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Aggressive venous invasion in the area of carcinoma correlates with liver metastasis as an index of metastasis for invasive ductal carcinoma of the pancreas

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ABSTRACT

Background: Invasive ductal carcinoma of the pancreas (IDCP) predominantly causes death through liver metastasis (LM) and peritoneal dissemination with local recurrence. However, whether its venous invasion is from the enlarged carcinoma accompanied by tumor growth, or from a distinct carcinoma group, for which venous invasion is facilitated by proximity to the origin, is unclear. We analyzed the correlation between LM and venous invasion in patients with small IDCP tumors.
Methods: Of 388 patients who were diagnosed with IDCP, 20 (5.2%) had tumors with diameters <2 cm. The follow-up period of the 20 patients with smaller tumors was 1–24 years.
Results: The small-tumor group ($n = 20$) included 11 men and 9 women, aged 51–80 years. Five died of liver metastasis (LM group, $n = 5$) and 15 patients (non-LM group, $n = 15$) were either alive without recurrence ($n = 11$) or died of peritonitis carcinomatosa following local recurrence, subarachnoid hemorrhage, primary lung cancer, or old age ($n = 1$ for each cause of death). The LM and non-LM groups did not significantly differ in numbers of venous invasion by the carcinoma in IDCP and non-IDCP area of the pancreas. However, median numbers of invaded veins in the area of IDCP and percentage of invaded vein/total number of vein in IDCP area were significantly higher in the LM group.
Conclusion: Among patients with small IDCP tumors, the LM group showed more aggressive venous invasion by IDPC. Patients in whom ≥60% of veins were invaded by IDCP should be prepared for LM.

Background

According to the Japanese Pancreatic Cancer Registry Report of 2007 [1], 5-year survival of patients with histologically confirmed invasive ductal carcinoma of the pancreas (IDCP) is 11.6%; their 3-year survival rates after pancreatectomy are 38.3% among those with T1 disease, 31.6% for T2, 25.1% for T3 and 6.5% for T4 (as classified by the UICC T system for primary tumors) [2]. Although resections for invasive pancreatic cancer (PC) are expected to leave no residual carcinoma (R0), patients' 5-year survival rate is only 37.4% [3].

The cause of poor prognosis after surgical resection of IDCP is recurrent carcinoma. Recurrent sites after pancreatic resection of IDCP are usually found in the liver and the local site, including the pancreatic bed, regional lymph nodes, or immediately adjacent structures [4]. Notably, survival for patients with liver metastasis (LM) is significantly shorter than for patients with local-site recurrences [4]. LM occurs even from small IDCP tumors [5,6]. Our previous report [7], which analyzed 14 patients with pT1 disease (ie, tumor limited to the pancreas, ≤ 2 cm in greatest dimension), also showed LM in 4 patients, all of whom died within 3 years after surgical resection. Effective diagnosis and treatment for LM is a primary step in improving IDCP prognosis.

Various factors affect LM from IDCP. Venous permeation by carcinoma is significantly higher in LM patients than in those with non-LM patients [8]. High peripheral microvessel density is associated with LM and poor PC prognosis [9]. Expression of vascular endothelial growth factor correlates with venous carcinoma permeation and hematogenous metastasis in gastric carcinoma [10], colon cancer [11] and IDCP [12,13]. Matrix metalloproteinases (MMP)-2 and MMP-9 are also associated with venous invasion [13].

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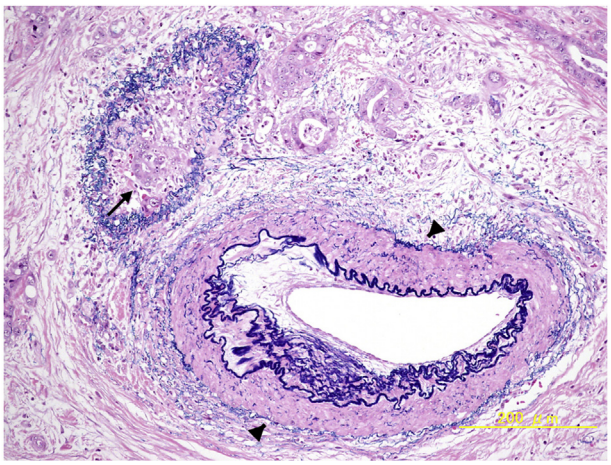

Fig. 1. Venous invasion by the carcinoma (Victoria blue–H&E stain; Case 4). Blue: stained elastic fibers. Arrow shows where the carcinoma has invaded the vein lumen; carcinomatous tubules invade the surrounding tissue. Arrowhead: artery along the vein.

However, these proteins are shown through immunohistochemical (IHC) stains, which are not a common part of clinical pathological diagnosis, due to the high cost of antibodies, and because they provide indirect findings that do not verify venous permeation by the carcinoma. Moreover, specimens include various-sized tumors, which obscures whether venous invasion by the carcinoma only reflects growth of tumor mass, or the carcinoma has an inherent potential for aggressive venous invasion. We analyzed the correlation between LM and venous invasion in patients with pancreatic tumors <2 cm.

Materials and methods

Between January 1982 and December 2015, 388 patients were diagnosed with IDCP at our hospital, of whom 20 (5.2%) had tumors with diameter < 2 cm. Their observation periods were 1–24 years. Their clinicopathological data were retrospectively analyzed according to their TNM classifications [14]. Handling of their surgical specimens was performed as previously described [15]. For the purpose of accuracy in diameters of IDCP tumors, we used sections at both side of the IDCP specimens. Residual carcinoma (R) status was defined as within 1 mm of a resection margin [16]. To evaluate venous invasion by the carcinoma, we used Victoria blue–hematoxylin and eosin (VB–HE), which is easy to use in daily pathological practice, and stains vascular elastic fibers. We compared LM and non-LM groups with regard to clinicopathologic factors and venous invasion by the carcinoma.

Assessment of vascular permeation by the carcinoma

We counted the numbers of invaded and non-invaded veins in the area of IDCP and surrounding pancreatic parenchyma without IDCP in the section, which were taken from the maximum diameter of the IDCP specimens with surrounding pancreatic tissue. The veins were recognized as having elastic fibers and lying along the artery. Venous invasion by the carcinoma was recognized where IDCP was found in the venous lumen or where venous wall was destroyed by the carcinoma (Fig. 1).

Statistical analysis

Statistical differences between clinical factors, histopathological evaluations and histochemical stains were analyzed using the χ^2 test between LM and non-LM groups. $P < 0.05$ was considered significant. The analysis was performed with StatView statistical software (Abacus Concept Inc., CA, USA).

Results

Clinicopathological findings

The study group included 11 men and 9 women, aged 51–80 years. Five died of liver metastasis (LM group, $n = 5$) and 15 patients (non-LM group, $n = 15$) were either alive ($n = 11$) or had died of

Table 1
Clinical features of patients with pT1 invasive ductal carcinoma of the pancreas.

	Age	Sex	Symptom	Location	Operative procedure	R	Prognosis	Comorbidity
1	61	F	Epigastralgia	Ph	PPPD	0	alive, 2 years	none
2	68	F	Follow-up of breast ca.	Ph	PPPD	0	died due to arachnoidal hemorrhage, 3 years	Breast ca.
3	77	M	CA19-9↑	Ph	PPPD	0	alive, 3 years	Diabetes mellitus
4	72	F	Amylase↑	Ph	PPPD	0	died due to LM, 6 month	none
5	72	M	Medical check	Ph	PPPD	0	alive, 10 years	Hypertension
6	51	F	Back pain	Pb	DP + SP + PR	0	alive, 13 years	Angioleiomyoma Glaucoma Collagen disease
7	61	F	Jaundice	Ph	PPPD	0	alive, 17 years	none
8	60	F	Medical check	Ph	PPPD	0	alive, 12 years	none
9	53	M	Jaundice	Ph	PPPD + PR	0	alive, 18 years	none
10	56	M	Medical check	Ph	PPPD	0	alive, 14 years	none
11	53	M	Medical check	Pb	DP + SP	0	died due to peritonitis carcinomatosa follow to local recurrence, 16 years	none
12	74	F	Epigastralgia	Ph	PPPD	0	died of old age, 21 years	none
13	70	M	Back pain	Ph	PPPD	0	alive, 6 years	none
14	66	M	Amylase↑	Pb	DP + SP	0	died due to LM, 19 month	none
15	80	F	Medical check	Pb	DP + SP	0	died due to LM, 31 month	Familial history
16	67	M	Amylase↑	Pb	DP + SP	0	died due to LM, 7 month	none
17	63	F	Back pain	Ph	PPPD	0	died due to LM, 8 month	none
18	65	M	Medical check	Pb	DP + SP	0	alive, 7 years	none
19	62	M	Amylase↑	Pb	DP + SP	0	died due to SqL, 4 years	none
20	64	M	BS↑	Ph	PPPD	0	alive, 7 years	Diabetes mellitus

BS: Blood sugar; DP: Distal pancreatectomy; Pb: Pancreas body; Ph: Pancreas head; PPPD: Pylorus-preserving pancreatoduodenectomy; RP: Resection of portal vein; SP: Splenectomy; SqL: Squamous cell carcinoma of the lung.

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