Histomorphologic and molecular phenotypes predict gemcitabine response and overall survival in adenocarcinoma of the ampulla of Vater

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Background. *The need for adjuvant chemotherapy after resection of ampullary cancer (PapCa) remains undefined. Recent data suggest that a different epithelial origin of PapCa might be associated with different tumor biology. The aim of the present study was to assess the clinical value of morphologic and immunohistochemic subclassification of PapCa into intestinal-type (IT) and pancreaticobiliary-type (PT) to predict chemotherapy response and overall survival (OS).*

Methods. *Via a prospective database, 112 PapCa were identified, of which 95 could be included in the present study. Those were compared with 206 matching patients with periampullary pancreatic cancer (ie, pancreatic ductal adenocarcinoma, PDAC). IT and PT PapCa were classified morphologically, and tissue microarray was prepared with immunohistochemistry for CK7, CK20, MUC2, CDX2, β-Catenin, and Villin. Multivariate survival analysis was performed.*

Results. *OS of PT patients was less compared with IT patients (25 vs 98 months;* $P < .001$*), whereas it was comparable with patients with PDAC (25 vs 14 months;* $P = .123$*). PT patients receiving adjuvant gemcitabine chemotherapy featured improved OS (32 vs 13 months;* $P = .013$*), whereas gemcitabine tended to be associated with decreased OS in IT patients (35 vs 112 months;* $P = .193$*). Besides histopathologic classification, expression of CK7 and MUC2 were important prognostic variables. PT patients with CK7-positivity or MUC2-negativity were segregated into an even poorer prognostic group.*

Conclusion. *PapCa is not a separate tumor entity. We demonstrate important differences between IT-PapCa and PT-PapCa not only in long-term survival but also in response to adjuvant gemcitabine. Tumor biology and clinical course of PT tumors resemble those of PDAC. PT tumors should therefore be treated like PDAC. (Surgery 2015;158:151-61.)*

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The prognosis of patients with carcinoma of the ampulla of Vater (PapCa) is far better than that of those with ductal adenocarcinoma of the pancreatic head (ie, pancreatic ductal adenocarcinoma; PDAC)[1-3] because their symptoms might appear earlier in the course of the disease.[2] Because the ampulla of Vater represents a boundary between different epithelia, the biology of tumors arising from this border may differ according to varying

genuine tumor origin (duodenal, biliary, or ductal pancreatic epithelia) and may thereby influence patients' clinical outcome.[4,5] Indeed, among patients with PapCa, there is a broad interindividual range of outcomes that impairs the prediction of specific outcomes and clinical decision making as to individual adjuvant therapy.[6-11] Kimura et al[12] suggested to subdivide PapCa into intestinal type (IT) and pancreaticobiliary type (PT) emphasizing those as main tumor "subtypes." Histologically, IT PapCa resemble tumors of intestine, whereas PT PapCa are similar to PDACs and those of extrahepatic bile ducts. This classification is performed on the basis of morphology.[4,11,12] Studies have suggested differences in tumor biology[2,11]; however, results have been contradictory probably because of the infrequency of this entity.[12-18] Furthermore, therapeutic implications of this stratification and its clinical utility have not been shown. Notably, suitability for predicting chemotherapy response has not been assessed.

Our aim was to investigate the outcome of a large, single-center population with PapCa who were undergoing partial pancreaticoduodenectomy compared with matched patients with periampullary PDAC. To the best of our knowledge, this is the first study to assess the clinical utility of histomorphologic and molecular classification of PapCa into IT and PT to predict chemotherapy response, hereby enabling decision making for tailored adjuvant therapy.

PATIENTS AND METHODS

Design and study population. The study was approved by the local Ethics Committee. Design, data-acquisition, statistical methods, and manuscript preparation were carried out according to Strengthening the Reporting of Observational Studies in Epidemiology (ie, STROBE) guidelines.[19] From the prospective database of the local pancreatic cancer center, which included 2,165 pancreatic surgeries, patients undergoing pancreatoduodenectomy (PD) between 1991 and 2012 for PapCa were identified (Fig 1). PapCa was defined as tumors primarily located in the ampulla of Vater, which was determined as previously reported.[6]

To define the origin, the epicenter of adenocarcinoma was assessed grossly and microscopically, and tumor components were evaluated carefully for the localization of an in situ carcinoma as well as the involvement of the papilla-of-Vater mucosa. Tumors with their epicenter in the ampullary region but sparing the mucosa of the papilla were excluded just

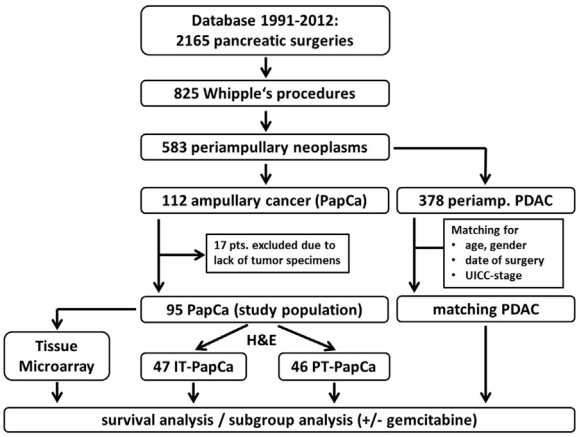

Fig 1. Study profile. Evaluation of more than 2,000 consecutive pancreatic surgeries revealed 112 PapCa patients. Of those, 95 were included in the present study and featured sufficient follow-up and tumor specimens for tissue microarray. For a matched analysis, patients with periampullary pancreatic ductal adenocarcinoma (PDAC) matching sex, age, date of surgery, and Union for International Cancer Control (UICC) stage were identified.

as those originating from the distal common bile duct or those with the main tumor mass outside the papilla. For comparison of survival, patients undergoing PD for periampullary PDAC were matched separately to those with PapCa and to the PT subgroup of PapCa, respectively (Fig 1 and Fig 2, *A* and *C*). Matching criteria were sex, age (±5 years), date of surgery (±5 years), and Union for International Cancer Control stage.[20] Comorbidities were stratified applying the classification according to the American Society of Anesthesiologists. Postoperative complications were assessed according to the validated Clavien-Dindo classification.[21] Patients underwent close outpatient follow-up at 3- and 6-month intervals. Overall survival (OS) was determined from date of surgery to date of death or last recall.

Histopathologic evaluation based on morphology. Histopathologic stratification of PapCa into IT and PT was carried out double-blinded on the basis of hematoxylin and eosin (H&E) stains of representative formalin fixed paraffin-embedded tissue specimen by 2 independent pathologists (S.R. and J.N.) according to criteria previously reported.[4,5,15] In brief, IT-PapCa was defined by tubular to elongated glands, cribriform, or solid nests of columnar cells with pseudostratified nuclei closely resembling colorectal adenocarcinoma (Fig 2, *F*). PT-PapCa consists of simple or branching glands as well as solid nests of mainly cuboidal cells with a high