Pathology (April 2014) **46(3)**, pp. 188–192

ANATOMICAL PATHOLOGY

Frozen section of the pancreatic neck margin in pancreatoduodenectomy for pancreatic adenocarcinoma is of limited utility

TONY C. Y. PANG[1,2], OLIVER WILSON[1], MANUEL A. ARGUETA[1], THOMAS J. HUGH[1,2], ANGELA CHOU[3,4], JASWINDER S. SAMRA[1,2] AND ANTHONY J. GILL[1,3,5]

[1]Sydney Medical School, University of Sydney, [2]Department of Upper GIT Surgery, Royal North Shore Hospital, St Leonards, [3]Cancer Diagnosis and Pathology Group, Kolling Institute of Medical Research, St Leonards, [4]Anatomical Pathology, Sydpath, St Vincent's Hospital, Darlinghurst, and [5]Department of Anatomical Pathology, Royal North Shore Hospital, St Leonards, NSW, Australia

Summary

The use of frozen section to assess resection margins intraoperatively during pancreaticoduodenectomy facilitates further resection. However, it is unclear whether this actually improves patient survival. We reviewed the overall survival and resection margin status in consecutive pancreaticoduodenectomies performed for carcinoma. An R1 resection was defined as an incomplete excision ($\leq$1 mm margin); R0(p) resection as complete excision without re-resection and R0(s) resection as an initially positive neck margin which was converted to R0 resection after re-resection. Between 2007 and 2012, 116 pancreatoduodenectomies were performed for adenocarcinoma; 101 (87%) underwent frozen section of the neck margin which was positive in 19 (19%). Sixteen of these patients had negative neck margins after re-excision but only seven patients had no other involved margins [true R0(s) resections]. Median survival for the R0(p), R0(s) and R1 groups were 29, 16, 23 months, respectively ($p = 0.049$; R0(p) versus R0(s) $p = 0.040$). Intra-operative frozen section increased the overall R0 rate by 7% but this did not improve survival. Our findings question the clinical benefit of intraoperative margin assessment, particularly if re-excision cannot be performed easily and safely.

Key words: Frozen section, pancreatic adenocarcinoma, pancreatoduodenectomy, surgical margins.

Received 27 August, revised 15 October, accepted 17 October 2013

INTRODUCTION

The use of frozen section to assess resection margins intraoperatively during pancreaticoduodenectomy (PD) is based on two premises. The first is that frozen section allows for the further resection of involved margins and therefore increases the rate of R0 resection.[1] The second is the assumption that a complete R0 resection improves outcome.[2–4] Whilst frozen section has been shown to increase the rate of R0 excision, two large retrospective studies have suggested that it does not improve overall survival.[1,5]

A major area of contention in the recent literature has been over the prognostic significance of positive resection margins in pancreatic cancer. Whilst some groups have reported that excision margin status does not hold prognostic significance, others have reported that it does. A fair reading of the literature suggests that when sub-specialist pathologists rigorously and systematically assess resection margin status after PD, there is usually a high rate of R1 excision (from 57% to 85%) and in these studies the excision status seems to be a strong predictor of outcome.[6–10]

In essence it appears that a low rate of incomplete excision may be a reflection of less rigorous (or at least less predictive) pathological assessment rather than being a true reflection of the excision margin status. Indeed without any other intervention, three separate groups have reported that the introduction of a standardised and rigorous approach to the pathological reporting of pancreatic cancers increased the number of PD reported as being incompletely excised from 40 to 57%, from 45 to 59% and from 14 to 76%.[6,7,9]

Studies which have previously failed to show a survival advantage for intraoperative frozen section examination have been criticised for demonstrating a low rate of R1 excision (23–30%) with the implication that pathological assessment of the final resection margin status may have been incomplete and that therefore some of the apparently R0 resections may actually represent false negatives of the final pathological assessment.[10]

Since mid-2006 all our PD specimens have been reported by experienced sub-specialist pathologists using a standardised reporting protocol with particular emphasis placed on rigorous assessment of resection margin status, particularly the periuncinate retroperitoneal margin.[7] Therefore, we sought to examine the impact of frozen section examination on this cohort of patients specifically to determine whether it improved the R0 excision rate or overall survival.

PATIENTS AND METHODS

All patients who underwent PD between 2007 and 2012 for pancreatic carcinoma at Royal North Shore Hospital, a tertiary referral centre in Sydney, were identified using the Department of Anatomical Pathology database. Specifically, ampullary cancers, neuroendocrine tumours, cholangiocarcinomas, intraductal papillary mucinous neoplasms and benign diseases were excluded from this study whilst pancreatic ductal adenocarcinomas, acinar cell carcinomas ($n = 1$), adenosquamous carcinomas ($n = 2$) and undifferentiated carcinomas ($n = 2$) were included. Basic demographic, clinical and pathological data were extracted from patient records.

An R1 resection margin was defined as tumour within 1 mm of any of the resection margins. R0 resection was defined as tumour beyond 1 mm of the

Print ISSN 0031-3025/Online ISSN 1465-3931
DOI: 10.1097/PAT.0000000000000072

resection margin. An R0 resection which was achieved without the need for re-resection was defined as 'primary R0 resection' [R0(p)]. Those patients with initially positive pancreatic neck margins who were converted to R0 resection after re-resection were classified as 'secondary R0 resections' [R0(s)]. None of the patients underwent an R2 resection.

Overall survival was defined by survival censored at last follow-up or at death by any cause.

Clinical protocol

Patients were excluded from resection if there was metastatic disease, tumour encasement or abutment of more than 180 degrees of the superior mesenteric artery or coeliac axis, or if there was an occluded mesentericoportal venous system.[11] Our surgical technique involves an aggressive approach to resection and reconstruction of the portal vein if it is safe to do so provided R0/R1 resection is thought to be possible.[12,13]

Frozen section assessment of the neck and common bile duct (CBD) margin was requested at the surgeons' discretion after resection and prior to reconstruction. If the pancreatic neck margin was found to be positive ($\leq$1 mm margin), re-resection was performed with the aim of achieving a clear pancreatic neck margin.

Pathological protocol

A standardised synoptic protocol was used for both macroscopic and microscopic pathological assessment as outlined previously.[7] Briefly, both the frozen section dissections and the final dissection of the formalin fixed, paraffin embedded tissue were performed under the direct supervision of an experienced pathologist with particular expertise in pancreatic cancer. At frozen section the entire pancreatic neck margin was embedded as serial sections perpendicular to the transected neck margin, usually three to four sections per case. Once the specimen was fixed, the pancreas was bivalved and as a minimum the following additional margins were sampled for histological analysis: the common bile duct margin (single transverse section, all embedded), duodenal and intestinal margins (single section each), anterior surface of the pancreas (single section minimum), the true posterior margin (which *in vivo* would abut the aorta and vena cava, single section minimum) and the superior mesenteric vein bed (minimum of one longitudinal section). Most importantly, the periuncinate retroperitoneal soft tissue margin (also known as the true retroperitoneal margin or the 'mesopancreatic margin' which is defined as the soft tissue on the posteromedial aspect of the uncinate process) was carefully identified and either all embedded or thoroughly sampled (3–4 blocks minimum).

Statistical methods

Descriptive statistics used mean (standard deviation) and median (interquartile range) as appropriate. Inferential statistical comparisons between groups used Fisher's exact test, Student's *t*-test (or analysis of variance) and Kruskal–Wallis test for categorical, parametric and non-parametric data, respectively. Each pair of groups was compared as a post-test, with *p* value correction with Sidak's method unless otherwise specified. Survival was described with Kaplan–Meier curves and comparison between groups was performed using log-rank test. Multivariate analysis was not performed due to the small sample size. A *p* value of less than 0.05 was considered statistically significant. All statistical analyses were performed with Stata SE version 11.2 for Windows (Statacorp, USA).

RESULTS

Patient and tumour characteristics

The patient and tumour characteristics are summarised in Table 1 and Fig. 1. Briefly, there were 116 patients with a mean age of 68 years. Sixty-four (55%) were males. There was one acinar cell carcinoma, two adenosquamous carcinomas and two undifferentiated carcinomas in the series, with the remainder being conventional adenocarcinomas.

Table 1 Summary of patient and tumour characteristics

		All patients	R0(p)	R0(s)	R1	*P* value	
		Mean (SD, range) or *n* (%)		Mean (95% CI) or *n* (%)		Overall	Multiple comparison*
Patient characteristics							
n		116 (100)	42 (36)	7 (6)	67 (58)	–	
Age (years)		68 (10, 34–85)	69 (66–72)	61 (46–76)	68 (66–70)	0.17	
Sex	F	52 (45)	23 (55)	1 (14)	28 (42)	0.10	
	M	64 (55)	19 (45)	6 (86)	39 (58)		
Tumour characteristics							
Size (mm)		37 (14, 8–100)	34 (30–39)	45 (28–61)	38 (35–41)	0.17	
Location	Head	108 (93)	41 (98)	7 (100)	60 (90)	0.24	
	Unc	8 (7)	1 (2)	0 (0)	7 (10)		
Grade†	G1	8 (7)	27 (66)	5 (71)	47 (70)	0.89	
	G2	71 (62)					
	G3	31 (27)	14 (34)	2 (29)	20 (30)		
	G4	5 (4)					
T stage†	T1	3 (3)	7 (17)	1 (14)	1 (1)	**0.013**	R0(p) vs R1 **0.009**;
	T2	6 (5)					R0(s) vs R1 0.13;
	T3	104 (90)	35 (83)	6 (86)	66 (99)		R0(p) vs R0(s) 1.00
	T4	3 (3)					
LN Involved	No	30 (26)	15 (36)	2 (29)	13 (19)	0.16	
	Yes	86 (74)	27 (64)	5 (71)	54 (81)		
Perineural invasion	No	33 (28)	20 (48)	3 (43)	10 (15)	**0.001**	R0(p) vs R1 **0.0003**;
	Yes	83 (72)	22 (52)	4 (57)	57 (85)		R0(s) vs R1 0.18;
							R0(p) vs R0(s) 1.00
Vascular invasion	No	40 (34)	18 (43)	2 (29)	20 (30)	0.36	
	Yes	76 (66)	24 (57)	5 (71)	47 (70)		
Survival							
Median OS (months)		25 (18–31)	29 (18–NR)	16 (5–28)	23 (16–31)	**0.049**	R0(p) vs R0(s) **0.040;**
							R0(s) vs R1 0.31;
							R0(p) vs R1 0.42

The neck margin described is that which was present prior to re-resection
* Multiple comparison post-test with Sidak's correction. Group comparisons only shown if global test were significant.
† Grade and T stage divided into two groups for statistical analysis (G1–2, G3–4 and T1–2, T3–4).
CI, confidence interval; F, female; LN, lymph node; M, male; NR, not reached; OS, overall survival; SD, standard deviation; Unc, uncinate process.