Preoperative gemcitabine-based chemoradiation therapy for pancreatic ductal adenocarcinoma of the body and tail: Impact of splenic vessels involvement on operative outcome and pattern of recurrence

Hidenori Takahashi, MD, Hirofumi Akita, MD, Kunihito Gotoh, MD, Shogo Kobayashi, MD, Shigeru Marubashi, MD, Norikatsu Miyoshi, MD, Keijiro Sugimura, MD, Masaaki Motoori, MD, Kentaro Kishi, MD, Shingo Noura, MD, Yoshiyuki Fujiwara, MD, Masayuki Ohue, MD, Hiroaki Ohigashi, MD, Masahiko Yano, MD, Masato Sakon, MD, *and* **Osamu Ishikawa, MD,** *Osaka City, Japan*

Background. *Among the various multimodal treatment strategies for pancreatic ductal adenocarcinoma (PDA), preoperative chemoradiation therapy (CRT) and subsequent operation is a promising strategy. The aim of this study is to evaluate the outcome of preoperative gemcitabine-based CRT for PDA of the body and tail, focusing on the associations among splenic vessel involvement, surgical outcomes, and pattern of recurrence.*

Methods. *A total of 99 patients with PDA of the body and tail received preoperative CRT. The status of tumor involvement of the splenic artery (SA) and vein (SV) were evaluated based on radiographical findings obtained before the initiation of preoperative CRT. We assessed the following in association with the status of SA and SV involvement: (1) resection rate, (2) survival, and (3) pattern of recurrence.*

Results. *The resection rate of SA-positive cases (71%) was significantly lesser than that of SA-negative cases (94%;* $P = .004$*), whereas SV involvement was not associated with the resection rate. The 5-year survival rates of the resected SA-negative and SA-positive cases were 76% and 20%, respectively* ($P < .001$*). The 5-year cumulative incidence of distant recurrence was significantly higher in the SA-positive patients than in the SA-negative patients (74% vs 17%;* $P < .001$*).*

Conclusion. *In preoperative CRT for PDA of the body and tail, positive SA involvement was associated with a lesser resection rate, and the survival rate for the patients with SA-positive tumors was lesser than that for patients with SA-negative tumors because of the greater incidence of distant recurrence in SA-positive patients. (Surgery 2015;157:484-95.)*

From the Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka City, Japan

PANCREATIC DUCTAL ADENOCARCINOMA (PDA) is one of the most lethal diseases, with a 5-year survival rate of approximately 6%.[1] PDA of the body and tail particularly has been associated with a dismal prognosis, even more so than PDA of the pancreatic head, because of a lack of specific clinical manifestations, such as obstructive jaundice, and a subsequent delay in detection.[2-5] Although operative resection with negative margins (R0) remains the only treatment option that could allow for a complete cure, PDA of the body and tail usually is diagnosed at an advanced and unresectable stage, yielding a low resection rate ranging from 10 to 13%.[2,6-8] Even in patients who undergo resection, the operative outcome still remains poor, with a 5-year survival rate ranging from 6 to 25%.[2,3,8-11] Recently, a variety of multidisciplinary treatment strategies for PDA have been actively implemented

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Reprint requests: Hidenori Takahashi, MD, Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3, Nakamichi, Higashinari-ku, Osaka City, Osaka Pref. 537-8511, Japan. E-mail: takahasi-hi@mc.pref.osaka.jp.

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and are considered essential for the improvement of the operative outcome because operative resection alone seems to provide the minimum survival benefit.[12-15]

Preoperative chemoradiation therapy (CRT) with subsequent operation is one of the promising multidisciplinary treatment strategies for PDA.[13-18] Meta-analyses of preoperative CRT for resectable PDA reported a resection rate of 65% and a median survival of 23 months.[16] In most previous reports, the outcome of preoperative treatment strategies was evaluated in patient populations with a mixture of pancreatic head and body/tail cancer, whereas some studies focused on pancreatic head cancer.[13-18] There is limited information, however, regarding the outcome of preoperative treatment strategies focused on PDA of the body and tail. In this context, the prognostic significance of clinicopathologic variables has not been fully investigated in preoperative CRT strategies for PDA of the body and tail, although various factors have been found to predict prognosis after operative resection in the upfront operative strategy for PDA of the body and tail.[3,8-10] Recently, the prognostic impact of the tumor invasion of splenic vessels has been emphasized in some reports. Partelli et al[8] and Kanda et al[9] reported the prognostic significance of splenic artery (SA) involvement, whereas Shimada et al[10] reported similar findings for splenic veins (SV). The prognostic significance of the tumor invasion of splenic vessels is also of interest in preoperative CRT strategies. Thus, we conducted this study with the aim of evaluating the outcome of preoperative gemcitabine-based CRT for PDA of the body and tail. Furthermore, the degree of SA and SV impingement was assessed in association with the outcomes and patterns of failure in the preoperative CRT strategies for PDA of the body and tail.

METHODS

Patients and eligibility criteria for preoperative gemcitabine-based CRT. A total of 99 treatment-naïve patients with PDA of the body and tail received preoperative gemcitabine-based CRT at our hospital between 2002 and 2012 as part of a prospective phase II clinical trial (UMIN-CTR: UMIN000001804) (Table I).[14] All protocols were conducted after obtaining written informed consent from all patients in accordance with the approved procedure at our hospital. All tumors required confirmation of invasive ductal adenocarcinoma of the pancreas, based on either histopathologic or cytologic examinations, before the initiation of preoperative CRT. For all potential candidates, radiographic evaluations, including thin-slice abdominal computed tomography and endoscopic ultrasound, were performed before the initiation of the preoperative treatment, and all patients eligible for this study were required to display the following radiologic features: (1) tumors primarily located in the pancreatic body and/or tail; (2) definite radiographic findings of tumor extension beyond the confines of the pancreas (ie, UICC-T3 tumor)[19]; (3) no evidence of distant disease (M0); (4) no evidence of tumor abutment of the superior mesenteric artery (SMA), celiac axis (CA), or common hepatic artery (CHA); and (5) no evidence of portal vein (PV) and superior mesenteric vein (SMV) distortion. More specifically, all patients included in this study had "resectable" pancreatic body and tail cancer according to the classification proposed by the National Comprehensive Cancer Network (version 1, 2014); in this study, we excluded tumors with CHA and/or CA involvement (ie, borderline resectable tumors according to the NCCN classification) even if an R0 resection was potentially feasible by performing distal pancreatectomy with en-bloc CA resection[20] or arterial resection and reconstruction.[21] Staging laparoscopy was also available in cases with suspicious peritoneal metastasis. Patients in whom peritoneal metastasis and/or positive cytology of peritoneal lavage or ascites was revealed by staging laparoscopy prior to the initiation of preoperative CRT were considered unresectable and were excluded from the study.

Protocol for preoperative gemcitabine-based CRT and subsequent operation. The details of our preoperative gemcitabine-based CRT have been described in a previous report.[14,15] In brief, 3-dimensional radiation was administered at a total radiation dose of 50 Gy with a daily fraction of 2 Gy 5 times per a week. The radiation targeted the following fields: the primary pancreatic tumor, the CA and SMA, the retroperitoneal soft tissue, and the para-aortic region. Intravenous administration of gemcitabine (1,000 mg/m^2) was initiated concurrently on days 1, 8, and 15 during each 4-week cycle; this procedure was performed repeatedly for 3 cycles, such that the preoperative CRT was completed 3 months after initiation.

Re-evaluation of the resectability of the PDA was performed at the completion of preoperative CRT and at laparotomy. The exclusion criteria for resection of the PDA were as follows: presence of distant diseases (M1); tumor invasion into the CA, SMA, or CHA; and tumor invasion into the PV/SMV without an appropriate option for venous resection and reconstruction. Our operative