High-grade pancreatic intraepithelial lesions: prevalence and implications in pancreatic neoplasia

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BACKGROUND: High-grade pancreatic intraepithelial neoplasia (PanIN-3), a precursor of pancreatic ductal adenocarcinoma (PDAC), is not universally detected in resected pancreatic neoplasms. We sought to determine the prevalence and prognostic relevance of PanIN-3 lesions in primary surgical resections of PDACs and intraductal papillary mucinous neoplasms (IPMNs).

METHODS: A retrospective review of a tertiary care center pathology database (1/2000-6/2014) was performed. Demographics, imaging, pathology, disease-recurrence, and survival data were reviewed.

RESULTS: A total of 458 patients who underwent primary pancreatic resection were included. "PanIN-3" lesions were found in 74 (16.2%) patients who either had PDAC (*n*=67) or main duct (MD)-IPMN (*n*=7). Among IPMN-MDs, PanIN-3 lesions were exclusively found in those with pathological evidence of chronic pancreatitis. For PDACs, the median overall survival (OS) for pancreata with PanIN-3 lesions was significantly better than those without (OS 1.12 years, interquartile range [IQR] 0.72, 2.05 years vs OS 0.86 years, IQR 0.64, 1.60 years respectively; *P*=0.04). Multivariate Cox regression analysis demonstrated that the presence of PanIN-3 lesions was associated with a reduced risk of death (HR=0.43; 95% CI: 0.23-0.82; *P*=0.01).

CONCLUSIONS: Following primary resection of pancreatic adenocarcinoma, the lower survival observed in patients without PanIN-3 lesions might suggest a state of complete or accelerated transformation. Further investigations are necessary to validate these findings that might impact disease prognosis and management.

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KEY WORDS: pancreatic intraepithelial neoplasia; intraductal papillary mucinous neoplasms; pancreatic neoplasia; pancreatic ductal adenocarcinoma

Introduction

Among gastrointestinal malignancies, pancreatic adenocarcinoma has the second highest incidence rate behind colon cancer. Unlike colon cancer, which has seen a significant improvement in the 5-year survival rate from 51% to 65% over the last 40 years, the survival rate in pancreatic cancer has remained dismally low with a marginal improvement from 2% to 6% in the same time period.[1] Surpassing breast, prostate, and colorectal cancers, pancreatic cancer is projected to become the second leading causes of cancer-related death by 2030.[2] The advancements in colon cancer survival can be attributed to increased screening with colonoscopy and close monitoring of precancerous and non-invasive lesions.[3-5] Unfortunately, while precursor lesions for pancreatic cancer have been identified, an effective screening modality has not yet been determined.

For pancreatic adenocarcinoma, several precursor lesions have been recognized including epithelial and cystic neoplastic lesions. Cystic precursor lesions have been classified and include intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs).[6] Epithelial adenocarcinoma precursor lesions

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were first described in 1905.[7] The lesions have since been defined in a multitude of terms including metaplasia, hyperplasia, and dysplasia in the literature. In 2001, a new uniform nomenclature system was put forth by international consensus that classified these lesions as pancreatic intraepithelial neoplasia (PanIN).[8] PanINs were then divided into 3 major subgroups: PanIN-1, PanIN-2, and PanIN-3. Like colon cancer, PanINs demonstrate a stepwise progression from a benign lesion to invasive pancreatic ductal adenocarcinoma (PDAC).[9] Two recent publications, however have suggested an association of higher grades of PanIN lesions in resected pancreata (part of the pancreas), with better overall survival.[10, 11] The objective of our study was to evaluate the prevalence and significance of PanIN-3 lesions in PDACs and IPMNs and the impact on overall survival.

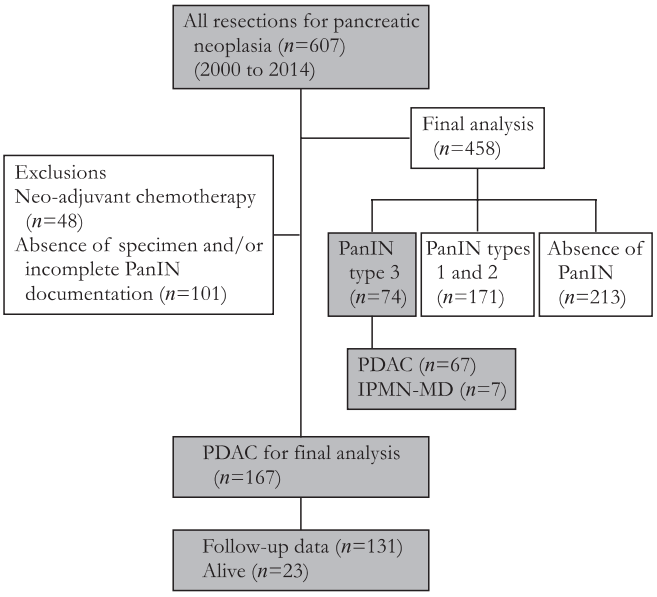

Fig. 1. Study schema. PanIN: pancreatic intraepithelial neoplasia; PDAC: pancreatic ductal adenocarcinoma; IPMN-MD: intraductal papillary mucinous neoplasm-main duct.

Methods

Patients

Our study is a retrospective pathology database analysis of all pancreatic resections between January 2000 and June 2014 at The Ohio State University Wexner Medical Center. An approval from the Institutional Review Board (IRB #: 2013C0044) was obtained prior to data collection and analysis. Inclusion criteria included all adult patients with surgical resections involving the pancreas for neoplastic lesions. Only patients with comprehensive pathology reports and where specimen was available for review were included in the final analysis. An independent pathologist was assigned for reviewing cases where pathology report was incomplete. Patients who received neo-adjuvant chemotherapy were excluded from the study (Fig. 1).

Variables

A comprehensive data collection involving patient history, demographics, imaging, endoscopic ultrasound (EUS), laboratory, histopathology, operative report, and follow-up were collected using the institution's electronic medical record system. When reviewing the pathology report, the highest PanIN grade documented was assigned to each patient. Furthermore, histopathological evidence of chronic pancreatitis, lymphovascular invasion (LVI), perineural invasion (PNI), tumor differentiation, and post-resection pathologic staging were included. The location of the resected pancreas lesion was determined through the patient's imaging, operative, pathology, and EUS report.

Definitions

Our institution utilized the PanIN definitions set forth by international consensus in 2001.[8] In accordance with 2001 guidelines, PanIN is defined as neoplastic epithelial proliferations in smaller caliber pancreatic ducts that measure less than 0.5 cm. PanIN has been divided into three major grades. PanIN-1 lesions are defined as flat, papillary, micropapillary, or basally pseudostratified lesions made of tall columnar cells with nuclei that are round to oval in shape. PanIN-2 lesions are defined as either flat or papillary epithelial lesions with nuclear atypia. PanIN-3 lesions are papillary, micropapillary, or rarely flat epithelial lesions with significantly more nuclear atypia including loss of nuclear polarity and dystrophic goblet cells. Cribiforming and luminal necrosis is also noted. While PanIN-3 does resemble pancreatic adenocarcinoma, there is no invasion through the basement membrane.[11, 12]

IPMNs and MCNs were defined as cystic mucin-producing pancreatic lesions per the World Health Organization (WHO) guidelines. Ovarian-type stroma and lack of communication with the main pancreatic duct is considered a distinguishing feature of MCN and assists in differentiating the two cystic lesions. IPMNs have conventionally been categorized as main duct (IPMN-MD), branch duct (IPMN-BD), and mixed lesions based on imaging or pathologic grossing and histology.[6]

The resection margin status was documented as per the American Joint Committee on Cancer guidelines. R0 resection was defined as a grossly complete resection with microscopically negative margins; an R1 resection was defined as a grossly complete resection with microscopically positive margins; and an R2 resection was