Gross Appearance of the Ampullary Tumor Predicts Lymph Node Metastasis and Outcome

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Key Words

Ampullary tumor • Carcinoma of the papilla of Vater, prognosis • Gross tumor appearance • Lymph node involvement • Pancreaticoduodenectomy • Papilla of Vater

Abstract

Background/Aims: Patterns of lymph node involvement in carcinoma of the papilla of Vater (CPV) have not been studied in detail to date, and factors associated with lymphatic metastases and surgical outcome of this disease remain to be determined. **Methods:** Lymph node involvement and surgical outcome of 51 CPV patients were evaluated by extended lymphadenectomy specimens. **Results:** Lymph nodes with high metastatic potential were posterosuperior pancreaticoduodenal nodes (group 13a, 18%), posterior-inferior pancreaticoduodenal nodes (group 13b, 22%), and nodes around the superior mesenteric artery (group 14, 18%). Gross appearance of the primary tumor and depth of tumor invasion correlated with lymph node involvement ($p < 0.05$, respectively). A correlation with positivity was also found in groups 13 and 14. Disease-specific survival correlated with the gross appearance of the primary tumor and nodal involvement. However, there was no relationship between survival and the level of nodal involvement. Multivariate analysis indicated that the gross appearance of the tumor was the only significant independent predictor of a poor outcome. **Conclusions:** Gross appearance of the tumor is the most important prognosticator of lymph node metastases in

CPV. Nodal dissection around the superior mesenteric artery may improve survival except in patients without invasion of the sphincter of Oddi. Pylorus-preserving pancreaticoduodenectomy is the treatment of choice.

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Introduction

Lymph node involvement is one of the most important prognostic factors in gastrointestinal carcinoma. To improve the prognosis of patients with pancreatobiliary carcinoma, systematic lymphadenectomy has been advocated [1–4], and anatomic and clinical studies detailing the pattern of lymphatic flow from the periampullary tumor to the para-aortic lymph nodes have been reported [1, 5].

Recently, the clinical significance of micrometastases to lymph nodes has been described in patients with carcinoma of the papilla of Vater (CPV) [6]. To establish which treatment strategies are effective for CPV, we conducted a retrospective study to determine the optimal surgical approach based on pre- and perioperative findings. An extended operation is not always necessary for early-stage cancer. Since the gross appearance of CPV is easily established preoperatively, we sought to investigate the relationship between gross appearance of the tumor and nodal involvement. The implications of our findings for the surgical treatment of CPV are also discussed.

Fig. 1. Lymph node metastases (groups 13a, 13b, 14a, 14b, and 14d) in patients with CPV. Each solid circle indicates an individual with lymph node metastasis. Metastases in the same patient are linked by a solid line. Asterisk indicates an isolated metastasis.

Patients and Methods

Fifty-one patients with CPV underwent curative resection between 1975 and 2004 at Kanazawa University Hospital. Far-advanced cases were excluded. Thirty-one men and 20 women, with a mean age of 61 years (range, 42–80 years), were enrolled. Pylo-rus-preserving pancreaticoduodenectomy (PD) and conventional PD were performed in 21 and 30 patients, respectively. A systematic lymphadenectomy including the nodes around the superior mesenteric artery was performed in all patients. Radical lymphadenectomy including the para-aortic lymph nodes was performed in 18 patients.

A histopathological analysis was performed in all cases to evaluate the extent of lymph node involvement. Pathological diagnoses were determined in accordance with the second English edition of the *Classification of Biliary Tract Carcinoma* proposed by the Japanese Society of Biliary Surgery [7]. CPV gross appearance was categorized into three groups as follows: (1) protruding, (2) mixed, and (3) ulcerative [2, 7].

Based on this classification, a numeric classification of the major lymph nodes was defined as follows: group 8, nodes along the common hepatic artery; group 9, nodes around the celiac artery; group 10, nodes at the splenic hilum; group 11, nodes along the splenic artery; group 12, nodes in the hepatoduodenal ligament; group 13, posterior pancreaticoduodenal nodes; group 14, nodes around the superior mesenteric artery; group 15, nodes along the middle colic artery; group 16, para-aortic nodes, and group 17, anterior pancreaticoduodenal nodes. For groups 13 and 17, two subgroups were defined: a, those cranial to the papilla of Vater, and b, those caudal to the papilla. For group 14, four subgroups were defined: 14a, nodes at the origin of the superior mesenteric artery; 14b, nodes at the origin of the inferior pancreaticoduodenal artery; 14c, nodes at the origin of the middle colic artery, and 14d, nodes at the origin of the jejunal arteries [1, 2, 7].

Nodal involvement in CPV was classified into four levels, as proposed by the Japanese Society of Biliary Surgery [7]: pN0, no evidence of regional lymph node involvement; pN1, nodal involvement in a primary lymph node group close to the tumor (group 13); pN2, lymph node metastasis in the secondary lymph node groups (group 12, 14, and 17), and pN3, lymph node metastasis in the third group (all nodes other than pN1 and pN2). In addition, depth of

tumor invasion was divided into three degrees in this study: m, invasion limited to the mucosa; od, invasion limited to the sphincter of Oddi, and od<, invasion beyond the sphincter of Oddi [7].

Statistical analyses included the χ^2 test with Fisher's exact test when appropriate. Patient survival was calculated by the Kaplan-Meier method [8], and the significance of differences between survival rates was determined using the generalized Wilcoxon method. $p < 0.05$ was considered to indicate statistical significance. Only variables that were statistically significant by univariate analysis were included in the multivariate analysis, which was performed using the Cox proportional hazard model [9]. Neither chemotherapy nor radiation therapy was offered to patients until tumor recurrence was obvious.

Results

Frequency of Lymph Node Involvement

The overall incidence of lymph node metastases was 45% (23 of 51 patients). Groups 9 and 12 had no metastases. In groups 8, 13a, 13b, 17a, and 17b, rates of metastases were 2, 18, 22, 2, and 2%, respectively. One or more lymph nodes from group 14 were involved in 9 (18%) of the 51 patients, and subgroups 14a, 14b, 14c, and 14d had rates of 4, 12, 0, and 6%, respectively. There were no metastases in the perigastric or para-aortic lymph nodes.

Gross Appearance of the Primary Tumor and Lymph Node Involvement

Eight of the 28 patients with a protruding type and 8 of the 16 patients with a mixed type had nodal involvement. However, all 7 patients with an ulcerative lesion had nodal involvement. Four of the 7 patients with an ulcerative lesion and 2 (7%) patients with a protruding lesion had metastasized to group 14 lymph nodes. There was a strongly significant relationship between gross appearance of the primary tumor and nodal involvement ($p < 0.01$).

Depth of Tumor Invasion and Lymph Node Involvement

None of the 7 patients with m disease had nodal involvement. Four (36%) of the 11 patients with od disease had lymph node involvement. On the other hand, 19 (58%) of the 33 patients with od< disease had lymph node involvement. There was a significant relationship between depth of tumor invasion and nodal involvement ($p < 0.05$).

Relationship among Lymph Nodes

Figure 1 demonstrates the relationships among the peripancreatic lymph node groups. No patient had metastasis to group 12 or 14c. All patients except for 2 patients (shown by asterisks) with group 14 lymph node me-

Table 1. Results of univariate and multivariate analyses

Risk factor	Patients n	Survival, %		p value	
		5 years	10 years	univariate	multivariate
Gross appearance					
Protruding	28	79	73	0.0018	0.0039
Mixed	16	67	67		
Ulcerative	7	14	14		
Depth of tumor invasion					
m	7	100	100	0.049	–
od	11	80	64		
od<	33	55	55		
Nodal involvement					
pN ₀	28	83	78	0.0059	–
pN ₁	14	46	46		
pN ₂	9	41	41		

tastasis also had group 13a or 13b lymph node metastasis. The gross appearance of the tumor in patients who had only group 14b lymph node metastasis was the nonexposed protruding type. The other patient without group 13 lymph node metastasis had group 14d lymph node involvement. The gross appearance of this tumor was the mixed type. The gross appearance of tumors in 2 patients with group 14a lymph node metastases was the mixed or ulcerative type.

Univariate and Multivariate Analyses of Survival

The 5-year survival rate for patients with the protruding type was 79% and that for patients with the mixed type was 67%. The prognosis of patients with the ulcerative type was dismal (14%). Differences between groups were significant ($p < 0.01$). The 5-year survival rates for 28 patients without and 23 patients with nodal involvement were 83 and 52%, respectively. Patients without nodal involvement had significantly longer survival than those with nodal involvement ($p < 0.01$). All patients with m disease lived >5 years. The 5-year survival rate for 23 patients with od< disease was 56%. There was a significant difference in survival according to the depth of tumor invasion ($p < 0.05$).

The depth of tumor invasion, lymph node involvement, and gross appearance of the tumor were important prognostic factors. Using the Cox proportional hazard model, a multivariate analysis of factors influencing survival in CPV patients was performed. The gross appearance of the tumor was the only independent predictor of a poor outcome ($p = 0.0039$; table 1).

Discussion

Lymphatic metastases, hematogenous spread, peritoneal dissemination, and local invasion are the routes of metastases, with lymph node involvement being the most important metastatic routes in CPV [1–4, 10–13]. A number of clinicopathologic factors which correlate with survival after resection of ampullary cancer have been identified: lymph node metastasis [2, 10, 14–16], depth of tumor invasion [10], histologic grade [14, 16], resection margin [12], perineural invasion [17], lymphovascular invasion [14], and intraoperative transfusion [14, 16]. Our study confirms that nodal involvement is a poor prognostic factor. In far-advanced cases, there is no benefit of surgical resection to pancreatobiliary carcinomas. Therefore, we limited our clinicopathologic analysis to patients who underwent a macroscopic curative resection. Lymph node involvement in resected specimens has been reported to range from 38 to 55% in patients with CPV [1–4, 6, 12–19], depending on the thoroughness of the examination. In their multivariate analysis, Monson et al. [4] reported that survival was negatively affected even by microscopic lymphatic invasion. Mizuno et al. [6] found that immunohistochemically detectable metastases had greater prognostic significance than lymph node metastases detected by light microscopy with hematoxylin and eosin staining. However, it seems unlikely that the true status of lymphatic infiltration can be determined preoperatively.

Currently, the major preoperative staging methods include computed tomography (CT), magnetic resonance imaging, angiography, and endoscopic ultrasonography (EUS). Chen et al. [20] reported that EUS was superior to routine ultrasonography (US) and CT in detecting lymph node metastasis (EUS, 47%; US, 7%, and CT, 33%). Shoup et al. [21] reported that neither modality is sensitive for detecting lymph node metastases (21 and 42% for EUS and CT, respectively), though their specificities are similar (80 and 73%). Preoperative imaging modalities are limited in their ability to diagnose regional lymph node metastasis. Generally speaking, it is difficult to obtain an accurate assessment of lymph node status even intraoperatively, and the full answer is obtained only after careful pathologic examination of the resected specimen. Therefore, in the absence of conclusive data, the relationship between clinicopathologic factors and nodal status provides some surgical guidelines.

The overall frequency of nodal involvement in our study was 45% (23 of 51 patients), with involvement of specific nodal groups 13a, 13b, and 14 in 18, 22, and 18%,

respectively. However, the precise manner of nodal involvement and relationships among different lymph node groups have received little attention. The lymphatics of the ampulla and duodenum have been reported by Rouviere [22] to drain into the posterior pancreaticoduodenal lymph node. Shirai et al. [3] also reported that 12 (31%) of 39 patients had lymph node metastases in the inferior pancreaticoduodenal artery nodal group (14b), and group 14a lymph node (trunk of the superior mesenteric artery) involvement was identified in 3 of their patients, in agreement with our current study (2 of 51 patients). Our study also showed that the group 14b lymph node had the highest metastatic rate among the group 14 subgroups. A correlation existed between positivity in groups 13 and 14 (fig. 1). Based on the study by Kitagawa et al. [23], lymph node metastases were limited to areas along the superior mesenteric artery via peripancreatic lymph nodes in patients with pancreatic head tumor confined to the ventral pancreas domain. Lymphatic flow from group 13 lymph nodes to group 14b or 14d lymph nodes is located on the right or posterior side of the superior mesenteric artery [2, 5].

The relationships between nodal involvement and other clinicopathologic factors were evaluated. de Castro et al. [17] reported that PD is recommended even for pT1 stage carcinomas because 28% of patients with pT1 stage disease have lymph node metastases. Their report concluded that in experienced hands, PD is an adequate treatment for fit patients with adenocarcinoma and for patients who are found to have invasive adenocarcinoma during or after local resection. Yoon et al. [24] reported that PD constituted adequate radical resection, even in CPV. Terasawa et al. [10] also reported that 20% of pT1 stage tumors had lymph node metastases. Balachandran et al. [14] reported that the tumor category did not influence survival, but our study demonstrated that the depth of tumor invasion affected survival. CPV with invasion of the pancreatic parenchyma is often associated with extensive nodal involvement [3].

The gross appearance of CPV is easily observed preoperatively, but the relationship between macroscopic structure and other clinicopathologic factors has not been examined precisely. The most interesting finding in our study was that the gross appearance of the tumor had the greatest prognostic significance and the strongest correlation with nodal involvement. Terasawa et al. [10] reported that the absence of ulcer formation was a good prognostic factor in pT1 CPV. Nakao et al. [25] reported that ulcer formation was a poor prognostic factor.

Although the role of extended lymphadenectomy for CPV is still a matter of debate, some authors have proposed that extended lymphadenectomy can improve the prognosis for patients with this tumor [1, 2, 15]. Klempnauer et al. [18] also reported that, in principle, systematic and radical lymphadenectomy should be performed in all patients with ampullary or pancreatic cancer. Terasawa et al. [10] stated that pylorus-preserving PD is the operation of choice for CPV, even for patients with pT1 stage tumors. Nowadays, PD can be safely done with very low mortality rates and good long-term survival [25]. In addition, the biologic behavior of CPV seems to differ from that of pancreatic cancer [1, 15]. Our data showed that the 5-year survival rates for patients with pN1 and pN2 disease were 46 and 41%, respectively. We believe that a pylorus-preserving PD including total lymph node removal around the superior mesenteric artery may improve the prognosis of patients with CPV, except in those patients with far advanced disease, i.e. patients with para-aortic lymph node involvement. However, in some patients with protruding-type or pT1 disease, group 14a lymph node dissection can be omitted.

In conclusion, we believe that nodal dissection around the superior mesenteric artery may improve outcome in CPV patients. Preoperative gross appearance of the tumor predicts a poor outcome. In some patients with protruding type or m disease, group 14a lymph node dissection can be omitted. All patients with the ulcerative type should be treated with adjuvant chemotherapy. Routine postoperative adjuvant chemotherapy may be appropriate given the high incidence of lymphatic metastases.

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