J Hepatobiliary Pancreat Surg (2006) 13:549–555
DOI 10.1007/s00534-006-1113-5

Journal of HBP Surgery

Nodal involvement as an indicator of postoperative liver metastasis in carcinoma of the papilla of Vater

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Abstract
Background/Purpose. Although lymph node metastatic involvement is one of the most important prognostic factors for carcinoma of the papilla of Vater, a detailed analysis of this factor in relation to prognosis has not been conducted.
Methods. From 1985 to 2003, 29 patients with carcinoma of the papilla of Vater underwent pancreaticoduodenectomy and dissection of regional lymph nodes at Yamagata University Hospital. We analyzed clinicopathologic variables in relation to prognosis and precisely evaluated nodal involvement in each patient to determine lymphatic flow. Furthermore, the relationship between recurrent site and nodal involvement was investigated.
Results. The overall survival rate was 55% at 5 years. The significant prognostic factors were morphological ulcer formation ($P = 0.04$), histological type ($P = 0.03$), nodal involvement ($P = 0.002$), and lymphatic invasion ($P = 0.03$). Multivariate analysis indicated no independent factor, but nodal involvement may be the strongest prognostic factor. The overall rate of nodal involvement was 41.4% (12 of 29 patients). The metastatic rates in the superior posterior pancreaticoduodenal lymph nodes, the inferior posterior pancreaticoduodenal lymph nodes, the superior mesenteric lymph nodes, and paraaortic lymph nodes were high (31.0%, 20.7%, 17.2%, and 13.8%, respectively). Patients with nodal involvement had a significantly higher rate of liver metastasis after surgery than those without it ($P = 0.02$). Ulcer formation and histological type were significantly correlated with nodal involvement ($P = 0.05$ and $P = 0.002$, respectively).
Conclusions. Nodal involvement is the most important prognostic factor in patients with carcinoma of the papilla of Vater. Patients with nodal involvement are at high risk of liver metastasis; therefore, adjuvant therapy may be necessary for the control of liver metastasis. Preoperative ulcer formation and histological type in the biopsy specimen are good indicators for extended lymph node dissection and adjuvant therapy, because these variables are correlated with nodal involvement. However, our data revealed only the sites of the positive nodes, without addressing the effect of extended lymph node dissection and adjuvant chemotherapy. To date, there has been reporting of extended lymph node dissection and adjuvant chemotherapy in patients with carcinoma of the papilla of Vater. Further studies will be necessary to resolve these problems.

Key words Carcinoma of the papilla of Vater · Ampullary cancer · Prognostic factor · Nodal involvement · Ulcer

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Received: March 31, 2005 / Accepted: February 18, 2006

Introduction

Carcinoma of the papilla of Vater is a relatively uncommon neoplasm, which accounts for approximately 6% of pericampullary tumors,[1] with an incidence of approximately 5.7 cases per million population per year.[2] Surgical series of periampullary tumors have demonstrated that patients with carcinoma of the papilla of Vater have a more favorable prognosis than those with pancreatic or bile duct tumors,[3–11] with 5-year survival rates between 30% and 60% in patients after resection.[5–10,12,13] Nodal status is one of the most important prognostic factors for carcinoma of the papilla of Vater; therefore, lymph node dissection is an important component of radical surgery.[12,14–16] Precise studies of the frequency of lymph node metastasis have been previously performed;[17,18] however, these previously reported data did not mention the relationship between nodal involvement and the recurrent site.

The present study examined the prognostic factors affecting survival in patients with carcinoma of the papilla of Vater, especially the pattern of lymphatic spread, by determining the frequency of nodal involvement in each patient. Moreover, we elucidated the correlation between nodal involvement and the recurrent site.

Patients and methods

From 1985 to 2003, 29 patients with carcinoma of the papilla of Vater underwent curative resection at Yamagata University Hospital, Yamagata, Japan. The 12 men and 17 women had an average age of 63.2 ± 9.45 years (range, 43 to 78 years). All patients received pancreaticoduodenectomy and regional lymphadenectomy (Whipple, 23; pylorus-preserving, 4; substomach-preserving, 2). Dissection of the paraaortic lymph nodes was performed in 10 of the 29 (34.5%) patients. The survival tiem of the patients ranged from 6 months to 18 years. The following parameters were examined: age (<65/≥65 years), sex (male/female), and preoperative serum levels of total bilirubin (<2.0/≥2.0). The surgically resected specimens were studied macroscopically to determine the size of the tumor (<30 mm/≥30 mm) and morphology (ulcer type/nonulcer type). For microscopic analysis, the resected specimens were fixed in 10% formaldehyde and sliced into 5-mm sections. After each section was sliced into 5-μm tissue sections and stained with hematoxylin and eoslin, we performed microscopic observation to determine histological type, lymph node metastasis, perineural invasion, duodenal invasion, pancreatic invasion, lymphatic invasion, and venous invasion.

Precise classification of the lymph nodes was based on the *General rules for surgical and pathological studies on cancer of biliary tract* proposed by the Japanese Society of Biliary Surgery[19] (Fig. 1). The nomenclature of the major lymph nodes was defined as follows: number 8, lymph nodes around the common hepatic artery; number 9, lymph nodes around the celiac trunk; number 10, lymph nodes at the hilus of the spleen; number 11, lymph nodes along the splenic artery; number 12, lymph nodes along the hepatoduodenal ligament; number 13, posterior pancreaticoduodenal lymph nodes; number 14, lymph nodes around the superior mesenteric artery; number 16, paraaortic lymph nodes; and number 17, anterior pancreaticoduodenal lymph nodes. For lymph node groups 12, 13, and 17, two subgroups were defined: those inferior to the bile duct were defined as 12b2, and the others were defined as 12; those above the papilla of Vater were defined as 13a and 17a; and those below the papilla were defined as 13b and 17b. Perigastric lymph nodes were defined as numbers 1 to 7.

The initial recurrent site was determined by computed tomography. Survival rates were calculated by using the Kaplan-Meier method, and differences between the curves were ascertained by using the log-rank test; significant prognostic factors were determined by multivariate Cox regression ananlysis. Statistical comparisons were made by χ^2 analysis. Statistical significance was noted if the P value was less than 0.05. The SPSS for Windows, release 11.0J (SPSS., Chicage, IL, USA) statistical package was used to generate these analyses.

Results

Prognostic factors

All patients tolerated the operation well and were discharged from out hospital without major complications. The overall survival rate was 55% at 5 years. Univariate

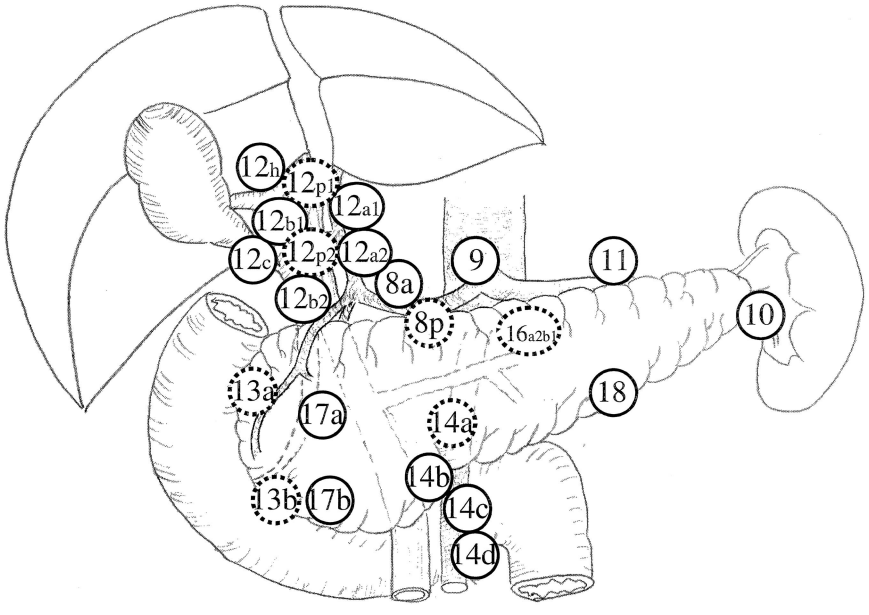

Fig. 1. Nomenclature of major lymph nodes involved with carcinoma of the papilla of Vater. *8*, Lymph nodes around the common hepatic artery; *9*, lymph nodes around the celiac trunk; *10*, lymph nodes at the hilus of the spleen; *11*, lymph nodes along the splenic artery; *12*, lymph nodes along the hepatoduodenal ligament; *13*, posterior pancreaticoduodenal lymph nodes; *14*, lymph nodes around the superior mesenteric artery; *16*, paraaortic lymph nodes; *17*, anterior pancreaticoduodenal lymph nodes; *18*, inferior body lymph nodes

Table 1. Univariate log-rank analysis of prognostic factors in patients with carcinoma of the papilla of vater

Factor	Number of patients	5-Year survival (%)	*P* value
Age (years)			
<65	14	50.9	
≥65	15	60.2	0.90
Sex			
Male	13	36.4	
Female	16	68.4	0.22
T-Bil			
<2.0	22	55.4	
≥2.0	7	50.0	0.92
Tumor size (mm)			
<30	19	58.5	
≥30	10	41.7	0.93
Morphology			
Ulcer type	9	29.6	
Nonulcer type	20	67.3	0.04
Histology			
Papillary or well-diff.	19	68.8	
Mod. or poorly diff.	10	33.8	0.03
Nodal involvement			
Present	12	21.4	
Absent	17	81.8	0.002
Perineural invasion			
Present	10	33.8	
Absent	19	65.2	0.07
Duodenal invasion			
Present	24	50.4	
Absent	5	75.0	0.33
Pancreatic invasion			
Present	16	40.0	
Absent	13	70.7	0.21
Lymphatic invasion			
Present	17	37.7	
Absent	12	85.7	0.03
Venous invasion			
Present	7	35.7	
Absent	22	62.1	0.11

log-rank ananlysis clarified that the significant prognostic factors were morphological ulcer formation (P = 0.04), histological type (P = 0.03), nodal involvement (P = 0.002), and lymphatic invasion (P = 0.03; Table 1). Kaplan-Meier survival graphs of carcinoma of the papilla of Vater as related to nodal involvement, histological type, and ulcer formation are shown in Figs. 2, 3, and 4, respectively. Multivariate Cox regression analysis was performed for the significant prognostic factors indicated by the univariate analysis, i.e., morphological ulcer formation, histological type, and nodal involvement. Lymphatic invasion was not included, because this factor was correlated to nodal involvement. Multivariate Cox regression analysis indicated nodal involvement as the strongest prognostic factor (P = 0.06; Table 2), but there was no independent prognostic factor.

Table 2. Multivariate analysis of prognostic factors in patients with carcinoma of the papilla of Vater

Prognostic factor	Odds ratio	*P* value	95% CI
Nodal involvement	6.6	0.06	0.92–46
Ulcer formation	1.4	0.61	0.38–5.3
Histological type	1.1	0.91	0.24–4.8

CI, Confidence interval

Frequency of nodal involvement and correlation of positive nodes

The number of dissected lymph nodes ranged between 8 and 36 (median number, 15) in the patients in this study. The frequencies of lymph node involvement are summarized in Fig. 5. The frequency was 6.9%, 13.8%,

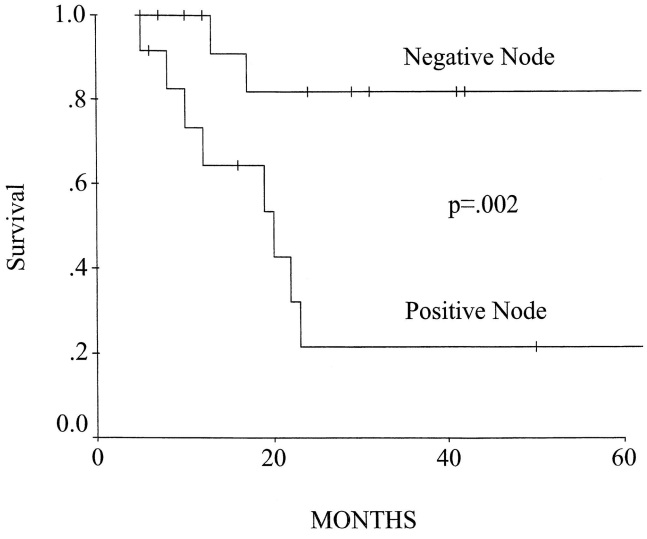

Fig. 2. Kaplan-Meier survival curves for patients with and without lymph node metastases after resection of carcinoma of the papilla of Vater. The node-negative patients ($n = 17$) had a better outcome than the node-positive patients ($n = 12$; $P = 0.002$)

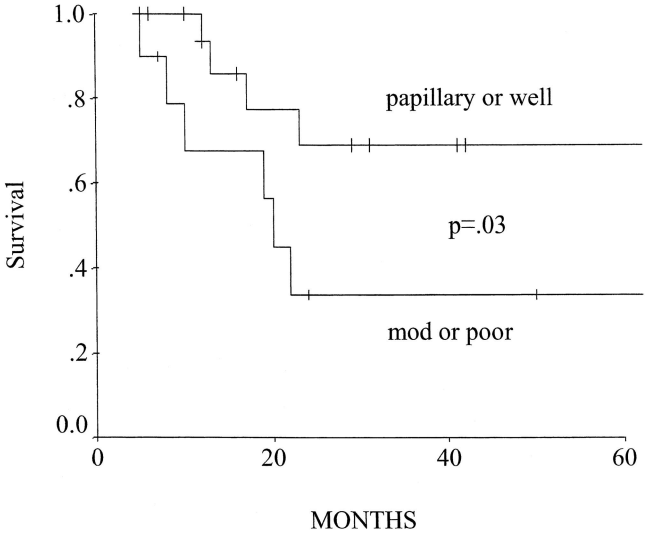

Fig. 3. Kaplan-Meier survival curves related to histological type in patients after resection of carcinoma of the papilla of Vater. The patients with papillary carcinoma or well-differentiated adenocarcinoma (*well*; $n = 19$) had a better outcome than those with moderately or poorly differentiated adenocarcinoma (*mod or poor*; $n = 10$; $P = 0.03$)

31.0% 20.7%, 17.2%, 13.8%, 3.4%, and 3.4%, in lymph node groups 8, 12, 13a, 13b, 14, 16, 17a, and 17b, respectively. There were no metastases in the perigastric lymph nodes. Figure 5 also demonstrates correlations of metastatic lymph node groups in each patient. All but two patients with nodal involvement showed involvement in group 13 lymph nodes. One of these patients had a solitary metastatic lymph node only in group 14, and the other had a solitary metastasis only in group 16.

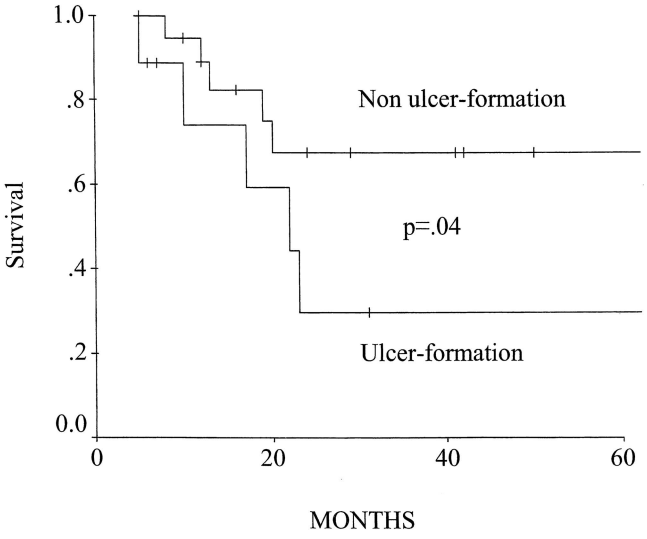

Fig. 4. Kaplan-Meier survival curves for patients with and without ulcer formation after resection of carcinoma of the papilla of Vater. The patients with ulcer formation ($n = 9$) had a worse outcome than those without ulcer formation ($n = 20$; $P = 0.04$)

Table 3. Relationship among gross appearance, histological type and nodal involvement (N)

	N (+)	N (–)	*P* value
Ulcer (+)	7	2	$P = 0.05$
Ulcer (–)	5	15	
Papillary or well-diff.	4	15	$P = 0.002$
Moderately or poorly diff.	8	2	

Relationship among gross appearance, histological type, and nodal involvemet

Table 3 shows the relationship among gross appearance, histological type, and nodal involvement. Seven of the nine patients with ulcer formation had nodal involvement. There was a significant difference between the two factors ($P = 0.05$). The patients with moderately and poorly differentiated adenocarcinoma showed a significant association with nodal involvement ($P = 0.002$). There was no significant correlation between ulcer formation and histological type ($P = 0.10$).

Correlation between nodal involvement and recurrent site

The initial recurrent site was determined by computed tomography. A total of nine patients died from recur-

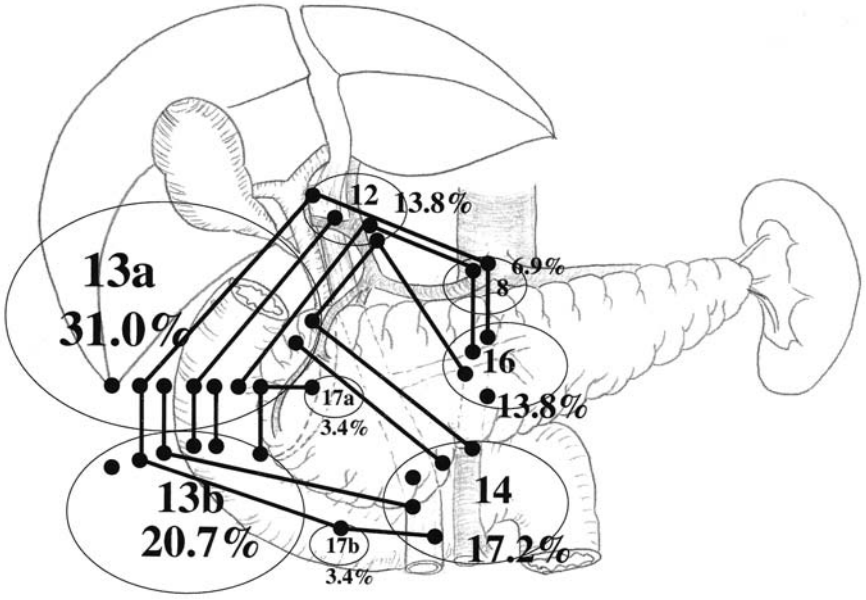

Fig. 5. Frequency of nodal involvement in 29 patients with carcinoma of the papilla of Vater, and correlation of metastatic lymph nodes in each patient. *Black dots* indicate lymph node metastasis. *Black dots* in the same patient are *linked by lines*. *Font sizes* and *sizes of outlined ellipses* are proportional to the frequency of nodal involvement

Table 4. Relationship between nodal involvement and recurrent site

Recurrent site	N (+) (n = 12)	N (–) (n = 17)	P value
Liver	5	0	0.02
Peritoneum	1	0	0.23
Lymph node	1	0	0.23
Unknown	1	1	—

Table 5. Risk of liver metastasis in patients with nodal involvement, determined logistic regression

Factor	P value	Odds ratio	95% CI
Nodal involvement	0.03	13.5	1.2–148.9

CI, Confidence interval

rence of carcinoma of the papilla of Vater; five of these patients had liver metastasis. One of the other four patients had nodal recurrence and one had peritoneal dissemination. In the other two patients, the site of recurrence could not be determined because of unsatisfactory evaluation. Patients with nodal involvement had significantly higher rates of liver metastasis (5/12) than those without it (0/17) (P = 0.02; Table 4). The risk of liver metastasis in patients in patients with nodal involvement is demonstrated in Table 5, showing an odds ratio of 13.5 (95% confidence interval, 1.2–148.9). The characteristics of liver metastasis were as follows: the timing of detection of liver metastasis was between 2 months and 11 years after resection and the metastatic site in the liver was the right lobe in two patients and bilateral in three.

Discussion

There has been controversy around prognostic factors in patients with carcinoma of the papilla of Vater after resection. Several factors have been variably associated with survival:[2–5,7–18,20–24] tumor size, histological differentiation, lymph node status, resection margin status, and perioperative blood transfusion. In the present series, ulcer formation, histological type, nodal involvement, and lymphatic invasion approached significance as prognostic predictors.

Ulcer formation is clinically important, because the gross appearance of carcinoma of the papilla of the Vater is easily observed by gastrointestinal endoscopy and is a significant prognostic factor. Futakawa et al.[25] have reported that submucosal invasion, invasion to the sphincter Oddi, pancreatic parenchymal invasion, and lymph node involvement were found more frequently in the ulcer-formation type than in the polypoid type without ulceration. Postoperative survival curves revealed that the prognosis was poor when ulceration was found.[25]

In carcinoma of the papilla of Vater, rates of nodal involvement have been reported to range from 31% to 52%.[11–18,20–24] Nakao et al.[17] reported that lymph node involvement in patients with carcinoma of the papilla of Vater was found in lymph node groups 4, 12, 13, 14, and 17 (4%, 4%, 41%, 11%, and 22%, respectively). Paraaortic lymph node involvement was not observed.

Kayahara et al.[18] reported that metastatic rates for lymph node groups 13a, 13b, 14, 17a, and 17b were 8%, 31%, 17%, 3%, and 0%. There were no metastases in the perigastric or paraaortic lymph nodes. Thus, these authors concluded that pylorus-preserving pancreaticoduodenectomy was feasible for carcinoma of the papilla of Vater.

In the present series, the overall frequency of lymph node metastasis was 41.4%. We found nodal involvement in lymph node groups 8, 12, 13a, 13b, 14, 16, 17a, and 17b (6.9%, 13.8%, 31.0%, 20.7%, 17.2%, 13.8%, 3.4%, and 3.4%, respectively) as shown in Fig. 5. Ohta et al.[26] reported sentinel navigation surgery for pancreatic head cancer, using lymph node group 13 as a sentinel lymph node. Group 13 lymph nodes were identified in 89% of their patients with pancreatic cancer; if group 13 was negative, an extended group 16 lymph node dissection was not performed, to reduce morbidity. In the present study, there were four patients with positive group 16 lymph nodes, and three of these patients also had group 12 and 13 lymph nodes that were positive. In only one patient was the involvement of lymph node group 16 not accompanied with other lymph node metastases. We have reported that there is a long descending lymphatic duct which directly connects group 16 lymph nodes in the pancreatic head.[27] We considered that the lymphatic flow to the paraaortic region in the patient with a solitary metastasis in group 16 lymph nodes was drained by this long lymphatic duct, which was located in the posterior pancreaticoduodenal area. Also, one patient had skip metastasis in group 14 lymph nodes. Kayahara et al.[18] have reported that the main lymphatic flow drains from group 13b lymph nodes to group 14 lymph nodes. We presumed that this lymphatic flow participated in the skip metastasis in the group 14 lymph nodes. There is little literature on skip metastasis in the carcinoma of the papilla of Vater. In carcinoma of the head of the pancreas, skip metastasis was associated with small cancer nests surrounded by dense fibrous connective tissues.[28] In patients with non-small-cell lung cancer, pN2 patients with mediastinal lymph node skip metastasis have a more favorable prognosis compared to pN2 patients with continuous infiltration of the regional lymph nodes.[29] In the current study, the patient with skip metastasis died within 20 months of operation. Precise studies in many populations may be necessary to elucidate the features of skip metastasis in carcinoma of the papilla of Vater.

Tumor recurrence is one of the most important causes of death in various cancer; however, precise details concerning the mode of recurrence of carcinoma of the papilla of Vater have not been reported, to our knowledge. In the current study, it was noted that patients with nodal involvement had significantly higher rates of liver metastasis. The relationship between lymph node metastasis and postoperative liver metastasis has not been resolved. It is presumed that when lymph vessels are blocked, some mechanism could make it easier for cancer cells to enter the portal blood flow, or, alternatively, lymph node involvement may merely represent cancer at an advanced stage that tends to metastasize to the liver. In the future, animal experiments should be conducted to ascertain the relationship between lymphatic flow and cancer metastasis.[30]

In conclusion, ulcer formation, histological type, nodal involvement, and lymphatic invasion are significant prognostic factors in patients with carcinoma of the papilla of Vater. Our data indicate that patients with nodal involvement are at high risk of postoperative liver metastasis. Adjuvant therapy may be necessary in patients with lymph node metastases, for the control liver metastasis. Ulcer formation and histological type are correlated with nodal involvement; therefore, preoperative ulcer formation and a positive pathological diagnosis of nodal involvement in biopsy speciments are good indications for extended lymph node dissection and adjuvant chemotherapy. However, our data revealed only the sites of positive nodes; we did not address the effect of extended lymph node dissection and adjuvant chemotherapy. To date, there has been no reporting of extended lymph node dissection and adjuvant chemotherapy in patients with carcinoma of the papilla of Vater.[31,32] Further studies will be necessary to resolve these problems.

References

1. Brennan MF. Surgical management of peripancreatic cancer. In: Bland KI, Karakousis CP, Copeland EM, editors. Atlas of surgical oncology. Philadelphia: W.B. Saunders; 1995. p. 711–22.
2. Neoptolemos JP, Talbot IC, Carr-Locke DL, Shaw DE, Cockleburgh R, Hall AW, et al. Treatment and outcome in 52 consecutive cases of ampullary carcinoma. Br J Surg 1987;74:957–61.
3. Warren KW, Choe DS, Plaza J, Relihan M. Results of radical resection for periampullary cancer. Ann Surg 1971;181:534–40.
4. Cohen JR, Kuchta N, Geller N, Shires GT, Dineen P. Pancreaticoduodenectomy: a 40-year experience. Ann Surg 1982;195: 608–17.
5. Lerut JP, Gianello PR, Otte JB, Kestens PJ. Pancreaticoduodenal resection: surgical experience and evaluation of risk factors in 103 patients. Ann Surg 1984;199:432–7.
6. Jones BA, Langer B, Taylor BR, Girotti M. Periampullary tumors: which ones should be resected? Am J Surg 1985;149:46–52.
7. Tarazi RY, Hermann RE, Vogt DP, Hoerr SO, Esselstyn CB Jr, Cooperman Am, et al. Results of surgical treatment of periampullary tumors: a 35-year experience. Surgery 1986;100:716–22.
8. Crist DW, Sitzmann JV, Cameron JL. Improved hospital morbidity, mortality, and survival after the Whipple procedure. Ann Surg 1987;206:358–65.
9. Michelassi F, Erroi F, Dawson PJ, Pietrabissa A, Noda S, Handcock M, et al. Experience with 647 consecutive tumors of the

duodenum, ampulla, head of the pancreas, and distal common bile duct. Ann Surg 1989;210:544–56.
10. Trede M, Schwall G, Saeger H-D. Survival after pancreaticoduodenectomy: 118 consecutive resections without an operative mortality. Ann Surg 1990;211:447–58.
11. Chan C, Herrera MF, de la Garza L, Quintanilla-Martinez L, Vargas-Vorackovo F, Richaud-Patin Y, et al. Clinical behavior and prognostic factors of periampullary adenocarcinoma. Ann Surg 1995;222:632–7.
12. Monson JR, Donohue JH, McEntee GP, Mcllrath DC, va Heerden JA, Shorter RG, et al. Radical resection for carcinoma of the ampulla of Vater. Arch Surg 1991;126:353–7.
13. Talamini MA, Moesinger RC, Pitt HA, Sohn TA, Hruban RH, Lillemoe KD, et al. Adenocarcinoma of the ampulla of Vater: a 28-year experience. Ann Surg 1997;225:50–60.
14. Howe JR, Klimstra DS, Moccia RD, Conlon KC, Brennan MF. Factors predictive of survival in ampullary carcinoma. Ann Surg 1998;228:87–94.
15. Nakao A, Harada A, Nonami T, Kishimoto W, Takeda S, Ito K, et al. Prognosis of cancer of the duodenal papilla of Vater in relation to clinicopathological tumor extension. Hepatogastroenterology 1994;41:73–8.
16. Shutze WP, Sack J, Aldrete JS. Long-term follow-up of 24 patients undergoing radical resection for ampullary carcinoma. Cancer 1990;66:1717–20.
17. Nakao A, Harada A, Nonami T, Kaneko T, Murakami H, Inoue S, et al. Lymph node metastases in carcinoma of the head of the pancreas region. Br J Surg 1995;82:399–402.
18. Kayahara M, Nakagawa T, Ohta T, Kitagawa H, Miyazaki I. Surgical strategy for carcinoma of the papilla of Vater on the basis of lymphatic spread and mode of recurrence. Surgery 1997;121: 611–7.
19. Japanese Society of Biliary Surgery. General rules for surgical and pathological studies on cancer of biliary tract. 5th ed. Tokyo: Kanehara; 2003.
20. Kimura W, Futakawa N, Yamagata S, Wada Y, Kuroda A, Muto T, et al. Different clinicopatholgic findings in two histologic types of carcinoma of papilla of Vater. Jpn J Cancer Res 1994;2:161–6.
21. Delcore R Jr, Conner CS, Thomas JH, Friesen SR, Hermreck AS. Significance of tumor spread in adenocarcinoma of the ampulla of Vater. Am J Surg 1989;158:593–7.
22. Matory YL, Gaynor J, Brennan M. Carcinoma of the ampulla of Vater. Surg Gynecol Obstet 1993;177:366–77.
23. Kimura W, Ohtubo K. Incidence, sites of origin, and immunohistochemical and histochemical characteristics of atypical epithelium and minute carcinoma of the papilla of Vater. Cancer 1988;7:1394–402.
24. Yamaguchi K, Enjoji M. Carcinoma of the ampulla of Vater: a clinicopathologic study and pathologic staging of 109 cases of carcinoma and 5 cases of adenoma. Cancer 1987;59:509–15.
25. Futakawa N, Kimura W, Wada Y, Muto T. Clinicopatholgical characteristics and surgical procedures for carcinoma of the papilla of Vater. Hepatogastroenterology 1996;43:260–7.
26. Ohta T, Kitagawa H, Kayahara M, Kinami S, Ninomiya I, Fujimura T, et al. Sentinel lymph node navigation surgery for pancreatic head cancers. Oncol Rep 2003;10:315–9.
27. Hirai I, Murakami G, Kimura W, Nara T, Dodo Y. Long descending lymphatic pathway from the pancreaticoduodenal region to the para-aortic nodes: its laterality and topographical relationship with the celiac plexus. Okajimas Folia Anat Jpn 2001;77:189–200.
28. Nakao A, Ichihara T, Nonami T, Harada A, Koshikawa T, Nakashima N, et al. Clinicohistopathologic and immunohistochemical studies of intrapancreatic development of carcinoma of the head of the pancreas. Ann Surg 1989;209:181–7.
29. Prenzel KL, Monig SP, Sinning JM, Baldus SE, Gutschow CA, Grass G, et al. Role of skip metastasis to mediastinal lymph nodes in non-small cell lung cancer. J Surg Oncol 2003;82:256–60.
30. Sasaki R, Takahashi M, Funato O, Nitta H, Murakami M, Kawamura H, et al. Prognostic significance of lymph node involvement in middle and distal bile duct cancer. Surgery 2001; 129:677–83.
31. Kimura W, Futakawa N, Zhao B. Neoplastic diseases of the papilla of Vater (review). J Hepatobiliary Pancreat Surg 2004;11: 223–31.
32. Fischer HP, Zhou H. Pathogenesis of carcinoma of the papilla of Vater (review). J Hepatobiliary Pancreat Surg 2004;11:301–9.