



## Reassessment of the clinical significance of portal–superior mesenteric vein invasion in borderline resectable pancreatic cancer

S. Hoshimoto<sup>a,\*</sup>, S. Hishinuma<sup>a</sup>, H. Shirakawa<sup>a</sup>, M. Tomikawa<sup>a</sup>,  
I. Ozawa<sup>a</sup>, S. Wakamatsu<sup>b</sup>, S. Hoshi<sup>b</sup>, N. Hoshi<sup>b</sup>, K. Hirabayashi<sup>b</sup>,  
Y. Ogata<sup>a</sup>

<sup>a</sup> Department of Hepato-Biliary-Pancreatic Surgery, Tochigi Cancer Center, 4-9-13 Yohnan, Utsunomiya, Tochigi, 320-0834, Japan

<sup>b</sup> Department of Pathology, Tochigi Cancer Center, 4-9-13 Yohnan, Utsunomiya, Tochigi, 320-0834, Japan

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### Abstract

**Objective:** The principal objective of this study is to clarify the prognostic significance of borderline resectable pancreatic cancer (BRPC). The second objective is to evaluate the prognostic impact of the depth of pathological venous invasion.

**Methods:** The study included 122 pancreatic cancer patients who underwent curative surgery. All computed tomography scans of the patients were retrospectively interpreted and classified according to the NCCN guidelines, version 1.2016, as resectable (–) or borderline resectable (+) in each arterial (BR-A) and venous (BR-PV) involvement.

**Results:** The overall survival (OS) rate was significantly higher in BR-A(–) patients (n = 94) than in BR-A(+) patients (n = 28) (P = 0.001), whereas there was no difference between BR-PV(–) (n = 101) and BR-PV(+) patients (n = 21) (P = 0.257). In a multivariate analysis, the independent predictors of OS included BR-A(+) (P = 0.002), lymph node metastasis (P = 0.008), pathological venous invasion (P = 0.003), and adjuvant chemotherapy (P = 0.001). Of 39 patients who underwent venous resection, no significant difference was observed between BR-PV(–) (n = 20) and BR-PV(+) patients (n = 19) in resection rate, lymph node metastasis, the presence of extrapancreatic nerve invasion, recurrence rate, frequency of initial recurrence at a liver or local site, and OS. Pathological venous invasion was significantly deeper in BR-PV(+) patients. However, the depth of invasion was not associated with OS.

**Conclusion:** The definition of venous involvement in the current guidelines predicted the depth of pathological venous invasion but not OS in BRPC patients. Further prospective, randomized studies are needed to establish treatment strategies for BRPC patients with isolated venous involvement.

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**Keywords:** Pancreatic neoplasms; Portal vein; Prognosis; Surgery; Survival

### Introduction

Pancreatic cancer (PC) continues to be a lethal disease and represents the fifth- and fourth-leading cause of cancer death in Japan and Western countries, respectively.<sup>1</sup> Despite recent advances in radiological imaging modalities, PC is frequently detected late in the disease. Successful surgical resection offers the only chance for a cure in PC patients, but the 5-year survival rate in PC patients undergoing

\* Corresponding author. Fax: +81 28 658 5669.

E-mail addresses: [sojunh@yahoo.co.jp](mailto:sojunh@yahoo.co.jp) (S. Hoshimoto), [shishinu@tochigi-cc.jp](mailto:shishinu@tochigi-cc.jp) (S. Hishinuma), [hshiraka@tochigi-cc.jp](mailto:hshiraka@tochigi-cc.jp) (H. Shirakawa), [mtomikaw@tochigi-cc.jp](mailto:mtomikaw@tochigi-cc.jp) (M. Tomikawa), [iozawa@tochigi-cc.jp](mailto:iozawa@tochigi-cc.jp) (I. Ozawa), [sahwakam@tochigi-cc.jp](mailto:sahwakam@tochigi-cc.jp) (S. Wakamatsu), [sayhoshi@tochigi-cc.jp](mailto:sayhoshi@tochigi-cc.jp) (S. Hoshi), [nobhoshi@tochigi-cc.jp](mailto:nobhoshi@tochigi-cc.jp) (N. Hoshi), [khirabay@tochigi-cc.jp](mailto:khirabay@tochigi-cc.jp) (K. Hirabayashi), [yogata@tochigi-cc.jp](mailto:yogata@tochigi-cc.jp) (Y. Ogata).

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complete resection remains 20–25% even when combined with adjuvant chemotherapy.<sup>2,3</sup> Borderline resectable pancreatic cancers (BRPC) were initially adopted by the National Comprehensive Cancer Network (NCCN) in 2006 to describe a challenging subset of pancreatic cancer manifestations that can potentially be surgically removed but that carry a high risk of positive margin resection or early disease progression following surgery.<sup>4</sup> Over the past decade, several groups have developed specific radiographic features to define BRPC, including those in the NCCN guidelines, the International Study Group of Pancreatic Surgery (ISGPS), the American Hepato-Pancreato-Biliary Association/Society of Surgical Oncology consensus criteria, and the M.D. Anderson criteria.<sup>5–8</sup> All of these criteria for BRPC include statements regarding the ability or inability of the surgeon to reconstruct the portal vein (PV) and/or superior mesenteric vein (SMV) or the common hepatic artery (CHA) involved with the tumor and exclude tumors involving greater than 180° of the superior mesenteric artery (SMA), whereas the difference between these criteria depends on the extent of tumor abutment of the celiac axis (CA) or PV-SMV involvement.

There is currently no consensus regarding the optimal treatment with either upfront surgery or neoadjuvant therapy followed by surgery or accurate patient selection criteria for neoadjuvant therapy in BRPC patients. No reliable data have been produced by randomized phase III trials regarding the role of neoadjuvant therapy for BRPC. Recently, several studies have demonstrated that neoadjuvant chemotherapy, with or without a radiation therapy regimen, can be effective in patients with BRPC.<sup>9–11</sup> The European Study Group for Pancreatic Cancer – Trial 5F (ESPAC-5F) is an ongoing feasibility phase II trial that is randomly assigning 100 patients with BRPC to 1 of 4 arms to compare neoadjuvant therapy to immediate surgical exploration,<sup>12,13</sup> the results of which are expected to standardize treatment strategies in BRPC patients. Because the above-mentioned definitions for BRPC are similar to each other and include two major factors, arterial and venous involvement, clinical trials on neoadjuvant therapy for BRPC have consisted of patients in a number of subgroups, including BRPC patients with arterial or venous involvement or both.

The most intriguing question is whether the indications are the same regarding neoadjuvant therapy for BRPC patients with venous or arterial involvement. Some earlier studies have demonstrated that patients who required arterial resection had comparable overall survival (OS) with those who underwent standard resection.<sup>14,15</sup> However, a meta-analysis showed significantly greater perioperative morbidity (53.6%) and mortality (11.8%) in patients undergoing arterial resection.<sup>16</sup> Currently, because of the limited oncological survival benefit and the higher incidence of morbidity and mortality than in standard pancreatotomy, the ISGPS does not recommend arterial resections on a routine basis.<sup>8</sup> However, several earlier studies

demonstrated the feasibility and efficacy of pancreatotomy combined with venous resection in PC patients with venous invasion, and comparable survival has been demonstrated in patients similarly treated but without venous resection.<sup>17,18</sup> These data might indicate advantages when using upfront surgery instead of neoadjuvant therapy in BRPC patients with venous involvement. The principal objective of this study is to clarify the prognostic significance of BRPC according to the definition of the latest NCCN guidelines. The second objective is to evaluate the prognostic impact of the depth of pathological venous invasion.

## Patients and methods

The study included 122 PC patients who underwent surgery with curative intent at our institution between September 2007 and September 2015. In our institution, the resectability of each case was determined based on the findings of triple-phase contrast-enhanced thin-slice computed tomography (CT) with three-dimensional reconstructions. Basically, patients who met the definition of BRPC according to the NCCN guidelines underwent upfront surgery. However, some exceptional cases received neoadjuvant chemoradiotherapy. If the CA abutment was involved in the tumor and exceeded 180° of its circumference, the case was considered for surgical indication if the gastroduodenal artery and the blood supply to the liver via the inferior pancreaticoduodenal artery could be preserved. Patients with extralymphatic metastasis, such as liver metastasis and peritoneal dissemination at laparotomy, were excluded from this study. This study was approved by the Institutional Review Board. The data obtained from reviewing medical records included clinical characteristics and radiological findings, the provided surgical procedures, histopathological findings, the administration of adjuvant chemotherapy, and clinical outcomes. The resection margin status of the specimens was defined as R1 when carcinoma was present at the margin (0-mm clearance). The tumor stages of each case were assigned according to the UICC TNM classification system based on the surgical and pathological findings.<sup>19</sup> Based on the experienced radiologists' reports, all CT scans of the patients who underwent surgery with curative intent were retrospectively reviewed, and the lesions were classified according to the NCCN guidelines, version 1.2016<sup>7</sup> (Table 1), as resectable (–) or borderline resectable (+) in each case of arterial (BR-A) and venous (BR-PV) involvement. In the present study, all cases that underwent distal pancreatotomy with CA resection were regarded as BR-A even if the solid tumor contacted the CA and exceeded 180° of its circumference. A total of 28 patients (30%) were classified as BR-A(+), including SMA abutment in 14 patients, CA abutment in 12 patients, and CHA abutment in 2 patients, and 94 (77%) patients were classified as BR-A(–). Regarding venous invasion, 21 patients (17%) were classified as BR-PV(+), and 101 (83%) patients were classified as BR-PV(–).

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