

## ORIGINAL ARTICLE

# Jaundice: an important, poorly recognized risk factor for diminished survival in patients with adenocarcinoma of the head of the pancreas

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## Abstract

**Objectives:** Jaundice impairs cellular immunity, an important defence against the dissemination of cancer. Jaundice is a common mode of presentation in pancreatic head adenocarcinoma. The purpose of this study was to determine whether there is an association between preoperative jaundice and survival in patients who have undergone resection of such tumours.

**Methods:** Thirty possible survival risk factors were evaluated in a database of over 400 resected patients. Univariate analysis was used to determine odds ratio for death. All factors for which a *P*-value of <0.30 was obtained were entered into a multivariate analysis using the Cox model with backward selection.

**Results:** Preoperative jaundice, age, positive node status, poor differentiation and lymphatic invasion were significant indicators of poor outcome in multivariate analysis. Absence of jaundice was a highly favourable prognostic factor. Interaction emerged between jaundice and nodal status. The benefit conferred by the absence of jaundice was restricted to patients in whom negative node status was present. Five-year overall survival in this group was 66%. Jaundiced patients who underwent preoperative stenting had a survival advantage.

**Conclusions:** Preoperative jaundice is a negative risk factor in adenocarcinoma of the pancreas. Additional studies are required to determine the exact mechanism for this effect.

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## Introduction

Adenocarcinoma of the head of the pancreas is an aggressive cancer with a poor prognosis. In 1886, Nicolas Senn, one of the fathers of pancreatic surgery, described the association of jaundice with cancer of the head of the pancreas in his book *Surgery of the Pancreas*.<sup>1</sup> He wrote: 'It is demonstrated that jaundice is an invariable symptom of primary scirrhous [referring to cancer] of the head of the pancreas, while it is uncommon when the disease

affects the body or tail of the organ.'<sup>1</sup> Jaundice is still recognized as one of the most common presenting signs in patients with ductal adenocarcinoma of the pancreatic head, and occurs in approximately 75% of this population.<sup>2</sup> Jaundice has been shown to cause immunosuppression in animals and humans.<sup>3-6</sup> It also reduces sinusoidal blood flow within the liver, which is associated with increased rolling and sticking of leukocytes.<sup>7</sup> As a result, jaundice may promote tumour growth or metastatic implantation in the liver. The purpose of this study was to determine whether there is an association between preoperative jaundice and longterm survival in patients who have undergone resection of such tumours.

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## Materials and methods

### Patients and database

All patients who underwent pancreaticoduodenectomy or total pancreatectomy for adenocarcinoma of the head of the pancreas during the period from 1 February 1995 to 28 February 2010 were selected from an institutional pancreaticoduodenectomy database. Since 2007, the database has been prospectively maintained. For the period prior to 2007, the database was populated from medical records. The database and studies derived from it are approved by the institutional review board. The database contains the variables listed in Table 1. The presence of 'jaundice' simply means that the medical record stated that clinical jaundice was observed before referral to the surgical service or developed after referral but prior to surgery. In almost all patients, the former was true. Results for serum bilirubin were the highest values available. However, in many cases patients were stented prior to referral and bilirubin levels at the primary institution were not retrospectively retrievable. Therefore, the bilirubin levels available were not necessarily the highest recorded at the time a patient presented with jaundice. The cut-off values for laboratory tests and tumour sizes were selected prior to analysis and were not altered based on results.

### Operative procedures

A Whipple procedure with antrectomy was the standard procedure performed. Pylorus-sparing pancreatoduodenectomy and total pancreatectomy were performed occasionally. Frozen sections of the pancreatic neck and bile duct margins were obtained routinely in the resected specimen. If the pancreatic neck margin was positive, additional pancreas was resected until a negative margin was obtained, or total pancreatectomy was performed. This was the main indication for total pancreatectomy.

### Pathological analysis

Surgical specimens were inked in the operating room in the presence of a pathologist. Four coloured inks were used for the pancreatic neck margin, mesenteric vein margin, uncinate margin and posterior margin, respectively. When a venous resection was performed, the intimal surface of the vein was not inked (i.e. the intravascular surface of the vein was not considered to be a margin). All margins were microscopically evaluated and graded as R0 (microscopically negative) or R1 (microscopically positive at margin or tumour within 1 mm of the margin). Specimens were also evaluated by microscopy for lymphatic, venous and nerve invasion. Cancers that arose in an intraductal papillary mucinous neoplasm (IPMN) or a mucinous cystic neoplasm, or which were described as having mucinous features were not included in the analysis. This was true whether these pathologies were identified preoperatively by imaging and in the pathological specimen or in the pathological specimen only. In the latter, the pathologist recorded that the tumour had mucinous features or appeared to arise in an IPMN.

**Table 1** Variables tested in 412 patients

Variable		Missing, n
Age at surgery, years, mean $\pm$ SD	65.4 $\pm$ 10.4	
Gender, male, n (%)	214 (51.9%)	
Race,		
White, n (%)	371 (90.1%)	
Other, n (%)	41 (10.0%)	
Weight loss, n (%)	265 (70.3%)	Missing 35
Jaundice, n (%)	333 (81.0%)	Missing 1
Hypertension, n (%)	218 (53.0%)	Missing 1
Diabetes mellitus, n (%)	132 (32.1%)	Missing 1
Chronic pancreatitis, n (%)	35 (8.5%)	Missing 1
Tobacco use, n (%)		Missing 4
Current	106 (26.0%)	
Past	157 (35.8%)	
Never	156 (38.4%)	
Family history of, n (%)		
Pancreatic cancer	36 (9.5%)	Missing 34
Other gastrointestinal cancer	58 (15.3%)	Missing 33
Non-gastrointestinal cancer	186 (48.4%)	Missing 28
Haematocrit <25, n (%)	8 (2.0%)	Missing 4
Platelet count <250 000/mm <sup>3</sup> , n (%)		Missing 9
Yes	185 (45.9%)	
No	218 (54.1%)	
AST >100 IU, n (%)	97 (24.6%)	Missing 17
Bilirubin >20 mg/dl <sup>a</sup> , n (%)	15 (3.8%)	Missing 13
Albumin <3.0 mg/dl, n (%)	34 (8.5%)	Missing 10
CA 19-9 >100 IU, n (%)	106 (46.9%)	Missing 186
ERCP stent, n (%)	274 (79.0%)	Missing 65
Surgery type, n (%)		Missing 7
Standard	336 (83.0%)	
Pylorus-sparing Whipple	41 (10.1%)	
Total pancreatectomy	28 (6.9%)	
Vascular resection, n (%)	131 (31.9%)	Missing 1
Estimated blood loss $\leq$ 500 ml, n (%)	167 (41.7%)	Missing 11
Tumour size, n (%)		Missing 17
<2.0 cm	94 (23.8%)	
2.0–2.9 cm	147 (37.2%)	
3.0–3.9 cm	97 (24.6%)	
$\geq$ 4 cm	57 (14.4%)	
Histological grade, n (%)		Missing 7
Good	24 (5.9%)	
Moderate	197 (48.6%)	
Poor	184 (45.4%)	
Lymphatic invasion, n (%)	227 (62.5%)	Missing 49
Venous invasion, n (%)	177 (49.3%)	Missing 53
Perineural invasion, n (%)	314 (84.0%)	Missing 38
Surgical margins, n (%)		Missing 3
R0	294 (71.8%)	
R1	115 (28.1%)	
N-stage, n (%)		Missing 4
N0	119 (29.2%)	
N1	289 (70.8%)	
M-stage, n (%)		
M0	408 (98.9%)	
M1	4 (1.1%)	

<sup>a</sup>Normal range: 0.1–1.0 mg/dl. Other patients may have had bilirubin levels as high as this before being stented at outside institutions. Such results, if they occurred, were unavailable. SD, standard deviation; AST, aspartate transaminase; CA 19-9, carbohydrate antigen 19-9; ERCP, endoscopic retrograde cholangiopancreatography; N-stage, nodal stage; M-stage, metastatic stage.

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