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Validation of Group B Borderline Resectable Pancreatic Cancer: Retrospective Analysis

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Background/Aims: Among borderline resectable pancreatic cancer (BRPC), group B BRPC patients have findings that are suggestive but not diagnostic of metastasis. In this study, we attempted to validate whether group B could truly be categorized as a borderline resectable group. **Methods:** We placed the BRPC patients into group A or group B. The survival outcomes were compared between the groups. **Results:** A total of 53 patients with pancreatic adenocarcinoma was classified as either group A or B borderline resectable. In group A, 23 (60.5%) of 38 patients underwent pancreatectomy after concurrent chemoradiotherapy or chemotherapy, but in group B, only five (33.3%) of 15 patients underwent pancreatectomy, mainly because of the progression of suspected distant metastasis. There was a significant difference in overall survival (OS) between group A and B patients (median OS, 21.2 months vs 10.2 months, respectively; p=0.007). Of the patients who underwent pancreatectomy, group B had a higher recurrence rate compared to group A (recurrence rate: 11 of 23 patients [47.8%] vs five of five patients [100%], respectively; p=0.033). **Conclusions:** This report is the first to validate the definition of BPRC. Group B had much worse outcomes, and whether group B BRPC can be categorized as BRPC together with group A is questionable. **(Gut Liver 2014;8:557-562)**

Key Words: Pancreatic neoplasms; Chemoradiotherapy; Chemotherapy; Prognosis

INTRODUCTION

Pancreatic cancer is usually diagnosed at an advanced stage, such that two-thirds of patients have locally advanced or metastatic disease at the time of diagnosis. For patients with American Joint Committee on Cancer (AJCC) stage I and II pancreatic adenocarcinoma who undergo a successful pancreatectomy, the 5-year survival rate is approximately 15% to 20%;[1] however, surgery is not an option for patients who are diagnosed with locally advanced (AJCC stage III) disease. Indeed, for these patients, the median survival is usually less than 12 months despite the use of chemotherapy and/or chemoradiation therapy.[2] Recently, the concept of borderline resectable pancreatic cancer (BRPC) was introduced. This type of pancreatic cancer is positioned on the spectrum between resectable and unresectable pancreatic cancer. It is potentially resectable and thus curable, but tumor free margins are hard to achieve and the surgical outcome is not as good as that for resectable pancreatic cancer.[3]

In 2006, Varadhachary *et al*.[1] from MD Anderson Cancer Center proposed an objectively defined BRPC. A computed tomography (CT)-based classification, which distinguished borderline resectable from both resectable and locally advanced pancreatic cancer, was reported.[1] In 2008, Katz *et al*.[2] reported 160 patients with borderline resectable disease treated at MD Anderson Cancer Center and introduced three types of borderline resectable disease, now often referred to as Katz type A, B, and C. All three groups of BRPC were categorized as borderline resectable because they had conflicting potential for either complete remission or disease progression such as distant metastasis. Recently, BRPC gains a lot of attention because there have been several reports that preoperative multimodality treatment can improve resectability rate and surgical treatment outcome. Specially in terms of treatment, concurrent chemoradiotherapy (CCRT) or chemotherapy can be the preoperative treatment options for

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BRPC. Preoperative therapy may downstage the borderline resectable disease and make complete resection possible and select patients suitable for surgery, which could translate to a survival benefit after resection.[4,5] Especially for group A, several studies reported that survival outcome could be improved with preoperative treatment.[6-9] For example, Kalser and Ellenberg[6] reported that BRPC had better survival outcome with preoperative CCRT compared to the patients without preoperative treatment (median survival, 20.0 months vs 10.99 months; p<0.05).

Still, an understanding of these groups of patients has not been established due to the inconsistencies and imprecision in both the definitions and standard treatment algorithms. Above mentioned approach is tested mostly in type A BRPC and, even though type B is categorized together with group A, there is not enough data to prove that type B could be treated like type A BRPC. Thus, in this study, we tried to validate whether group B BRPC could be truly categorized in the borderline resectable group.

MATERIALS AND METHODS

1. Study population

All patients who were evaluated for group A or B BRPC and received CCRT or chemotherapy between November 2005 and April 2012 were enrolled in this study. The patients in this study were divided into group A or B according to the MD Anderson criteria. We defined group B patients who had suggestive metastatic lesions. Suggestive metastasis includes suspicious distant lymph node, liver metastasis, or carcinomatosis. Suspicious distant lymph node was defined as 8 mm sized or more for short axis diameter at distant lymph node area such as paraaortic area. But, all of lymph node was not definite for metastasis depend on radiologists' decision. Suspicious liver metastasis or carcinomatosis was decided based on location, size, and characteristics of the lesions. The decision was made by radiologist. Even if careful and experienced radiologic review was done, some metastatic lesion could not be concluded whether the lesion is malignant or not. For such cases, we defined these patients as group B and we tried to conclude malignancy potential by follow-up of imaging study after chemotherapy or CCRT. Group C BRPC and patients included in both group A and B were not included in our study. Patients with mucinous cystic neoplasm, invasive intraductal papillary mucinous neoplasm, and other nonpancreatic adenocarcinomas of the periampullary region were also excluded. Baseline characteristics of all patients were based on a basic blood test (complete blood count and blood chemistries) and contrast-enhanced CT, magnetic resonance imaging (MRI) of the abdomen, and endoscopic ultrasound. Serum CA19-9 levels were recorded at the time of diagnosis. The rate of operation, recurrence rate, disease-free survival (DFS), progression-free survival (PFS), and overall survival (OS) were compared between group A and group B BRPC.

2. Treatment modality and follow-up

All patients received initial treatment with CCRT or chemotherapy. In case of CCRT, the total radiation therapy dose was approximately 5,040 cGy. Representative concomitant chemotherapy consisted of 5-fluorouracil, gemcitabine, or capecitabine at radiosensitizing doses. In case of chemotherapy, gemcitabine-based chemotherapy was performed. For response evaluation of CCRT or chemotherapy, abdominal CT or MRI was done. Based on result of follow-up imaging study, a Whipple's operation, pancreaticoduodenectomy, or distal pancreatectomy was performed if the cancer lesion was judged operable. After the operation, patients were evaluated every 1 to 2 months by physical examination, complete blood count, blood chemistries, tumor marker (CA19-9) level, and abdominal CT or MRI. All patients who underwent surgery were recommended to receive adjuvant chemotherapy. Patients who could not undergo surgery received gemcitabine-based systemic chemotherapy.

3. Statistical analysis

The primary end points were OS, DFS, and PFS. OS was calculated from the date of diagnosis until death from any cause or the patient's last visit to the hospital. DFS was calculated from the date of operation until the date of recurrence or the day of the last radiological evaluation such as CT or MRI. PFS was calculated from the date of diagnosis until the date of progression or the day of the last radiological evaluation.

The OS, DFS, PFS, and 3-year survival rate were calculated using the Kaplan-Meier method. Differences between OS curves were assessed by the log rank test. All analyses were performed with the SPSS statistical program version 18.0 (IBM Co., Armonk, NY, USA). A p<0.05 was considered statistically significant.

RESULTS

1. Baseline characteristics and clinical variables

Fifty-three of 703 patients (7.5%) with pancreatic adenocarcinoma were classified as borderline resectable, with 38 type A (71.7%) and 15 type B (28.3%). The median age of patients was 62 years (range, 38.0 to 83.0 years), and the sex ratio (male:female) was 32:21. Most of the BRPC cases in our study were located at the head of the pancreas (45, 84.9%). The median pretreatment CA19-9 level was 295 U/mL (range, 0.1 to 5,320 U/mL). The baseline characteristics of group A and B BRPC are described in Table 1. Between group A and B BRPC, there were no significant differences for the median patient age, gender, and pretreatment CA19-9 level.

2. Treatment

All 53 patients completed scheduled CCRT or chemotherapy. Mean duration of induction therapy was about 5 weeks. After

Table 1. Baseline Characteristics of Group A and B Borderline Resectable Pancreatic Cancer Patients

Characteristic	All patients	Borderline resectable type		p-value
		Group A	Group B	
Total patients, no.	53	38	15	
Age, yr	62 (38–83)	59 (38–83)	64 (44–80)	0.974
Gender				0.972
Male	32 (60.4)	23 (60.5)	9 (60.0)	
Female	21 (39.6)	15 (39.5)	6 (40.0)	
Tumor location in pancreas				0.001
Head/Uncinate	45 (84.9)	36 (94.7)	9 (60.0)	
Body/Tail	8 (15.1)	2 (5.3)	6 (40.0)	
Pretreatment CA19-9, U/mL				
All	295 (0.1–5,320)	272 (0.1–5,320)	417 (0.1–1,810)	0.371
Underwent pancreatectomy	272 (0.1–3,540)	304 (0.1–3,540)	57 (0.1–452)	0.226
Did not undergo pancreatectomy	417 (0.1–5,320)	148 (0.1–5,320)	522 (0.1–1,810)	0.628
Pancreatectomy performed				0.074
Yes	28 (52.8)	23 (60.5)	5 (33.3)	
No	25 (47.2)	15 (39.5)	10 (66.7)	

Data are presented as median (range) or number (%).

Table 2. A Comparison of the Survival Outcomes between Groups A and B Borderline Resectable Pancreatic Cancer for All 53 Patients

	Group A	Group B	Total	p-value
Total, no.	38	15	53	
Induction therapy				0.036
Response rate				
Progression	11 (28.9)	9 (60)	20 (37.7)	
Nonprogression	27 (71.1)	6 (40)	33 (62.3)	
Resected	23 (60.5)	5 (33.3)	28 (52.8)	0.074
Overall survival, mo	21.2	10.2	18.5	0.007
Progression-free survival, mo	12.2	5.2	10.1	0.001
3-Year survival rate, %	40	13	31	

Data are presented as number (%).

Table 3. The Preoperative and Operative Data for 28 Patients Who Underwent Pancreatectomy

Characteristic	All patients	Group A	Group B	p-value
Total patients, no.	28	23	5	
Restaging (postoperative) CA 19-9, U/mL	66.1 (0.1–1,230)	70.2 (0.1–1,230)	34.0 (0.1–845)	0.899
Surgical procedure				0.448
PPPD	21 (75.0)	18 (78.3)	3 (60.0)	
Whipple's operation	5 (17.9)	4 (17.4)	1 (20.0)	
Distal pancreatectomy	2 (7.1)	1 (4.3)	1 (20.0)	
Etc.	0	0	0	
Vascular resection				0.502
Hepatic artery	0	0	0	
SMV/PV	13 (46.4)	10 (43.5)	3 (60.0)	
Margin status				0.393
R0	21 (75.0)	18 (78.3)	3 (60.0)	
R1	7 (25.0)	5 (21.7)	2 (40.0)	
Adjuvant chemotherapy	18 (64.3)	14 (60.9)	4 (80.0)	0.418

Data are presented as median (range) or number (%).
PPPD, pylorus preserving pancreatoduodenectomy; SMV/PV, superior mesenteric vein/portal vein.

that, 33 of 53 patients (62.3%) had a favorable response. Six patients (11.3%) had a partial response, 27 patients (50.9%) had stable disease, and 20 patients (37.7%) had disease progression. In a subgroup analysis, group B had fewer favorable responses compared to group A. Eleven out of 38 patients (28.9%) in group A and nine out of 15 patients (60%) in group B had disease progression (Table 2). Among nine patients of group B who had disease progression after induction therapy, seven patients (77.8%) had progression of suspicious metastatic lesions. At the time of restaging evaluation, 28 of 53 patients (52.8%) were determined to be eligible for operation. In group A, 23 of 38 patients (60.5%) underwent pancreatectomy, but in group B, only five of 15 patients (33.3%) underwent pancreatectomy. Group B BRPC (33.3%) had the tendency to have a lower rate of operation compared to group A BRPC (60.5%) (p=0.074). Preoperative and operative data for 28 patients who had a pancreatectomy are described in Table 3. Venous resection was performed in 13 out of 28 patients (46.4%) and none of these patients required short-segment resection of the common hepatic artery. Through surgical pathologic evaluation, 18 of 23 patients (78.3%) in group A and three of five patients (60.0%) in group B were confirmed to have R0 resection (p=0.418). Regarding the pathological nodal stage, one of 23 patients (3.6%) in group A and one of five patients (20.0%) in group B had confirmed to have lymph node metastasis (p=0.218).

3. Survival outcome

The median follow-up time was 13.6 months. The 3-year OS rate of patients with BRPC was 31%. At the time of last follow-up, 17 of 38 (44.7%) and 11 of 15 patients (73.3%) in group A and B BRPC died, respectively (p=0.060). The OS of group A was longer than that for group B (median OS, 21.2 months vs 10.2 months; p=0.007) (Fig. 1). In addition, the PFS of group A was longer than that for group B (median PFS, 12.2 months vs

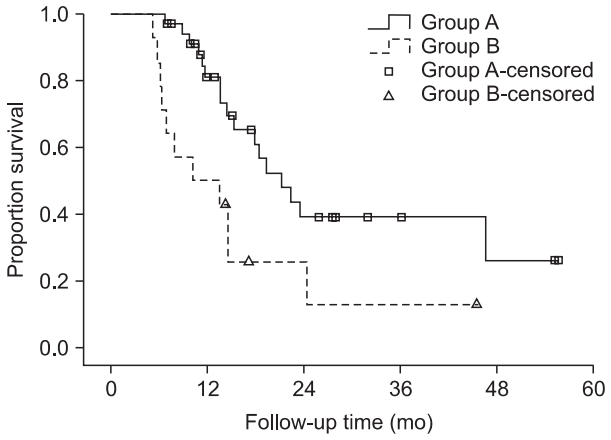

Fig. 1. Kaplan-Meier overall survival curves for group A and B borderline resectable pancreatic cancer (p=0.007).

5.2 months; p=0.001) (Table 2). Of the patients who underwent pancreatectomy, group B patients (five of five patients, 100%) had a significantly higher recurrence rate compared to group A patients (11 of 23 patients, 47.8%; odds ratio, 1.455; 95% confidence interval, 1.045 to 2.024; p=0.033). When we compared the characteristics of recurrence type among the patients who had surgery, among group A patients who had recurrence after surgery, four of 11 patients (36.4%) had metastatic recurrence and seven of 11 patients (63.6%) had local recurrence. In five patients of group B who had recurrence after surgery, four of five patients (80%) had metastatic recurrence and only one of five patients (20%) had local recurrence. Due to insufficient patients' number who had surgery in group B, despite lower R0 resection rate in group B, local recurrence rate in group B was lower than group A. The portion of metastatic recurrence was higher in group B patients compared to group A patients. Group B also showed a shorter DFS compared to group A (median DFS, 29.0 months vs 8.3 months; p=0.054) (Table 4).

4. Subgroup analysis of group B borderline resectable pancreatic cancer

Among group B patients, 10 of 15 patients were suspicious of distant lymph node metastasis such as paraaortic lymph node metastasis, three of 15 patients were suspicious of carcinomatosis, and two of 15 patients were suspicious of liver metastasis. After CCRT or surgery, five of 10 patients were confirmed distant lymph node metastasis, two of three patients were confirmed carcinomatosis, and two of two patients were confirmed liver metastasis. Among the six patients who still had inconclusive lesion even after chemotherapy or CCRT, five patients had favorable response for first induction therapy. Compared to the group B patients who were concluded to have metastatic lesion after induction therapy, these six patients could be expected better prognosis.

Table 4. A Comparison of the Prognoses between Groups A and B Borderline Resectable Pancreatic Cancer for 28 Patients Who Underwent Pancreatectomy

	Group A	Group B	Total	p-value
Total, no.	23	5	28	
Overall survival, mo	38.3	18.1	35.4	0.088
Recurred, no. (%)	11 (47.8)	5 (100.0)	16 (57.1)	0.033
Disease-free survival, mo	29	8.3	24	0.054

DISCUSSION

Group A BRPC is defined by the following anatomic characteristics: tumor abutment (≤180° of the circumference of the vessel) of the superior mesenteric artery or celiac axis; tumor abutment or encasement (>180° of the circumference of the vessel) of a short segment of the hepatic artery; or short-segment occlusion of the superior mesenteric vein (SMV), portal vein (PV), or SMV-PV confluence. Group B borderline resectable disease raises a concern for possible extrapancreatic metastatic disease. This subgroup of borderline resectable patients includes those with CT findings suspicious for, but not diagnostic of, metastatic disease. Based on the decision regarding suspicious metastatic lesions, group B BRPC can be categorized as both resectable and unresectable. Thus, it has been classified as a borderline resectable group. Patients of group C have borderline resectable disease due to a marginal performance status. Group C also encompasses patients with a better performance status and a severe pre-existing medical comorbidity.[10] Due to equivocal anatomical characteristics of group A, the potential for distant metastasis in group B, and the equivocal general condition for group C, all three types of BRPC have been categorized as borderline resectable. But, whether all three types of BRPC had similar potential for resectabiliy is questionable and these three groups had distinctly different characteristics. Especially for group B BRPC, its definition is ambiguous.

Until now, in contrast to group A BRPC, it had not been determined whether group B BRPC could truly be considered BRPC. Potential resectability is a quality consistent with BRPC, but the chance of systemic spread is not. Whether group B BRPC can truly be categorized as borderline resectable is an important point when deciding treatment options. If it can be considered a localized disease just like group A BRPC, surgery possibly with vascular resection after local induction therapy such as CCRT is a logical approach; however, if it is considered a systemic disease, then systemic therapy is more suitable, and the chance of resection will not be high. Until now, it seems that both group A and B have been regarded just as BRPC, and the treatment approach has not been very different for the two categories.[11] In this study, we showed that unfortunately, group B BRPC had a worse treatment outcome than group A. The rate of operation was low, and the recurrence rate was high. All patients in group

B who underwent surgery had recurrence. Considering resection rate was low and recurrence rate was high, it was questionable that group B could be a candidate for surgery and classified as BRPC. Among group B patients in our study, some of them had CCRT as local treatment and the other had chemotherapy as systemic treatment. Heterogeneity of treatment option could be the reason for poor prognosis in group B. If we considered only systemic treatment alone, we could expect better treatment outcome. Our result suggested that treatment approach for group B BRPC had to be changed from considering resection to systemic approach.

In terms of treatment, preoperative CCRT or chemotherapy have several advantages, including the potential for down-staging advanced pancreatic cancer, the avoidance of unnecessary exploratory laparotomy for patients who have rapidly progressive disease,[12,13] and the expectation for both local and systemic treatment.[14,15] In the case of group B BRPC, there are not enough studies about treatment algorithms. The biggest concern in treating group B BRPC is preexisting micrometastases.[13] Asiyanbola *et al*.[16] reported a high incidence and clinical significance of pre-existing micrometastases in patients with radiographically localized pancreatic cancer. The high rate of recurrence among patients with resected cancers with or without postoperative therapy suggests that disseminated cancer cells were undetected and incompletely treated.[17,18] Our study showed that group B BRPC had a poor response rate for CCRT or chemotherapy, and preoperative treatment could not raise resectability rate and lower recurrence rate. In addition, resection in group B BRPC should be reserved for carefully selected patients whose cancers are confirmed to not be systemic. Pancreatic cancer not progressing after chemotherapy or presence of no distant metastasis was not adequate criteria for surgery in group B unlike group A. Having Future clinical trials of preoperative induction therapy for BRPC should include group A and group B BRPC separately.

There were some limitations of our study. First, induction treatment was not uniform and the number of patients was too small. Second, we could not show long-term follow-up results due to poor survival outcomes. Third, patients' number is too small for accurate validation because we excluded the patients who had both characteristics of group A and B BRPC. But, excluding the patients who had both characteristics of group A and B BRPC is inevitable for accurate analysis. Clearly, further studies are necessary to establish stage-specific treatment algorithms for this clinically diverse group of patients. Further prospective, long-term studies will be needed.

This is the first report for the validation of group B BRPC. Group B BRPC had lower resectability, poorer survival outcomes, and a higher recurrence rate compared to group A BRPC. Group A and B BRPC cannot be categorized together as BRPC since group B has very low chance of surgical resection and worse prognosis. Group B BRPC is more like borderline systemic disease rather than borderline resectable disease.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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