Fifteen patients had a negative nodal sampling of groups 8 and 12 and also had a negative final nodal status for metastatic adenocarcinoma. The second group, which included nine patients, had a negative nodal sampling for groups 8 and 12, but had a positive nodal status in

Table III. Nodal status and tumor characteristics in 31 consecutive patients undergoing PD for malignant periampullary tumors.

Tumor/nodal status	Negative	Positive
Nodes	18 (58)	13 (41.9)
Margins	20 (64.5)	11 (35.4)
Lymphatic invasion	19 (61.2)	12 (38.7)
Perineural invasion	16 (51.6)	15 (48.3)
Microscopic vascular invasion	27 (87)	4 (12.9)

Thirty-one patients included in this study are shown based on their pathologic characteristics. Patients are separated into two groups based on final nodal status.

the final pathology report. Therefore, the negative predictive value of nodal sampling in prediction of final nodal status for metastatic adenocarcinoma was 0.625 (95% confidence interval (CI) 0.14–0.50). The third and final group included four patients that were positive on both nodal sampling and final nodal status results for metastatic adenocarcinoma. The positive predictive value of nodal sampling in prediction of final nodal status for metastatic adenocarcinoma was 1.0 by definition. The difference between the groups that were node-positive on overall evaluation compared with the group that was regionally node-positive (nodes 8 and 12) was statistically significant by the χ^2 test ($p = 0.035$).

Discussion

This study examining the predictive value of nodal sampling on final nodal status suggests that intraoperative assessment of nodal groups 8 and 12 is not warranted. The data presented here would support the decision to perform PD without interruption of the surgery for intraoperative nodal evaluation. While this may seem obvious to experienced pancreatic surgeons, this analysis will encourage those surgeons who may not be so experienced to proceed with PD without the added time and expense of submitting nodes for frozen section nodal analysis.

Herein we have reported our data on the predictive value of nodal sampling of group 8 and 12 in predicting the overall nodal status in patients with a diagnosis of malignant periampullary tumor. In recent years, there has been increasing interest regarding the role of lymphatic involvement in gastrointestinal malignancies. One of these interesting issues is the role of nodal sampling and the search for a sentinel lymph node in gastric and colon cancers [15–17]. Similarly the idea of nodal sampling in periampullary cancer is under active investigation [18,19]. Our data would suggest that nodes 8 and 12 are not the sentinel nodes in this disease process.

The first step in operative assessment of periampullary cancer is determination of resectability. In past decades peripancreatic lymph node involvement was considered an absolute contraindication to resectability. In many cases the concern for perioperative mortality and morbidity were the factors favoring a

conservative approach. Over the past decade, several studies have shown an improved outcome for PD in high volume, experienced centers, including our own [1–7,9]. Yet the overall survival for periampullary tumors remains poor [4]. There are many prognostic factors affecting the long-term survival in these patients including lymph node metastasis [10–12], tumor differentiation [11], margin status [12], and tumor size [11,12,20]. Among these factors, lymph node involvement is one of the most significant prognostic factors affecting the long-term survival. Despite the poor prognosis of PD in patients with nodal involvement, data from high volume centers suggest that PD can be performed in this subgroup safely and with some potential benefit [2,13].

To address the issue, we routinely sampled nodal groups 8 and 12 (based on the classification system of the Japan Pancreas Society [14]), during our dissection. These lymphatic groups were selected as they are easily visualized and biopsied during the standard dissection. Connor et al. [21] have shown a significant decrease in survival with the involvement of group 8. In another recent study [22], involvement of groups 8 and 12 was associated with a significantly poorer outcome. Interestingly, Maithel et al. recently reported that a common bile duct (CBD) node (group 12) short-axis size of >10 mm in CT scan predicts tumor unresectability [23]. These data do not provide insight into the predictive value of these nodes on overall nodal status.

In our cohort all of 31 consecutive patients with a diagnosis of periampullary malignancy underwent a standard resection. The negative predictive value for prediction of final nodal status was only 0.625, suggesting that the finding of a negative node 8 and 12 was not a good indicator of a negative final nodal status. The positive predictive value was 1.00, as would be expected as positive nodes 8 and 12 would result in a positive overall nodal status in all patients. Interestingly, most patients (54%) with a positive final nodal status also had a positive margin, which also correlated closely with perineural and lymphatic invasion.

The question of what to do if there is a known positive node is challenging and interesting. There are data to support proceeding with PD if an R0 resection is possible. Data from France suggests that involvement of greater than two lymph nodes results in a worse survival [24], a concept that is corroborated by several international studies suggesting that lymph node number and ratio may, in fact, be key prognostic factors [22,25,26]. These data need to be tempered with the surgeon's personal experience. We feel that PD should be performed even in the face of positive nodal disease if the surgeon can perform the operation with a reasonably low risk of mortality, and with the clear understanding of all involved that PD will likely be non-curative in this patient population.

The extent of the lymph nodal dissection is another point of controversy. There has been interest in extended lymph nodal dissection in PD. Surgical literature from Germany and Japan suggests that radical nodal dissection does not affect overall survival and may in fact be associated with an increased risk of complications [27,28]. Similar conclusions were reached by several groups in North America [29–31] including a multi-institution randomized study [32]. It is the authors' preference to perform an 'anatomically correct' dissection; this includes skeletonizing the vena cava to preserve the posterior capsule to the pancreatic head (the 'mesopancreas'), in a similar way to preserving the mesorectum. We do not make an additional effort to take aortocaval nodes, but will visualize both gonadal veins. Similarly, respecting the arterial structures and keeping in the plane of the 'glistening vessel' will result in reasonable portal nodal clearance.

In conclusion, we have demonstrated that the intraoperative nodal sampling of groups 8 and 12 is not an optimal way to predict the final nodal status and should not be used as treatment selection criterion. However, the finding of a positive metastatic focus in nodes 8 and 12 does suggest a more aggressive disease, as this was correlated with positive surgical margin status, and lymphatic and perineural invasion. Overall, it is our recommendation that intraoperative evaluation of nodes 8 and 12 should not be routinely performed, as it does not correlate with final nodal status. PD should be performed when technically possible based on resectability status and not nodal evaluation.

Acknowledgements and disclosures

References

[1] Halsted WS. Contribution to the surgery of the bile passage, especially of the common bile duct. Boston Med Surg J 1899; 141:645–54.

[2] Balcom JH IV, Rattner DW, Warshaw AL, Chang Y, Fernandez-del Castillo C. Ten-year experience with 733 pancreatic resections. Arch Surg 2001;136:391–8.

[3] Whipple A, Parson WB, Mullins CR. Treatment of carcinoma of the ampulla of Vater. Ann Surg 1935;102:763–79.

[4] Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J, et al. 1423 pancreaticoduodenectomies for pancreatic cancer: a single institution experience. J Gastrointest Surg 2006;10:1199–210; discussion 1210–11.

[5] Riall TS, Cameron JL, Lillemoe KD, Winter JM, Campbell KA, Hruban RH, et al. Resected periampullary adenocarcinoma: 5-year survivors and their 6- to 10-year follow-up. Surgery 2006;140:764–72.

[6] Trede M, Schwall G, Saeger H-D. Survival after pancreaticoduodenectomy: 118 consecutive resections without an operative mortality. Ann Surg 1990;211:447–58.

[7] Fernandez-del Castillo C, Ratner DW, Warshaw AL. Standards for pancreatic resections in 1990s. Arch Surg 1995;130: 295–300.

[8] Birkmeyer JD, Siewers AE, Finlayson EV, Stukel TA, Lucas FL, Batista I, et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002;346:1128–37.

[9] Rassadi R, Vo A, Jeyarajah DR. Feasibility and safety of pancreaticoduodenectomy (the Whipple procedure) in a high volume community center. HPB 2007;9(Suppl 1):49.

[10] Cameron JL, Crist DW, Earle CC. Factors influencing survival after pancreaticoduodenectomy for pancreatic cancer. Am J Surg 1991;161:120–4.

[11] Geer RJ, Brennan MF. Prognostic factors for survival after resection of pancreatic adenocarcinoma. Am J Surg 1993;165: 68–72.

[12] Yeo CJ, Cameron JL, Lillemoe KD, Sitzman JV, Hruban RH, Goodman SN, et al. Pancreaticoduodenectomy for cancer of the head of pancreas. 201 patients. Ann Surg 1995;221:721–31.

[13] Lillemoe KD, Cameron JL, Yeo CJ. Pancreaticoduodenectomy; does it have a role in the palliation of pancreatic cancer? Ann Surg 1996;223:718–28.

[14] Japan Pancreas Society. Classification of pancreatic carcinoma, 2nd English edn. Tokyo: Kanehara, 2003.

[15] Aikou T, Higashi H, Natsugoe S, Hakita S, Baba M, Tako S. Can sentinel node navigation surgery reduce the extent of lymph node dissection in gastric cancer? Ann Surg Oncol 2001;8(9 Suppl):90s–93s.

[16] Hiratsuka M, Miashiro I, Ishikawa O, Furukawa H, Matomura K, Ohigashi H, et al. Application of sentinel node biopsy to gastric cancer surgery. Surgery 2001;129:335–40.

[17] Esser S, Reilly WT, Riley LB, Eyvazzadeh C, Arcona S. The role of sentinel lymph node mapping in staging of colon and rectal cancer. Dis Colon Rectum 2001;44:850–4.

[18] Ohta T, Kitagawa H, Kayahara M, Kinami S, Ninamiya I, Fushida S, et al. Sentinel lymph node navigation surgery for pancreatic head cancer. Oncol Reports 2003;10:315–9.

[19] Shimada K, Sakamoto Y, Sano T, Kosuge T. The role of paraaortic lymph node involvement on early recurrence and survival after macroscopic curative resection with extended lymphadenectomy for pancreatic carcinoma. J Am Coll Surg 2006;203:345–52.

[20] Fortner JG, Klimstra DS, Senie RT, Maclean BJ. Tumor size is the primary prognosticator for pancreatic cancer after regional pancreatectomy. Ann Surg 1996;223:147–53.

[21] Connor S, Bosonnet L, Ghaneh P, Alexakis N, Hartley M, Campbell F, et al. Survival of patients with periampullary carcinoma is predicted by lymph node 8a but not by lymph node 16b 1 status. Br J Surg 2004;91:1592–9.

[22] Sierzega M, Popiela T, Kulig J, Nowak K. The ratio of metastatic/resected lymph nodes is an independent prognostic factor in patients with node-positive pancreatic head cancer. Pancreas 2006;33:240–5.

[23] Maithel Sk, Khalili K, Dixon E, Guindi M, Callery MP, Cattral MS, et al. Impact of regional lymph node evaluation in staging patients with periampullary tumors. Ann Surg Oncol 2007;14:202–10.

[24] Zacharias T, Jaeck D, Oussoultzoglou E, Neuville A, Bacheller P. Impact of lymph node involvement on long-term survival after Ro pancreaticoduodenecetomy for ductal adenocarcinoma of the pancreas. J Gastrointest Surg 2007;11:350–6.

[25] Sakata A, Shirai Y, Wakai T, Yokoyama N, Sakata E, Akazawa K, et al. Number of positive lymph nodes independently affects long-term survival after resection in patients with ampullary carcinoma. SRSO 2007;33:246–351.

[26] Pawlik T, Gleisner AL, Cameron JL, Winter JM, Assumpcao L, Lillemoe KD, et al. Prognostic relevance of lymph node ratio following pancreaticoduodenectomy for pancreatic cancer. Surgery 2007;141:610–8.

[27] Michalski W, Kleeff J, Wentel MN, Diener MK, Buchler MW, Friess H. Systemic review and meta-analysis of standard and extended lymphadenectomy in pancreaticoduodenectomy for pancreatic cancer. Br J Surg 2007;94:265–73.

[28] Nakagohri T, Kinoshita T, Konoshi M, Takahashi S, Tanizawa Y. Clinical results of extended lymphadenectomy and intraoperative radiotherapy for pancreatic adenocarcinoma. Hepatogastroenterology 2007;54:564–9.

[29] Kennedy E, Yeo CJ. Pancreaticoduodenectomy with extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma. Surg Oncol Clin N Am 2007;16:157–76.

[30] Riall TS, Cameron JL, Lillemoe KD, Campbell KA, Sauter PK, Coleman J, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma- Part 4; update on 5-year survival. J Gastrointest Surg 2005;9:1191–206.

[31] Reddy SK, Tyler DS, Pappas TN, Clary BM. Extended resection for pancreatic adenocarcinoma. Oncologist 2007; 12:654–63.

[32] Farnell MB, Pearson RK, Sarr MG, DiMagno EP, Burgart LJ, Dahl TR, et al. A prospective randomized trial comparing standard pancreaticoduodenectomy with pancreacreaticoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. Surgery 2005;138:618–30.