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Carcinomas of the ventral and dorsal pancreas exhibit different patterns of lymphatic spread

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1. ABSTRACT

In patients with carcinoma of the head of the pancreas with positive lymph nodes, the extent of an adequate lymph node dissection beyond peripancreatic area has remained controversial. Based on the two anlagens, the ventral or dorsal pancreas, we assessed the lymphatic spread pattern in 58 primary adenocarcinoma of head of the pancreas. Detection of lymph node mestastasis was based on microscopic detection of carcinoma in consecutive serial sections of resected specimens including lymph nodes. When the tumor was confined to the ventral pancreas domain (n=20), the lymph node metastases were limited to areas along the superior mesenteric artery (SMA) besides peripancreatic lymph nodes. When the tumor was in the dorsal pancreas domain (n=6), the lymph node metastases were limited to areas along the common hepatic artery (CHA) and the hepatoduodenal ligament besides peripancreatic lymph nodes. When the tumor was extended into both domains (n=32), the lymph node metastases were distributed widely in areas along the SMA, CHA and the hepatoduodenal ligament besides peripancreatic lymph nodes. Based on these findings, the lymphatic spread of carcinomas of the head of the pancreas can be divided into two patterns by tumor location based on the two anlagens of the pancreas.

2. INTRODUCTION

Over the past several years, radical resection has evolved to be most commonly defined as a wide *en bloc* pancreaticoduodenal resection, incorporating a wide soft tissue resection margin including extrapancreatic nerve plexuses, combined with the harvest of specific lymph node stations and a retroperitoneal lymphadenectomy (1-4). The rationale for more extensive surgery was based on the observation that a standard operation fails to remove nodal groups that even in patients with small neoplasms often are involved with microscopic disease. However, dismal complications affecting the quality of life, particularly disturbances in digestive absorption such as diarrhea, are a significant morbidity associated with this type of surgery (3, 5). Furthermore, many of those patients who die after a potentially curative resection die from local recurrences (6). Four prospective randomized trials have compared a standard pancreatoduodenectomy versus one with an extended lymphadenectomy for patients with potentially curative pancreatic head adenocarcinoma (5, 7-9). All were unable to detect an improvement in survival with the more radical operation. Therefore many surgeons have asked how one should treat patients with positive lymph nodes and peripancreatic soft tissue invasion. There currently is no consensus on what constitutes an adequate lymph node

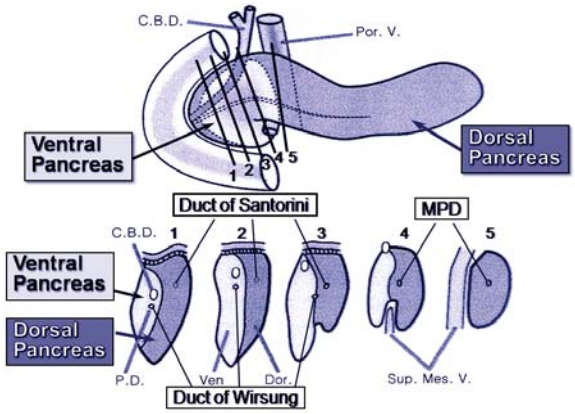

Figure 1. The distribution of the ventral and dorsal anlagen after fusion. (Suda's original (11)).

dissection and peripancreatic soft-tissue resection, nor how extensive a lymph node dissection should be to ensure that there is adequate stage assignment.

The pancreas arises from two anlagen on an embryological basis. Both anlagen fuse at about the 6-7th fetal week (10). The smaller ventral bud forms the caudal part of the pancreatic head and uncinate process, whereas the cephalic part of the pancreatic head as well as the body and tail are derived from the larger dorsal bud. The distribution of the ventral pancreas after fusion is the dorsal portion of the head containing the area surrounding the intrapancreatic common bile duct and the uncinate process.

We carefully investigated the correlation between the pattern of cancer spread and the tumor location in the pancreas head microscopically by consecutive serial sections of resected specimens. These results were compared with multi detector computed tomography (MD-CT) images. We noticed a spread pattern that could be attributed to the tumor location and we speculated that this phenomenon is correlated with the embryological structure of pancreas. In this study, we analyzed the nodal positivity of Group 2 lymph nodes as correlated with tumor location based on the two anlagen.

3. MATERIALS AND METHODS

3.1. Patients

Fifty-eight patients underwent a pancreatoduodenectomy as a treatment for invasive ductal carcinoma of the pancreas head between 1997 and 2005 at the Department of Gastroenterologic Surgery, Kanazawa University, Japan. Patients underwent a D2 resection, and the anterior and posterior pancreaticoduodenal nodes (No.17, No.13), the nodes in the hepatoduodenal ligament (No.12), the nodes along the common hepatic artery (CHA) (No.8), the nodes along the superior mesenteric artery (SMA) (No.14) and the infrapyloric lymph nodes (No.6) were harvested *en bloc*. The portal vein (PV) and/or the superior mesenteric vein (SMV) were resected in 45 of 58 patients undergoing pancreatoduodenectomy. All study subjects underwent the resection with curative intent.

3.2. Histology and immunohistochemical staining

The resected specimens with the attached peripancreatic lymph nodes and nerve plexuses were immediately fixed in 10% neutral-buffered formaldehyde solution for at least 10 days. After the specimens were cut perpendicular to the body axis (similar to the slices in a CT scan) in 5-mm tissue blocks, the blocks were embedded in paraffin and 5-μm sections were stained with hematoxylin and eosin (H/E). Immunohistochemical staining with an anti-pancreatic polypeptide (PP) was performed using the EnVision+ system (Dako Cytomation, Glostrup, Denmark). The sections were deparaffinized and treated with 0.3% hydrogen peroxidase for 10 minutes to inactivate endogenous peroxidase. They were then washed in phosphate-buffered saline for 15 minutes. The sections were incubated with a rabbit antibody against human PP (diluted 1:600; Dako Cytomation) for 60 minutes at room temperature. After washing, the sections were incubated with EnVision labeled polymer (Dako) for 60 minutes. Finally, the reaction products were developed in a 0.02% 3, 3' -diaminobenzidine tetrahydrochloride solution (Dako). The sections were counterstained with hematoxylin.

3.3. Statistical Analysis

Statistical analysis was performed with the chi-square or Fisher exact tests for independence.

4. RESULTS

4.1. Tumor location and size

Differentiation of the ventral and dorsal pancreas was determined as described by Suda *et al.* (Figure 1) (11-13). The duct of Wirsung, intrapancreatic common bile duct, the duct of Santorini, and PV/SMV are available to distinguish both; therefore, the area around the duct of Wirsung and the intrapancreatic common bile duct is commonly derived from the ventral anlagen, while the area around the duct of Santorini is derived from the dorsal anlagen. Moreover, the PV lies behind the dorsal pancreas and the SMV lies forward of the ventral pancreas; therefore, the ventral bud rotates backward behind the duodenum, and eventually its tip lies behind the SMV. Sections perpendicular to the body axis (similar to a CT scan) were stained immunohistochemically with anti-PP. Stained cells were mainly detected in the ventral pancreas (Figure 2A). On the CT scan images, we distinguished the ventral and dorsal pancreas using the duct of Santorini, the duct of Wirsung, the PV/SMV, and the bile duct as landmarks. The head of the pancreas could be divided into the dorsal and ventral pancreas by a line linking the PV / SMV and the anterior edge of the intrapancreatic bile duct (Figure 2B). This corresponded to the differentiation between ventral and dorsal pancreas by immunostaining with PP. The location of the tumor based on the organogenesis of the pancreas was analyzed microscopically by consecutive serial sections of the resected specimens and compared with the MD-CT images with the aid of a pathologist and radiologist. These cases were divided three groups as follows, confined to the ventral pancreas (V), confined to the dorsal pancreas (D), extension into both areas (VD). The maximum diameter of the tumor was measured on histological examination. Local

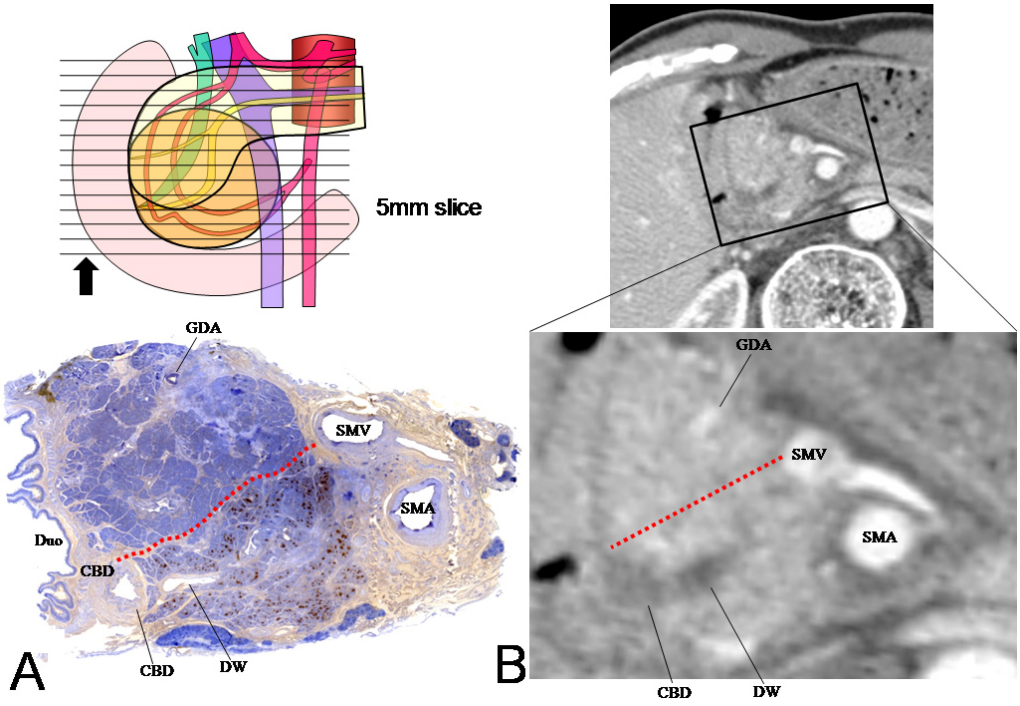

Figure 2. Distinction of the ventral and dorsal pancreas in the head of pancreas. A: Immunohistochemical staining for pancreatic polypeptide in the pancreas head. B: CT images of same slice. After the specimens were cut perpendicular to the body axis similar to a CT scan into 5-mm tissue blocks, the sections were stained immunohistochemically with an anti-pancreatic polypeptide. Positive staining cells were mainly detected in the ventral pancreas (A). The duct of Wirsung, the intrapancreatic common bile duct, the duct of Santorini, and the superior mesenteric vein are available landmarks to distinguish the ventral from dorsal pancreas. On the CT scan image, the head of the pancreas could be divided into the dorsal and the ventral pancreas by a red dotted line linking the PV / SMV and the anterior edge of the intrapancreatic bile duct (B). This corresponds to the ventral and dorsal pancreas identified by immunostaining with pancreatic polypeptide. GDA: gastroduodenal artery, Duo: duodenum, CBD: common bile duct, SMV: superior mesenteric vein, SMA: superior mesenteric artery, DW: duct of Wirsung.

extension was categorized as follows: S: serosal invasion, RP: retropancreatic tissue invasion, PVS: portal venous system (SMV, PV, and splenic vein) invasion, A: arterial system (celiac artery, CHA, SMA, and splenic artery) invasion, DU: duodenal invasion, CH: distal bile duct invasion, PL: extrapancreatic nerve plexus invasion. Nomenclature for nodal station and extrapancreatic neural plexuses was based on the Japan Pancreas Society: Classification of Pancreatic Carcinoma (second English Edition) (14). Group 1 lymph nodes consist of those usually removed during a resection of the head of the pancreas and include the lymph nodes on the posterior (No.13) and anterior (No.17) aspect of the head of the pancreas. Group 2 and 3 were classified on the basis of lymph flow, rate of involvement by metastasis, and outcome. Group 2 lymph nodes include the infrapyloric lymph nodes (No.6), the lymph nodes along the CHA (No.8), the lymph nodes in the hepatoduodenal ligament (No.12), and lymph nodes along the SMA (No.14). Group 3 lymph nodes include the lymph nodes around the stomach except the infrapyloric lymph nodes, the lymph nodes along the left gastric artery, the lymph nodes along the celiac artery, the lymph nodes at the splenic hilum, the lymph nodes along the splenic artery, the lymph nodes along the middle colic artery, and the lymph nodes around the abdominal aorta.

A typical case of pancreatic carcinoma confined to the ventral pancreas is shown in Figures 3 and 4. Figure 3 shows the MD-CT images, a weakly enhancing tumor (white arrows) is detected behind the SMV, and in front of this tumor, the duct of Santorini is intact and not apparently invaded by tumor. H/E staining and immunohistochemistry for PP of the resected specimen of this patient shows cancer localized to the uncinate process of the ventral pancreas with extrapancreatic nerve plexus invasion (Figure 4). A typical case of pancreatic carcinoma confined to the dorsal pancreas is shown in Figures 5 and 6. Figure 5 shows the MD-CT images, a weakly enhanced tumor (white arrows) extending to the front with occlusion of the main pancreatic duct and pressing upon the SMV and intrapancreatic bile duct posteriorly. The duct of Wirsung is intact and not involved with tumor. H/E staining and immunohistochemistry for PP of the resected specimen shows cancer localized to the dorsal pancreas with serosal invasion (Figure 6). The SMV is pushed posteriorly.

The location of the tumor based upon embryonic origin and the averages of the tumor diameter in the patients in this study with pancreatic head carcinoma are shown in Table 1. Of the 58 cases of pancreas head carcinoma, the tumor was localized to the ventral pancreas (V) in 21 cases (36%), localized to the dorsal pancreas (D)

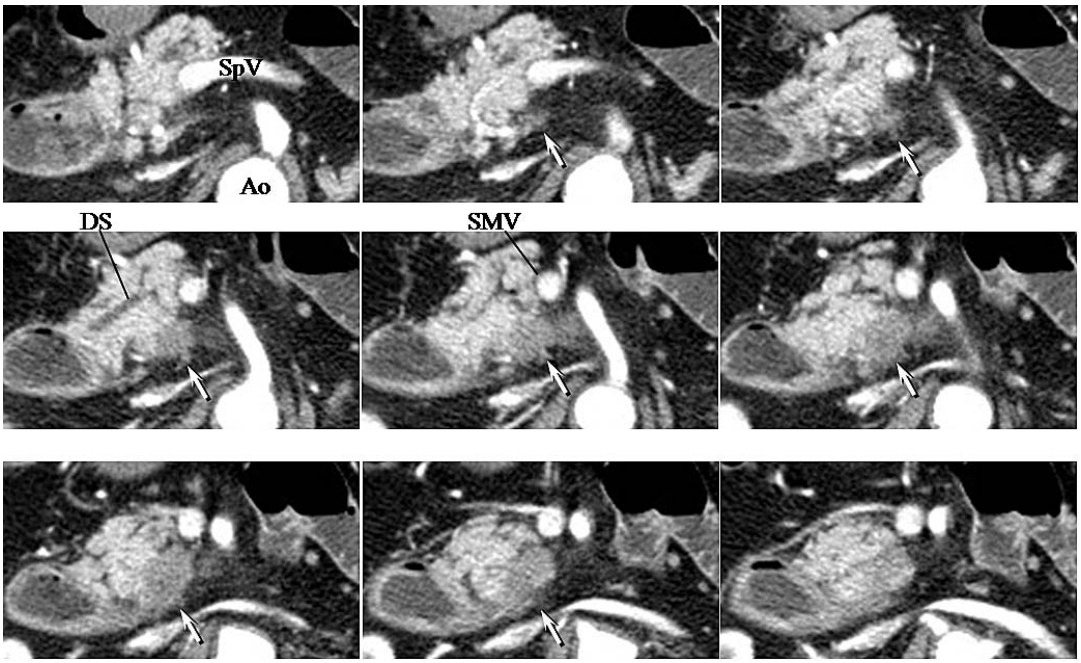

Figure 3. A case of pancreatic head carcinoma confined to the ventral pancreas. MD-CT images show a weakly enhancing tumor (white arrows) behind the SMV. In front of this tumor the duct of Santorini is intact and not invaded by tumor.

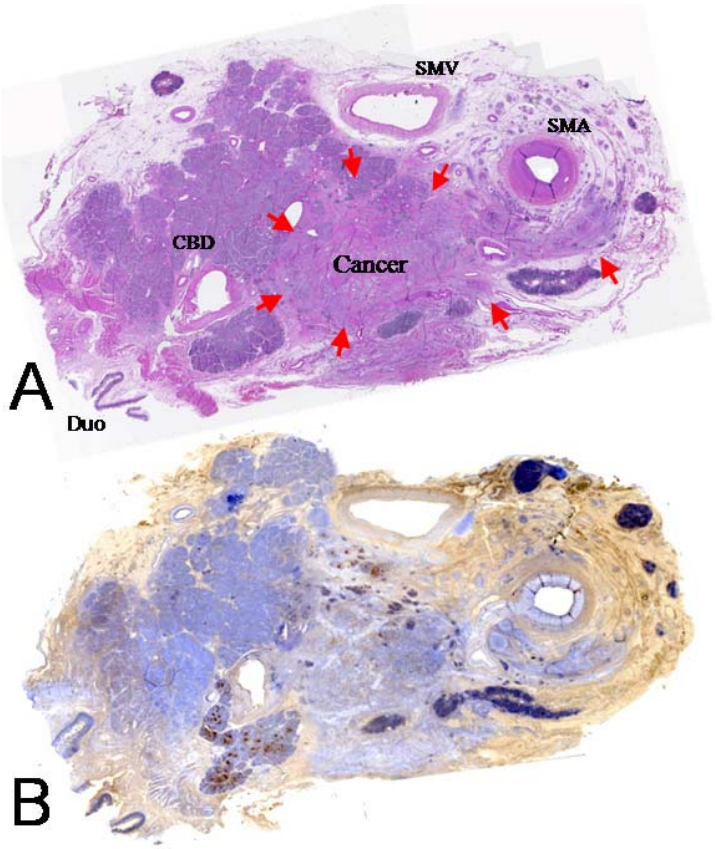

Figure 4. H/E staining and immunohistochemistry for pancreatic polypeptide of the resected specimen shows cancer limited to the uncinate process of the ventral pancreas with extrapancreatic nerve plexus invasion (red arrows).

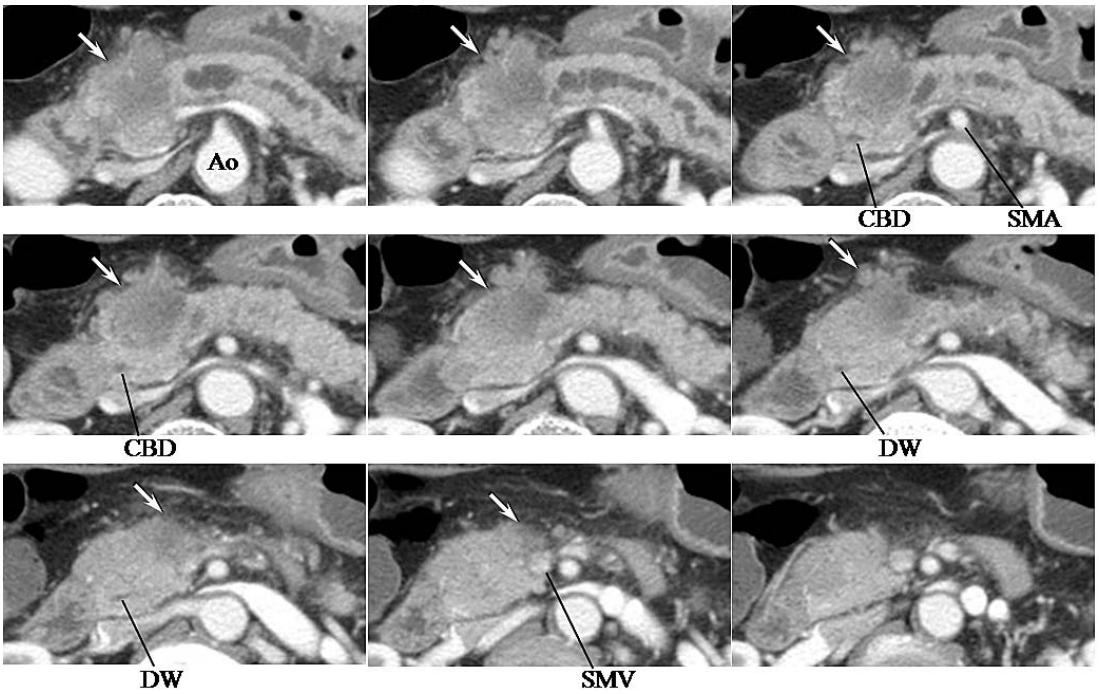

Figure 5. A case of pancreatic head carcinoma confined to the dorsal pancreas. MD-CT images show a weakly enhancing tumor (white arrows) extend to front side with occlusion of the main pancreatic duct, and press SMV and intrapancreatic bile duct to retroside. The duct of Wirsung is intact and not invaded by tumor.

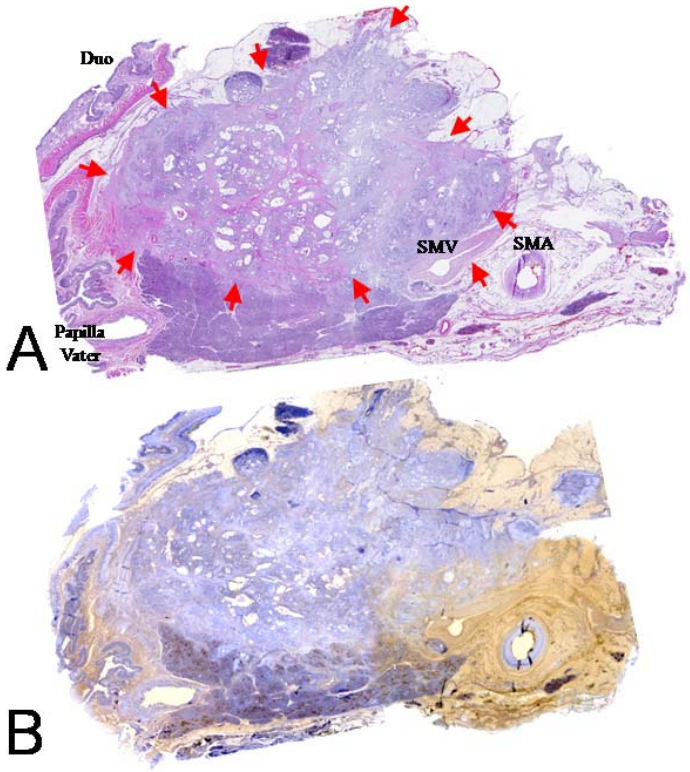

Figure 6. H/E staining and immunohistochemistry for pancreatic polypeptide of the resected specimen shows cancer limited to the dorsal pancreas with serosal invasion (red arrows). The SMV is pushed posteriorly.

Table 1. Tumor location based upon embryology and the average of the tumor diameter in patients with pancreatic head carcinoma

Location	No. (%)	Size of Tumor (mm) (mean ± SD)
Ventral (V)	21 (36%)	32 ± 13
Dorsal (D)	6 (10%)	35 ± 8
Both areas (VD)	31 (54%)	41 ± 11

Table 2. Local extension by pathological examination and tumor location based upon embryology

	Local extension by pathologic examination [No. (%)]						
Location(No.)	S	RP	PVS	A	DU	CH	PL
V (21)	6 (29%)	20 (95%)	13 (62%)	5 (24%)	9 (43%)	14 (67%)	17(81%)
D (6)	4 (67%)	2 (33%)	2 (33%)	2 (33%)	5 (83%)	5 (83%)	3(50%)
VD (31)	20 (65%)	28 (90%)	27 (87%)	12 (39%)	22 (71%)	14 (45%)	26 (84%)
Total (58)	30 (52%)	50 (86%)	42 (72%)	19 (33%)	36 (62%)	43 (74%)	46 (79%)

S: serosal invasion, RP: retropancreatic tissue invasion, PVS: portal venous system invasion, A: arterial system invasion, DU: duodenal invasion, CH: distal bile duct invasion, PL: extra pancreatic nerve plexus invasion.

Table 3. The relationship between lymph node metastases and tumor location based upon embryology

	Lymph nodes metastases [No (%)]			
Location (No.)	N0	N1	N2	N3
V (21)	5(24%)	3(14%)	12(57%)	1(5%)
D (6)	1(17%)	2(33%)	3(50%)	0(0%)
VD (31)	4(13%)	3(10%)	14(45%)	10(32%)
Total (58)	10(17%)	8(14%)	29(50%)	11(19%)

Table 4. The relationship between the stations of the Group 2 lymph node metastases and tumor location based upon embryology

	Group 2 lymph nodes metastases [No. (%)]			
Location (No.)	No.6	No.8	No.12	No.14
V (21)	0(0%)	0(0%) *	0(0%) **	11(52%) ***
D (6)	0(0%)	2(33%)	2(33%)	0(0%)
VD (31)	1(3%)	6(19%)	7(23%)	25(81%)
Total (58)	1(2%)	8(14%)	9(16%)	36(62%)

*: p = 0.043 vs. the corresponding values in D group, **: p = 0.043 vs. the corresponding values in D group, ***: p = 0.027 vs. the corresponding values in D group, No.6: infrapyloric lymph nodes, No.8: lymph nodes along the common hepatic artery, No.12: lymph nodes in the hepatoduodenal ligament, No.14: lymph nodes along the superior mesenteric vessels.

in 6 cases (10%), and extended to both areas (VD) in 31 cases (54%). The diameter of tumor were 32 ± 13, 35 ± 8, and 41 ± 11 mm, respectively, in the V group, D group, and VD group.

4.2. Local extension

The local extension of the tumor based upon the pathologic examination and tumor location are summarized in Table 2. Invasion into retropancreatic tissue (RP), the portal venous system (PVS), the arterial system (A), and the extrapancreatic nerve plexus (PL) were detected in 50 (86%), 42 (72%), 19 (33%), and 46 (79%) cases, respectively.

4.3. Nodal metastasis

The median number of resected nodes was 63 (range, 15-135). The relationship between the tumor location and the degree of lymph node involvement is summarized in Table 3. Nodal metastases were found in 48 cases (83%). There were 8 (14%) N1 (metastasis limited to Group 1 lymph nodes) cases, 29 (50%) N2 (metastasis limited to Group 2 lymph nodes) cases, and 11 (19%) N3 (metastasis to Group 3 lymph nodes) cases. The relationship between the tumor location and the stations of the Group 2 lymph node metastases are shown in Table 4. No. 8 and No. 12 lymph nodes metastases were detected in D group tumors, but not in V group tumors (p = 0.043, p = 0.043). On the other hand, No.14 lymph node metastases were detected in V group tumors, but not in D group tumors (p = 0.027). There is a statistically close relationship between the tumor location and No. 8, No. 12, and No.14 lymph nodes metastases. In the VD group, there were extensive lymph node metastases in the Group 2 nodes.

5. DISCUSSION

The pancreas arises embryologically from two distinct anlagen. Both anlagen fuse at about the 6-7th fetal week. After fusion, it appears and functions as one mature organ. In the adult pancreas, the body and tail are derived from the dorsal pancreas, and the embryological origin of the head is complex. However, previous studies advocated that it is possible to discriminate between the ventral pancreas domain and the dorsal pancreas domain, because the shape of the islet, the percentage of fat, and the distribution of PP producing cells are different from each other (11-13, 15). Generally, the superior anterior portions around the duct of Santorini are derived from the dorsal pancreas, and the inferior dorsal portions around the duct of Wirsung, including the uncinate process, are derived from the ventral pancreas. The PV ends up between the ventral pancreas and dorsal pancreas by their rotation and fusion. The circumference of the lower bile duct is composed of

the ventral pancreas. Therefore, we distinguished the ventral pancreas from the dorsal pancreas using the duct of Santorini, the duct of Wirsung, the PV, and the bile duct as landmarks. It corresponds with the identification of the ventral and dorsal pancreas by immunostaining for PP in the adult pancreas. Moreover, the boundary of the ventral and dorsal pancreas nearly corresponds to the line linking the PV/SMV and the anterior edge of the intrapancreatic bile duct. Based on this result, we investigated the tumor location based upon this embryological consideration in 58 patients with pancreatic head cancer who were resected in our institute. In twenty-one cases (36%) tumors were localized to the ventral pancreas, in 6 cases (10%) tumors were localized to the dorsal pancreas, and in 31 cases (53%) the tumors extended into both areas. The frequency of tumors localized to only the dorsal pancreas was relatively low in our series. This may have been due to the relatively small volume of the dorsal pancreas in the pancreas head, leading to a low incidence of pancreas head cancer in this area. Moreover, the CHA and hepatoduodenal ligament are close to the dorsal pancreas and these are easily involved with tumor, so surgical treatment with curative intent would be difficult in many cases.

The lymphatic pathways in pancreas cancer have been studied by many investigators. According to Hagihara's radioisotope study (16), two routes of lymphatic drainage were observed: 1. a pathway from the pancreas head to the lymph nodes around the celiac axis, and 2. a pathway to the lymph nodes around the SMA. Nagai (17) reported that dye injected into the posterior region of the pancreas head drained toward the right or posterior side of the SMA and finally to the para-aortic lymph nodes. According to the study by Deki and Sato (18), three major pathways were identified on the anterior surface of the head of the pancreas: the upper pathway belonged to the common hepatic group, while the middle and lower routes were associated with the superior mesenteric nodal group. Our previous study (2) found that there were four patterns of combinations with statistically significant relationships: No.13 - No.14; No.14 - No.16; No.17 - No.8; No.13 - No.17, and that the lymphatic flow proceeds as follows: pancreas head → No.14 → No.16. Thus, some patterns of the lymphatic spread of pancreas head carcinoma have already been elucidated, but none have analyzed the relationship between tumor location and lymphatic spread that might permit optimal lymph node dissection.

In the Classification of Pancreatic Carcinoma (second English Edition) (14), the lymph nodes removed in a conventional resection are categorized as Group 1, and the other lymph nodes are categorized into Group 2 and 3 depending on lymph flow, lymph node metastasis rate, and outcome. Moreover this classification noted that Group 3 lymph node metastases should be treated as distant metastases. Therefore, the treatment of Group 2 lymph nodes may be very important clinically (19).

Four prospective randomized trials have compared standard pancreatoduodenectomy versus pancreatoduodenectomy plus extended lymphadenectomy for patients with potentially curative pancreatic head adenocarcinoma (5, 7-9). All were unable to detect an improvement in survival for the more radical operation. Consequently many surgeons are uncertain as to how to treat patients with positive lymph nodes and peripancreatic soft tissue invasion. This question relates to the adequacy of the lymph node dissection and peripancreatic soft tissue resection, and how many lymph nodes should now be resected to ensure that there is adequate stage assignment.

In this study, we analyzed the sites of Group 2 lymph node metastases of the pancreas head carcinoma as it correlated with the two pancreatic anlagen. We noticed that the lymphatic spread pattern could be attributed to tumor location and we speculated that this phenomenon is correlated with the embryological structure of pancreas. When the tumor is confined to the ventral pancreas domain, lymph node metastases are limited to areas along the SMA. When the tumor is confined to the dorsal pancreas domain, the lymph node metastases are limited to areas along the CHA and the hepatoduodenal ligament. However, in the case of cancers which extended into both domains, the lymph node metastases were distributed widely in areas along the SMA, CHA, and the hepatoduodenal ligament. These results indicate that lymphatic spread of the embryological ventral and dorsal domains of pancreas head carcinomas may be independent of each other even after the fusion of these domains.

For the purpose of adequately resection the tumors, the area of resection should be guided by the tumor location. The targeting of the resection area would be expected to reduce surgical morbidity such as intraoperative blood loss volume and operative times, as well as the attenuation of quality-of-life. Therefore the tumor location could be assessed preoperatively, "i.e., is the tumor localized to the ventral pancreas, the dorsal pancreas or both areas this can be assessed using imaging studies such as MD-CT, Magnetic resonance imaging (MRI), or endoscopic retrograde pancreatography (ERP) and anatomical structures such as the duct of Santorini, the duct of Wirsung, the PV, and the bile duct as landmarks. In the case of tumors confined to the ventral pancreas, the area of resection should be focused along the SMA, while tumors confined to the dorsal pancreas, the area of resection should be concentrated along the CHA and around the hepatoduodenal ligament. If a tumor extends to both areas, dissection including along the SMA, along the CHA and in the hepatoduodenal ligament is recommended. Therefore, the cases of dorsal pancreas were small in this series by aforementioned reason; the additional prospective studies are advancing to confirm these results.

The incidence of No.6 lymph node involvement is not high in pancreatic cancer (2): there is only one case of No.6 lymph node involvement in our series in a patient with a tumor involving both areas. Generally, pylorus preservation is maintained in pancreatoduodenectomy for pancreas head cancer without direct invasion to the vicinity of the pyloric ring and No.6 lymph node involvement. The pyloric ring exist closely and adherent to the superior anterior portions of the pancreatic head which are derived from the dorsal pancreas. Therefore, pylorus-preserving pancreatoduodenectomy is a good choice for cancer limited

to the ventral pancreas domain. Pylorus preservation contributes to reducing surgical morbidity in comparison with a conventional pancreatoduodenectomy with a partial gastrectomy in our analysis (data not shown).

6. CONCLUSION

Lymphatic spread of the pancreas head carcinomas can be divided into two patterns based upon an embryological division of the pancreas and the tumor's location. These phenomena indicate that the adequacy of lymph node dissection in pancreas head carcinoma might be dependent upon a tumor's location based on the embryology of the head of the pancreas. The dissection area should be guided by the tumor location in order to clear the cancer and ensure adequate stage assignment.

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Abbreviations: MD-CT: multi detector computed tomography, PV: portal vein, SMV: superior mesenteric vein, H/E: hematoxylin and eosin, PP: pancreatic polypeptide, CHA: common hepatic artery, SMA: superior mesenteric artery, V: ventral pancreas, D: dorsal pancreas, MRI: magnetic resonance imaging, ERP: endoscopic retrograde pancreatography

Key Words: Pancreas Head Carcinoma, Lymph Node Metastasis, Embryological Structure Of Pancreas, Ventral Pancreas, Dorsal Pancreas

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