

ORIGINAL ARTICLE

# Assessment of the effect of interval from presentation to surgery on outcome in patients with peri-ampullary malignancy

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## Abstract

**Background:** Delay between diagnosis of peri-ampullary cancer (PC) and surgery may allow tumour progression and affect outcome. The aim of this study was to explore associations of interval to surgery (IS) with pathological outcomes and survival in patients with PC.

**Method:** A database review of all patients undergoing surgery between 2006 and 2014 was undertaken. IS was measured from diagnosis by imaging. Potential association between IS and survival was measured using Cox regression analysis, and between IS and pathological outcome with multivariate logistic analysis.

**Results:** 388 patients underwent surgery. The median IS was 49 days (1–551 days), and was not associated with any of the evaluated outcomes in patients with pancreatic (149) or distal bile duct (46) cancer. For patients with ampullary cancer (71) longer IS was associated with improved survival, with median survival of 27.5 months for patients waiting  $\leq$  median IS (35) and 38.3 months for patients waiting  $>$  median IS (36) for surgery ( $p = 0.041$ ). A higher rate of margin positivity (31.4%) was also noted among patients who waited less than the median IS compared to those waiting longer than this interval (11.4%) ( $p = 0.032$ ).

**Conclusion:** For patients with ampullary cancer there is a paradoxical improvement in outcome among those with a longer IS, which may be explained by progression to inoperability of more aggressive lesions.

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## Introduction

Peri-ampullary cancer (PC) most commonly originates within the pancreas, the distal common bile duct, or the duodenal ampulla. The organ of origin of PC is usually determined by pathological examination after resection and has important implications for prognosis. Five-year survival after surgical resection varies from 6.5%–20% for pancreatic cancer,<sup>1–7</sup> 19.2%–30% for bile duct cancer<sup>1,3,5,6,8,9</sup> and 33%–45% for ampullary cancer.<sup>1,3,5,6</sup> For many patients their disease is

inoperable at the time of presentation due to local invasion or the presence of distant metastases. For those with operable tumours there will usually be an interval between radiological diagnosis and surgery, to allow referral, assessment and operative planning. In England, the National Cancer Plan stipulates a maximum interval of 62 days from primary referral to treatment for most solid cancers,<sup>10</sup> although this figure is not based on evidence of safety for each tumour type. Tumour progression may take place during this interval, rendering tumours inoperable and long-term survival may potentially be affected.

Within any patient cohort there is likely to be a range of intervals between diagnosis and surgery, with some patients

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undergoing surgery very quickly, and some waiting many months. As PC is an aggressive malignancy, this period may constitute a significant part of the natural history of the disease. Analysis of the potential association of interval to surgery with pathological and surgical outcomes may reveal aspects of the behaviour of these tumours, and determine if the 62 day target to surgery disadvantages patients by allowing tumour progression.

This study aimed to investigate the interval to surgery in a consecutive series of patients undergoing surgery with the intention to resect PC and to explore the association of IS to resectability, tumour stage and overall survival.

## Material and methods

Review of a prospectively maintained database of consecutive patients undergoing surgical exploration for suspected PC between January 2006 and May 2014 was undertaken. Referrals came from five hospitals in a cancer network with a population of 1.7 million. The study cohort included patients with a histological diagnosis of pancreatic, bile duct or ampullary cancer, or those where the tumour was unresectable and biopsy confirmed the presence of adenocarcinoma. Patients receiving neoadjuvant chemotherapy were excluded. No patients were excluded from surgery due to disease progression in the interval between referral and surgery. Demographic and clinical data were retrieved. Pre-operative biliary obstruction was defined as any abnormality in liver function tests sufficient to prompt investigation by cross sectional imaging. As the time of receipt of the initial referral is variable and subject to administrative delays, the interval to surgery (IS) was measured from the date of the first imaging modality undertaken which raised the possible diagnosis of PC to the time of the surgical intervention, by review of individual radiology records. Surgical resection was performed by a classic Whipple resection with reconstruction by pancreatico-

gastrostomy. Pathological reporting was undertaken according to Royal College of Pathologists guidelines<sup>11</sup> with axial slicing of the resection specimen. Tumours were classified according to histological origin (pancreatic, bile duct or ampullary) and nodal status and margin involvement status were retrieved from histology reports.

Continuous variables were compared with Kruskal–Wallis test and categorical variables by Chi square test. The mean and variance of tumour size across different tumour types were compared using Bayesian double generalised linear models.

Dates of death were determined by access to General Practice records and survival times calculated from the time of diagnosis. Kaplan–Meier survival analysis and Cox Proportional Hazard models were used to assess the effect of interval to surgery on post-operative survival. Multivariate logistic regression models were then used to explore potential associations between pre-operative variables including IS as a binary variable (< or  $\geq$  median) with histological tumour stage.

## Results

388 patients (223 (57%) males) with a median (range) age 67 (41–86) years fulfilling the study criteria underwent surgical exploration during the study period and resection was completed in 266 patients (69%). In 122 (31%) patients the tumour was found to be inoperable due to local invasion of vascular structures ( $n = 70$  (57%)) or the development of distant metastases ( $n = 47$  (63%)). Operative details could not be retrieved in three (1%) patients, tumour mass could not be identified in one patient and one patient did not tolerate surgery. Lateral resections of a small venous patch were undertaken in 32 (12%) patients. The median IS for 388 patients was 49 (1–551) days, and was similar in groups undergoing resection (49 days, range 1–551) or surgical exploration only (50 days, range 11–512) ( $p = 0.940$ ).

**Table 1** Interval to surgery and pathological outcome among 266 patients undergoing resection of peri-ampullary cancer

n = 266 (%)	Cancer Origin			p
	Pancreas n = 149 (56%)	Bile duct n = 46 (17%)	Ampulla n = 71 (27%)	
Median age (range)	67.9 (41.3–82.1)	65.7 (43.7–84.1)	66.2 (41.2–86.4)	0.312
Gender (% male)	55	69.6	53.5	0.171
ASA (%)				0.056
1	6 (4)	4 (8.7)	9 (12.7)	
2	84 (56.4)	22 (47.8)	42 (59.2)	
3	44 (29.5)	15 (32.6)	14 (19.7)	
4	1 (0.7)	0	0	
Missing	14 (9.4)	5 (10.8)	6 (8.4)	
Median IS (range) (days)	48 (1–551)	50 (5–294)	51 (14–477)	0.881
Median tumour size (range) (mm)	30 (12–70)	22 (10–70)	25 (5–80)	0.002
Involved lymph nodes (%)	127 (85.2)	26 (56.5)	40 (56.3)	0.0001
Involved resection margin (%)	119 (79.9)	23 (50)	15 (21.1)	0.0001
30 day post-operative mortality	3 (2)	0	3 (4.2)	0.275

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