Systematic review

Meta-analysis of radical resection rates and margin assessment in pancreatic cancer

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Background: **R0 resection rates (complete tumour removal with negative resection margins) in pancreatic cancer are 70–80 per cent when a 0-mm margin is used, declining to 15–24 per cent with a 1-mm margin. This review evaluated the R0 resection rates according to different margin definitions and techniques.**

Methods: **Three databases (MEDLINE from 1946, PubMed from 1946 and Embase from 1949) were searched to mid-October 2014. The search terms included 'pancreatectomy OR pancreaticoduodenectomy' and 'margin'. A meta-analysis was performed with studies in three groups: group 1, axial slicing technique (minimum 1-mm margin); group 2, other slicing techniques (minimum 1-mm margin); and group 3, studies with minimum 0-mm margin.**

Results: **The R0 rates were 29 (95 per cent c.i. 26 to 32) per cent in group 1 (8 studies; 882 patients) and 49 (47 to 52) per cent in group 2 (6 studies; 1568 patients). The combined R0 rate (groups 1 and 2) was 41 (40 to 43) per cent. The R0 rate in group 3 (7 studies; 1926 patients) with a 0-mm margin was 72 (70 to 74) per cent The survival hazard ratios (R1 resection/R0 resection) revealed a reduction in the risk of death of at least 22 per cent in group 1, 12 per cent in group 2 and 23 per cent in group 3 with an R0 compared with an R1 resection. Local recurrence occurred more frequently with an R1 resection in most studies.**

Conclusion: **Margin clearance definitions affect R0 resection rates in pancreatic cancer surgery. This review collates individual studies providing an estimate of achievable R0 rates, creating a benchmark for future trials.**

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Paper accepted 5 June 2015

Published online 9 September 2015 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.9892

Introduction

Pancreatic cancer has a poor prognosis, with only around 20 per cent of patients having potentially resectable disease after staging[1]. After full assessment including co-morbidities, only 7–12 per cent of patients undergo operative resection[2,3]. Worldwide rates of complete tumour resection with negative resection margins (R0 resection) on final pathology have ranged between 70 and 80 per cent for pancreatic cancer surgery in the past. Since 2005, with the advent of detailed three-dimensional pathological assessment in Europe, R0 resection rates have declined remarkably to 15–24 per cent[4–7].

Although many centres in Europe and Australia have adopted the minimum 1-mm margin to define an R0 resection, some centres still use the 0-mm minimum margin definition[8,9]. These differences make comparisons between studies and trials difficult. However, a recent consensus statement by the International Study Group

of Pancreatic Surgery (ISGPS)[10] on borderline resectable tumours has suggested a 1-mm margin for R0 resection with recommendations on minimum reporting on seven margins, which include the anterior, posterior, superior mesenteric vein (SMV) groove, superior mesenteric artery (SMA), bile duct (BD) and enteric margins. However, the paper does cite Jamieson and colleagues[11], who found no prognostic significance associated with involvement of the anterior margin and posterior margins. Although the 1-mm margin is increasingly endorsed, a more rigorous margin clearance of 2 mm has been proposed as a superior prognostic factor for overall survival[12].

Recent studies have reported wide variation in R0 resection rates. The reasons for this lie in the lack of international consensus on the definition of microscopic margin involvement, the definition of what constitutes the circumferential resection margin in pancreaticoduodenectomy specimens, and the lack of a standard protocol for the examination of these specimens[13].

The aims of this meta-analysis were to evaluate the rates of R0 and R1 (resection margin involved by tumour cells) resection among patients undergoing pancreatic resection for pancreatic cancer according to the minimum 1- and 0-mm margin clearance definitions, and to assess whether differences in pathological examination affected the R0 rates and the sites of margin involvement. Correlations with recurrence and survival were also examined among studies reporting these outcomes.

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[14]. Three databases (MEDLINE from 1946, PubMed from 1946 and Embase from 1949) were searched to the second week of October 2014. The search terms included 'pancreatectomy OR pancreaticoduodenectomy' and 'margin'.

Study selection

The studies included patients who underwent a pancreatic resection (pancreaticoduodenectomy, distal pancreatectomy and total pancreatectomy) for pancreatic adenocarcinoma. Studies were included only if their method of margin assessment was clearly described and margins were analysed with either a 0- or 1-mm margin. Studies that included combined results for other periampullary cancers such as ampullary, distal BD and duodenal cancers were excluded. Studies restricted to borderline or advanced pancreatic cancers, as defined by the authors, or that combined data from several different pathological assessment techniques during the course of the study, were excluded. Studies that were unclear in their pathological assessment of margins were also excluded, as were non-English-language studies.

Data extraction

Data extraction was done using a standard form. Information collected included: year of publication, origin, number of pancreatic resections, margin assessment, slicing techniques (axial *versus* other), R0/R1 rates by 0- *versus* 1-mm definitions, size of tumours if available, stage of tumours if available, survival data if available, use of neoadjuvant and adjuvant treatment, and vascular resection rates.

Study groups by pathological margin assessment

Studies were analysed according to their minimum margin assessment of 0 *versus* 1 mm. Studies that analysed a 1-mm margin using the axial slicing technique were grouped together, because this technique has been reported to be associated with the lowest R0 rates[15], in order to form a more homogeneous group in terms of pathological technique. The data were analysed in three groups: group 1, axial slicing technique with minimum 1-mm margin for R0; group 2, other slicing techniques with minimum 1-mm margin for R0; and group 3, studies that used a minimum 0-mm margin for R0.

In R1 resections, reported site of margin involvement was analysed. Margins reported in the studies were the medial margin, SMA margin, retroperitoneal margin, uncinate margin, SMV/portal vein (PV) margin, pancreatic transection margin, BD margin, proximal gastric or duodenal margin, distal duodenal/jejunal margin and anterior surface. Owing to the different terminology used for margin reporting, some margins were grouped together for analysis. Studies reporting involvement of the SMA, medial, uncinate and retroperitoneal margins had these margins grouped together as one category, the SMA/medial margin. Some studies described the medial margin as the vascular margin, and may have assessed the PV/SMV margin rather than the SMA margin. The PV/SMV margin, where reported, was analysed as a distinct margin category.

Statistical analysis

The R0 rates from each of the identified trials were pooled using the inverse-variance method to obtain the overall pooled proportion together with 95 per cent c.i. (fixed-effect model) using the statistical program StatsDirect[16]. The degree of heterogeneity present was

quantified using the I^2 statistic and tested using Cochran's Q test, with $P < 0{\cdot}050$ indicating the presence of statistical heterogeneity. I^2 values of 25, 50 and 75 per cent corresponded to low, moderate and high degrees of heterogeneity respectively[17]. Publication bias was quantified using Egger's regression model[18].

Differences in survival between R0 and R1 are described as hazard ratios (R1/ R0). Studies that reported recurrence rates are analysed with descriptive statistics to assess for trends in terms of recurrence with either an R0 or R1 resection.

Results

Nineteen studies[4–6,12,19–33] met the inclusion criteria (*Fig. 1*). There were eight[4–6,12,19–22] studies in group 1 (axial slicing technique; 882 patients) and six[23–28] in group 2 (other slicing techniques; 1568) reporting the R0 resection rate using the minimum 1-mm margin (*Table 1*). There were seven studies[19,23,29–33] in group 3 (1926 patients) that reported R0 resection using the minimum 0-mm margin (*Table 2*). The studies by Chang and colleagues[23] and Delpero and co-workers[19] included assessment of both 0- and 1-mm margins, and were each included in two groups.

Studies reporting a minimum 1-mm margin for R0 resection

R0 rates with a 1-mm margin

The majority of studies using the axial slicing technique assessed a minimum of six margins, with six[4,5,19–22] of eight studies analysing seven margins (*Table 1*). The pooled R0 rate in group 1 using the axial slicing technique was 29 (95 per cent c.i. 26 to 32 per cent). There was high heterogeneity between studies ($I^2 = 76$ per cent, $P < 0{\cdot}001$) and little evidence of publication bias ($P = 0{\cdot}81$) (*Fig. 2*). When the study by Gebauer and colleagues[12], which is an outlier in this group, was excluded from analysis, the heterogeneity between studies disappeared ($I^2 = 14$ per cent, $P = 0{\cdot}33$) with only a small change in the results. The latter study assessed only five margins, unlike the majority. Given that neoadjuvant treatment could increase R0 rates, the R0 rate in group 1 was also analysed after excluding studies that employed neoadjuvant treatment[19,20]. The R0 rate dropped slightly from 29 per cent to 28 (24 to 32) per cent.

Studies using other slicing techniques reported assessment of a minimum of four margins, with two[23,26] of six studies analysing more than six margins (*Table 1*). The pooled R0 rate in group 2 with other slicing techniques was 49 (47 to 52) per cent. There was high heterogeneity

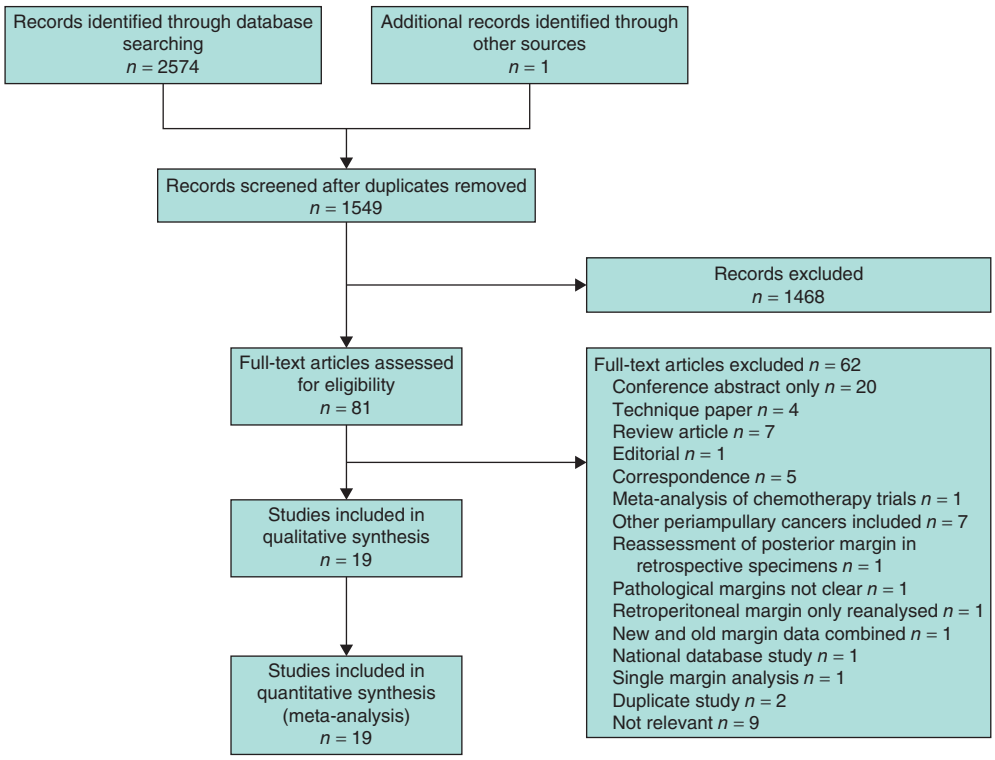

Fig. 1 PRISMA flow diagram showing selection of articles for review

Table 1 Studies reporting R0 resection with a minimum 1-mm margin according to pathological slicing technique

Reference	Slicing technique	Margins examined	*n*	R0 (%)	Median overall survival (months)	Hazard ratio (R1/R0)
Group 1: axial slicing technique						
Campbell *et al.*[6] (2009)	Axial	PT, MM, PM, PG, DD, BD	163	21	R0: 25·4 R1: 15·4	0·61
Delpero *et al.*[19] (2014)	Axial (median 12 slices, studied in 0·5-mm increments)	PT, SMA, PV/SMV, PM, PG, DD, BD	150	32	n.r. Analysed with minimum 0-mm margin	n.a.
Esposito *et al.*[5] (2008)	Axial 3–5 mm slices	PT, PV/SMV, PM, PG, DD, BD, AS	111	24	Median not reached 1-year overall survival R0: 86% R1: 64% Median overall survival from this and a larger cohort[8] R0: 30·9 R1: 19·7	0·34
Gebauer *et al.*[12] (2015)	Axial	PT, PV/SMV, PM, BD, AS	118	48	R0: 17·3 R1: 13·5	0·78
Jamieson *et al.*[20] (2013)	Transverse plane from D2 lumen into head of pancreas	PT, MM, PM, PG, DD, BD, AS	217	28	R0: 26·6 R1: 16·5	0·62
John *et al.*[21] (2013)	Axial	PT, PV/SMV, PM, PG, DD, BD, AS	70	26	R0: 22.4 R1: 16·3	0·73
Menon *et al.*[22] (2009)	Axial	PT, PV/SMV, PM, PG, DD, BD, AS	27	19	R0: not reached at 55 months' follow-up R1: 14	n.a.
Verbeke *et al.*[4] (2006)	Axial	PT, PV/SMV, PM, PG, DD, BD, AS	26	15	R0: 37 R1: 11	0·30
Overall pooled R0 rate			*882*	*29 (26, 32)*		
Group 2: other slicing techniques						
Chang *et al.*[23] (2009)	Combination of longitudinal (perpendicular to pancreatic duct) and axial	PT, SMA, PV/SMV, RPM (left-sided resections), PG, DD, BD	365	48	R0: 18·5 R1: 15·6	0·84
Gnerlich *et al.*[24] (2012)	n.a.	PT, PV/SMV, PM, uncinate, BD	285	66	R0: 21·7 R1: 16·4	0·76
Konstantinidis *et al.*[25] (2013)	Perpendicular sectioning	PT, SMA, PM, BD	554	36	R0: 35 R1: 15	0·43
Pang *et al.*[26] (2014)	Entire or near entire (minimum 3 or 4 blocks) periuncinate margin embedded	PT, uncinate, PV/SMV, PM, PG, DD, BD, AS	116	42	R0: 29 R1: 23	0·79
Sugiura *et al.*[27] (2013)	Radial 5-mm sections	PT, SMA, PM, BD	208	64	R0: 26 R1 (0 mm): 23	0·88
Westgaard *et al.*[28] (2008)	Serial perpendicular sectioning of RPM	PT, RPM, PG, DD, BD	40	55	R0: 1.3 years R1: 0·9 years	0·69
Overall pooled R0 rate			*1568*	*49 (47, 52)*		

Values in parentheses are 95 per cent c.i. PT, pancreatic transection margin; MM, medial margin; PM, posterior margin; PG, proximal gastric/duodenal margin; DD, distal duodenal/jejunal margin; BD, bile duct margin; SMA, superior mesenteric artery margin; PV, portal vein margin; SMV, superior mesenteric vein margin; n.r., not reported; n.a., not available; AS, anterior surface of pancreas; RPM, retroperitoneal margin. Fuller details can be found in *Table S1* (supporting information).

Table 2 Studies reporting R0 resection with a minimum margin of 0 mm (group 3)

Reference	Slicing technique	Margins examined	*n*	R0 (%)	Median overall survival (months)	Hazard ratio (R1/R0)
Chang *et al.*[23] (2009)	Combination of longitudinal (perpendicular to pancreatic duct) and axial	PT, SMA, PV/SMV, RPM (left-sided resections), PG, DD, BD	365	64	R0: 19·6 R1: 13·2	0·67
Delpero *et al.*[19] (2014)	Axial	PT, SMA, PV/SMV, PM, PG, DD, BD (PT, BD positivity not included)	150	70	R0: 32·9 (22·7, not reached) R1: 17·7 (11·7, 36·4)	0·54
Howard *et al.*[29] (2006)	n.a.	PT, RPM, PG, DD, BD	226 (5 R2)	70	R0: 14 R1: 9 Above calculated from survival > 3 years R0: 17% R1: 6%	0·63
Kimbrough *et al.*[30] (2013)	*En face*	PT, RPM/uncinate	283	73	R0: 22·7 R1: 15·0	0·66
Mathur *et al.*[31] (2014)	Perpendicular, *en face* for BD, SMA	PT, SMA, uncinate, PM, BD, PG, DD, AS	448	75	R0: 20 R1: 12 R1 → R0 (after intraop. frozen-section analysis and further resection in 40 patients): 14	0·60
Raut *et al.*[32] (2007)	*En face* section (2–3 mm) for BD/PT/SMA After 2000, SMA margin perpendicular sections	PT, SMA, BD	360	83	R0: 27·8 R1: 21·5	0·77
Rau *et al.*[33] (2012)	Axial (median 4 (range 3–6) axial sections)	PT, MM (includes SMV), PM, PG, DD, BD, AS	94 (1 Rx)	48	R0: 18·0 (3·8, 84·8) R1: 13·8 (2·1, 48·2)	0·77
Overall pooled R0 rate			*1926*	*72 (70, 74)*		

Values in parentheses are 95 per cent c.i. PT, pancreatic transection margin; SMA, superior mesenteric artery margin; PV/SMV, portal vein/superior mesenteric vein margin; RPM, retroperitoneal margin; PG, proximal gastric/duodenal margin; DD, distal duodenal/jejunal margin; BD, bile duct margin; PM, posterior margin; n.a., not available; AS, anterior surface of pancreas; MM, medial margin. Fuller details can be found in *Table S2* (supporting information).

between studies ($I^2 = 95$ per cent, $P < 0{\cdot}001$) and no publication bias ($P = 0{\cdot}49$) (*Fig. 3*).

In a study of 554 patients by Konstantinidis and colleagues[25], 397 patients had an R0 resection and 157 had an R1 resection using a 0-mm margin. Some 339 (85 per cent) of 397 patients with an R0 resection were assessed using the 1-mm minimum margin clearance, of whom 170 (50 per cent) of 339 had an R0 resection. For the present analysis, it was assumed that half of the 397 patients had an R0 resection using the minimum 1-mm margin in order not to underestimate the R0 rate. This equated to 199 (36 per cent) of 554 R0 resections.

Most commonly involved margins with R1 resections

The most commonly involved margins in R1 resections with the axial slicing technique were the PV/SMV margin, which was involved in over 50 per cent of R1 resections in five[4,5,19,21,22] of six studies reporting this, and the posterior margin, which was involved, in over 50 per cent of resections in five[4,6,19,21,22] of eight studies (*Table 3*). In three studies[6,19,20] that reported the SMA/medial margin, this was involved in 36–54 per cent of R1 resections with the axial slicing technique. All studies reported pancreatic neck margin involvement, which ranged from 4 to 30 per cent of R1 resections.

The most commonly involved margin in R1 resections (tumour-positive resection margins) with the other slicing techniques was the SMA/medial margin, which was involved in 48–78 per cent of R1 resections in four studies[24–27] reporting this margin. Three studies[24,25,27] reported involvement of the posterior margin in over 30 per cent of R1 resections. Two studies[24,25] reported

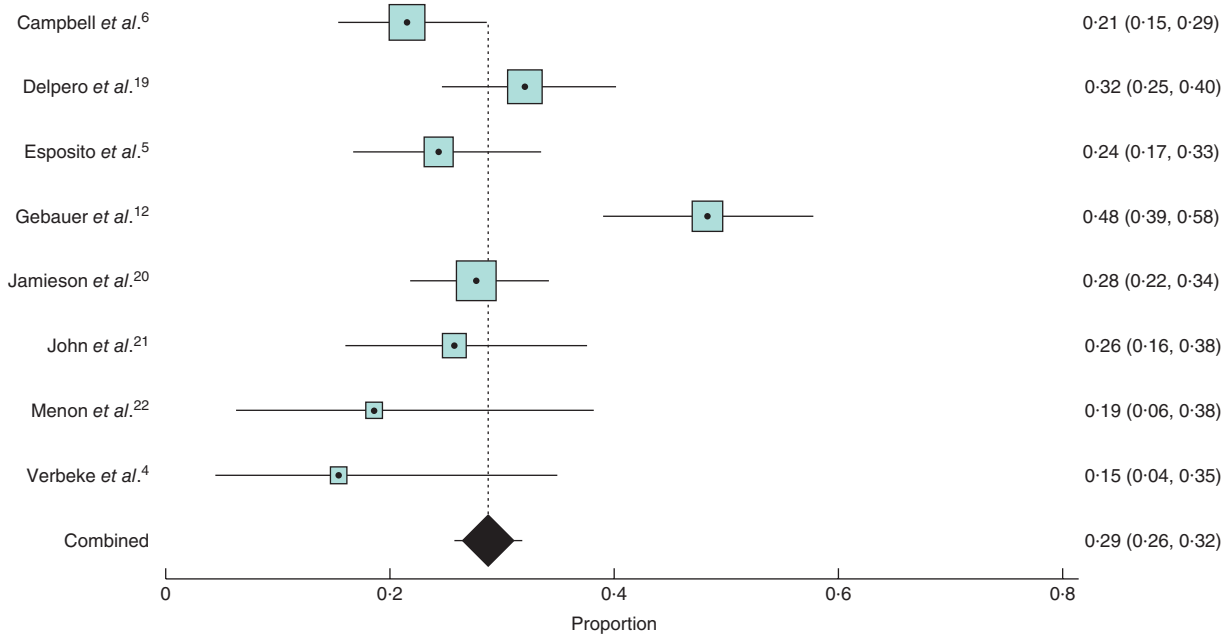

Fig. 2 Meta-analysis of R0 rates (1-mm margin) using the axial slicing technique. Rates are shown with 95 per cent c.i. A fixed-effect model was used for meta-analysis. Test for heterogeneity $P < 0{\cdot}001$, $I^2 = 76$ per cent; publication bias $P = 0{\cdot}81$

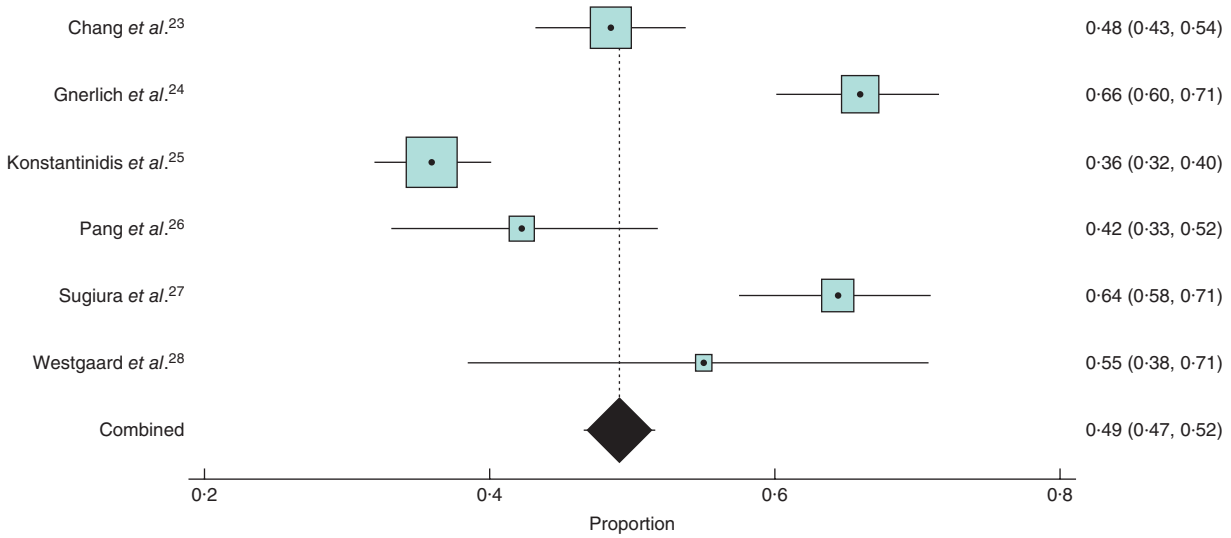

Fig. 3 Meta-analysis of R0 rates (1-mm margin) using the other slicing techniques. Rates are shown with 95 per cent c.i. A fixed-effect model was used for meta-analysis. Test for heterogeneity $P < 0{\cdot}001$, $I^2 = 95$ per cent; publication bias $P = 0{\cdot}49$

involvement of the PV/SMV margin in 26 and 63 per cent of R1 resections respectively. Four studies[24–27] reported pancreatic neck margin involvement, which ranged from 10 to 39 per cent.

Survival hazard ratios

The survival hazard ratios (R1/R0) with the axial slicing technique ranged from 0·30 to 0·78; patients with an R0 resection therefore had a minimum 22 per cent reduction in risk of death compared with patients with an R1 resection.

The survival hazard ratios (R1/R0) with other slicing techniques in group 2 ranged from 0·43 to 0·88; patients with an R0 resection therefore had a minimum 12 per cent reduction in their risk of death compared with patients with an R1 resection.

Table 3 Margin involvement in R1 resections

	Margins positive in R1 resections							
	Pancreatic neck margin	Superior mesenteric artery/medial/uncinate/ retroperitoneal margin	Portal vein/ superior mesenteric vein margin	Posterior margin	Proximal gastric/ duodenal margin	Distal duodenal/ jejunal margin	Bile duct margin	Anterior surface of pancreas
Group 1	80 of 628 (13)[4–6,12,19–22]	186 of 387 (48)[6,19,20]	199 of 343 (58)[4,5,12,19,21,22]	304 of 628 (48)[4–6,12,19–22]	10 of 369 (3)[5,6,20]	0 of 285 (0)[6,20]	17 of 584 (3)[5,6,12,19–21]	88 of 398 (22)[4,5,12,20–22]
Group 2	50 of 256 (20)[24–27]	143 of 256 (56)[24–27]	67 of 164 (41)[24,25]	80 of 238 (34)[24,25,27]	n.r.	n.r.	3 of 159 (2)[26–28]	0 of 18 (0)[28]
Group 3	96 of 285 (34)[19,23,32,33]	188 of 285 (66)[19,23,32,33]	31 of 177 (18)[19,23]	11 of 45 (24)[19]	3 of 180 (2)[23,33]	0 of 132 (0)[23]	10 of 237 (4)[19,23,32]	n.r.

Values in parentheses are percentages. n.r., Not reported.

Recurrence rates

Most of the studies did not provide data on recurrence. In the axial slicing group, Esposito and colleagues[5] reported that local recurrence developed after 10 per cent of R1 resections. Jamieson *et al.*[20] noted local recurrence after 38 per cent of R0 resections, and 44 per cent of R1 resections; distant recurrence rates were 28 and 40 per cent respectively.

In the other slicing techniques group, Gnerlich and co-workers[24] reported local recurrence after 27 per cent of R0 resections and 39 per cent of R1 resections. Sugiura and colleagues[27] reported that local recurrence developed after 8 per cent of R0 resections and 34 per cent of R1 resections; respective distant recurrence rates were 88 and 81 per cent.

Studies reporting a 0-mm margin for R0 resection

R0 rates with a 0-mm margin

Four[19,23,31,33] of seven studies reported assessment of a minimum of six margins (*Table 2*). The pooled R0 rate using a 0-mm margin (group 3) was 72 (95 per cent c.i. 70 to 74) per cent. There was high heterogeneity between studies ($I^2 = 91$ per cent, $P < 0{\cdot}001$) (a random-effects analysis yielded substantially similar results) and significant publication bias ($P = 0{\cdot}04$) (*Fig. 4*). The study by Rau and colleagues[33] had the lowest R0 rate, which may relate to their modified Verbeke technique for margin assessment, with a median of 4 sections (range 3–6 sections). Exclusion of the studies[19,32] that included patients with neoadjuvant treatment resulted in the R0 rate falling from 72 per cent to 69 (67 to 72) per cent.

Most commonly involved margins (R1 resections)

The most commonly involved margin in R1 resections with a 0-mm margin was the SMA/medial margin, which was involved in 33–92 per cent of R1 resections in four[19,23,32,33] studies reporting this (*Table 3*). Four studies[19,23,32,33] reported involvement of the pancreatic neck margin in 18–49 per cent of R1 resections.

Survival hazard ratios

The survival hazard ratios (R1/R0) with a 0-mm margin ranged from 0·54 to 0·77; patients with an R0 resection therefore had a minimum 23 per cent reduction in risk of death compared with patients who had an R1 resection.

Recurrence rates

Most of the studies did not provide data on recurrence. Raut and colleagues[32] reported local recurrence after 8 per cent of R0 resections and 7 per cent of R1 resections; distant recurrence rates were 42 and 45 per cent respectively. Rau *et al.*[33] reported that local recurrence developed following 33 per cent of R0 resections and 58 per cent of R1 resections; corresponding distant recurrence rates were 58 and 51 per cent.

Discussion

This review has shown that the definition of margin clearance (0 *versus* 1 mm) and the method of pathological margin assessment is an important factor in R0 resection rates reported in different series. Studies with a minimum 1-mm margin employing the axial slicing technique (group 1) examined more margins and had the lowest R0 rate. These studies evaluated a minimum of six margins with R0 rates of 29 (95 per cent c.i. 26 to 32) per cent, whereas studies using other slicing techniques (group 2), which evaluated a minimum of four margins, had R0 rates of 49 (47 to 52) per cent. The combined R0 rate when a minimum 1-mm margin was used (groups 1 and 2) was 41 (40 to 43) per cent and may serve as a more relevant baseline in studies that employ a variation in histopathological assessment of margins. The R0 rates achieved with a 0-mm margin were much higher (group 3) at 72 (70 to 74) per cent.

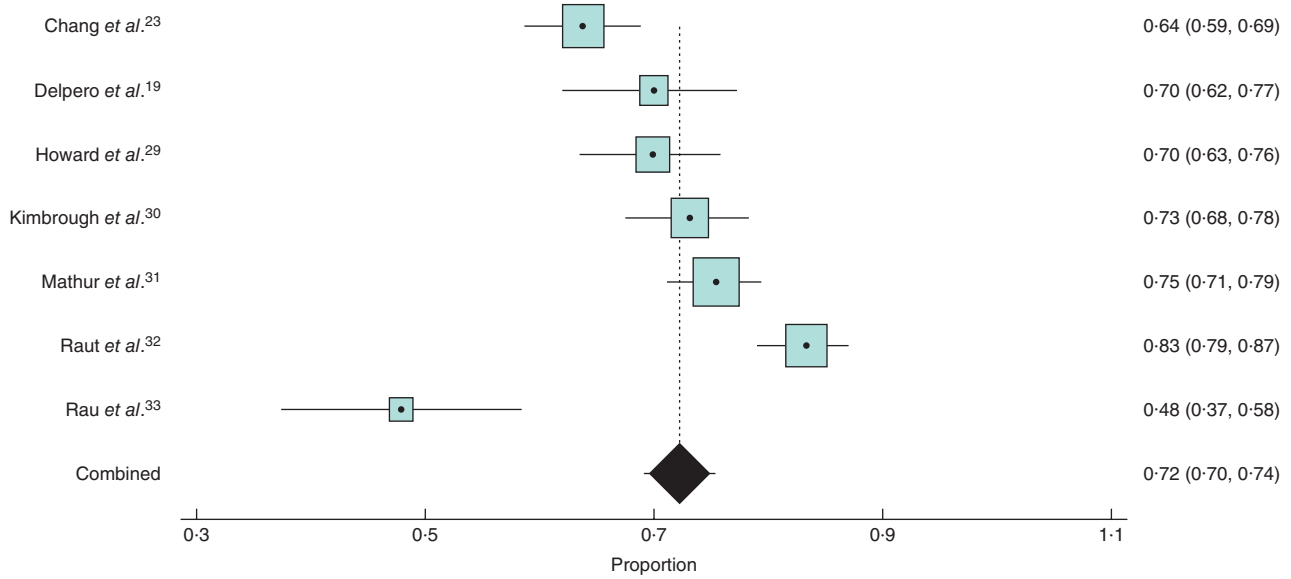

Fig. 4 Meta-analysis of R0 rates in studies that used a 0-mm margin. Rates are shown with 95 per cent c.i. A fixed-effect model was used for meta-analysis. Test for heterogeneity $P < 0{\cdot}001$, $I^2 = 91$ per cent; publication bias $P = 0{\cdot}04$

Although it is well known that the definition of margin clearance affects R0 rates, this review provides a comprehensive overview of studies giving some indication of achievable R0 rates in pancreatic cancer surgery depending on pathological assessment. A limitation of many of these studies, and hence the present combined analysis, is that it is not clear how much differences in patient selection and variation in surgical techniques may have contributed to the R0 rates. Neoadjuvant treatment did not seem to influence the R0 resection rate to a great extent. Based on studies reported by Chang and colleagues[23] and Delpero *et al.*[19], where R0 rates were reported for both the 0- and 1-mm margin clearance definitions in the same patient population, it is clear that margin definition is a major driver of R0 rates. Ultimately, technical factors and biology need to be factored in to assess the impact of margin outcomes more fully, but this was beyond the scope of this article given the limited data reported on this[41].

This review indicates that the most commonly involved margins are the SMA/medial, PV/SMV and posterior margins. However, these margins do not have equal prognostic significance. Multifocal margin involvement with an R1 resection was reported in 32–45 per cent of R1 procedures in three[4–6] studies. Jamieson and colleagues[11] analysed pancreatic margins by mobilization margins (anterior and posterior margins) and transection margins (pancreatic transection margin, medial margin and adjacent transection margins). Involvement of the mobilization margins alone was associated with a much longer median survival than involvement of the transection margin (median survival 18·9 *versus* 11·1 months; $P < 0{\cdot}001$). Delpero *et al.*[19] similarly found that a positive posterior margin had no impact on progression-free survival. It is clear from this that the anterior and posterior margins have a lesser impact on survival than the pancreatic transection margins, and that each margin may have different prognostic significance. It was not possible to analyse the data to extrapolate the prognostic role of each individual involved margin. This would be useful in future studies, but will depend on studies reporting a minimum set of margins.

Increasing margin clearance has been shown to affect survival. The use of the 0-mm margin in adjuvant pancreatic cancer studies may explain why R1 status was not identified as a significant factor for survival in a meta-analysis of adjuvant randomized clinical trials[1]. The transition to using a minimum 1-mm margin has been driven by the observation that resection with an overtly involved margin at 0 mm has similar outcomes to resections in which tumour is found within 1 mm of the resection margin[6,25]. In the studies by Chang and colleagues[23] and Jamieson *et al.*[20], it was not until the resection margin was clear by more than 1·5 mm that long-term survival was achieved. Gebauer and co-workers[12] reported that median overall survival in patients with a tumour margin clearance of less than 2 mm was lower than that in patients with a margin clearance of 2 mm or more (15·1 *versus* 22·2 months; $P = 0{\cdot}046$). This may mean that dispersed cancer cells can remain despite a clear resection margin, requiring greater clearance to

ensure no cancer is left behind. This may explain the improvement in survival with greater margin clearance[15].

Although increasing the minimum margin to 2 mm may well further define those with improved survival, it is clear that this will also reduce the achievable R0 rates. In a large series of 1071 consecutive patients, Hartwig and colleagues[8] showed that the newly revised R0 rate using a 1-mm margin was an independent positive predictor for survival on multivariable analysis. This suggests that, in large series with standardized pathology, an R0 rate endpoint should be based on a minimum margin of 1 mm to assess the gains from surgery in improving survival in resectable pancreatic cancer.

The survival hazard ratios (R1/R0) across both margin definitions in groups 1 and 3 were consistent with a minimum 22–23 per cent reduction in the risk of death from an R0 resection compared with an R1 resection. Although the survival hazard ratios show a similar proportional reduction in the risk of death, this does not take into account the baseline risk or therefore the absolute risk reduction, as a 22 per cent reduction in the risk of death at 10 months is not the same as a similar risk reduction at 20 months. Therefore, although the hazard ratios are similar across definitions, this does not mean that baseline survival across definitions or the absolute benefit from an R0 resection are similar. It was not possible to calculate a pooled estimate of median survival in those with an R0 or R1 resection because the data are heterogeneous in terms of follow-up time and use of neoadjuvant and adjuvant treatment, which significantly affects survival. Of note, studies with a high R0 rate do not necessarily have the longest survival, and a low R0 rate in a given study may not necessarily equate to poorer survival for the study group. This suggests that survival in pancreatic cancer is more affected by a complex interplay of numerous factors, including tumour characteristics and biology, as well as the use of adjuvant and neoadjuvant treatment, rather than the extent of surgery. Studies using neoadjuvant therapy in primarily resectable cancers tend to report better survival. This may in part be explained by the exclusion of patients with early systemic progression.

Several studies have shown that pursuing negative margins after positive intraoperative frozen-section analysis portends a poorer survival than that in patients with negative margins on initial intraoperative frozen sections, and the pursuit of negative margins did not result in the intended survival benefit[26,31,42–44]. It has been proposed that R1 tumours may be inherently more biologically aggressive; this may relate to differences in tumour size or stage, but this finding has not been consistent across all the studies reviewed[45]. It would make sense that larger tumours are more likely to result in R1 resections. Kimbrough *et al.*[30] found that R1 resections had a higher incidence of microvascular invasion, positive lymph node ratio and perineural invasion, without any differences in tumour size between R0 and R1 tumours. Similarly, Gebauer and colleagues[12] reported that, although R1 tumours were more likely to have nodal and lymphovascular invasion, there was no statistical difference in the size of R0 and R1 tumours. However, in other studies[25,31,32], R1 tumours were larger than R0 tumours. This was similarly found in the study by Campbell and co-workers[6], where increasing tumour size significantly increased the likelihood of an R1 resection.

The pattern of recurrence and failure following pancreatic resection offers insight into the poor survival with this disease. Most of the studies did not provide data on recurrence. Local recurrence developed more frequently after R1 than R0 resection in most studies. Although local recurrence has been shown to occur frequently from an autopsy study in patients who had curative resection of pancreatic cancer, this is rarely the cause of death[46]; most patients die from metastatic disease. The aim of radical surgery is to remove all site-specific macroscopic and microscopic tumour, but this has no effect on occult systemic disease. The aim of multimodal therapies is to eliminate this micrometastatic disease. As systemic therapies improve outcomes, durable local control becomes more important to the quality of patients' subsequent survival.

The variable follow-up in all studies to date makes it difficult to evaluate the impact of achieving an R0 resection on recurrence. To make meaningful inferences from recurrence data, the assessment for recurrence and the follow-up time for this needs to be prospective, uniform and standardized. This is relevant for future studies because local control becomes more important as survival improves with systemic treatment; local recurrence causes substantial morbidity and compromises effective palliation and quality of life. The ability to predict the risk of local and distant recurrence by margin status will help guide the use of adjuvant local therapies such as radiation, and also guide the development of neoadjuvant treatments that increase resectability, and in so doing potentially affect both survival and local control.

Although a high R0 rate is clearly desirable, it is evident that the more rigorous the pathological assessment, the less likely a high R0 rate is to be achieved. This review revealed that there were several different terms used for the same margins. The medial margin was also referred to as the uncinate or SMA margin in the reviewed studies. The retroperitoneal margin included the posterior margin in some studies in addition to the SMA margin. The PV/SMV margin was another margin reported by some

Table 4 Proposal for standardized pancreatic margin reporting

Minimum margin	Clearly defined and reported
	Both 0- and 1-mm margin clearances noted
Slicing techniques	Axial slicing
Number of sections	3–5-mm sections
Minimum margin assessment	8 margins
Individual margin reporting	Pancreatic neck margin
	Superior mesenteric artery margin (not using terms such as medial or uncinate margin)
	Portal vein/superior mesenteric vein margin
	Anterior surface
	Posterior margin (mobilization margin)
	Bile duct margin
	Proximal gastric/duodenal margin
	Distal duodenal/jejunal margin

studies; although this is known as the margin adjacent to the PV/SMV venous groove, this was not clearly defined in the studies. These different terminologies cause confusion and make comparisons between studies difficult, as the terms are synonymous in some instances but not in others[44,47]. Although examining more margins meticulously with extensive tissue sampling clearly increases the R1 rate, consensus on terminology, definition of microscopic margin involvement and the use of synoptic reporting for standard assessment[15] is essential to allow valid and robust comparison between centres, and to avoid the current wide variations in reported R0 and R1 rates[48,49]. It is clear from *Table 3* that studies do not report all the margins they analysed. Other unresolved issues include the number of sections examined, which can reduce the risk of underestimating margin involvement as a result of a sampling error. For example, if two standard tissue blocks are taken from a 1-cm area suspected of tumour involvement, only 1/1000th of the tissue of interest is examined[15]. Furthermore, the definition of a positive margin needs to be standardized; consideration needs to be given to the implications of tumour cells within blood vessels, lymphatics, perineural spaces and lymph nodes, and 'isolated solitary ductal units' that appear in the adipose tissue, on margin status[6,15,50].

Future pancreatic cancer trials should adopt uniform approaches to pathological assessment and interpretation of margins. These should include a standard approach to macroscopic dissection, and use of standard terminology for different anatomical margins, which should probably be a minimum of eight margins. Standard interpretation of involved margins should include a set cut-off for the definition of involved margins, noting both the 0- and 1-mm margin clearances (*Table 4*). This will require a collaborative effort from surgeons and pathologists in marking and staining the specimens adequately to identify these individual margins. Although the axial technique has gained popularity in Europe, it is practised less elsewhere, and it would be useful if this technique were adopted internationally to allow comparisons between trials. Although some margins clearly have a greater prognostic role than others, standard reporting of a minimum of eight margins – the pancreatic neck margin, the SMA margin (and doing away with other terms such as the medial or uncinate margin, as previously suggested[51]), PV/SMV margin, anterior surface, posterior margin, BD margin, proximal gastric/duodenal margin and distal duodenal/jejunal margin – will allow more robust data analysis to assess the prognostic significance of each individual margin and also whether these relate to recurrence patterns. The initiators of this study identified the most active hepatopancreatobiliary surgeons in Australia to ensure the broadest diversity of views so that a consensus was likely to be broadly acceptable. This study will hopefully lead closer towards standard margin reporting and assessment; once this is in place, it will be possible to assess properly whether margin status is an independent measure of recurrence and metastatic risk.

Margin reporting was examined in neoadjuvant studies in resectable pancreatic cancer to compare the impact of different regimens on R0 rate (*Table S3*, supporting information). It was found that neoadjuvant studies in resectable pancreatic cancer are not necessarily clear or similar in the assessment of pathological margins. Because this review demonstrates that these definitions affect the ultimate reported R0 rate, comparisons of R0 rates across studies are difficult. Future trials must address inconsistent terminology and pathological definitions to enable useful international multicentre comparisons to be made.

This review has highlighted that inconsistent terminology, lack of agreement on synoptic reporting guidelines, variation in pathological techniques and inconsistent pathological definitions are hampering international comparative analysis of outcomes and assessment of multimodal treatments for these difficult tumours. An international consensus definition for margin assessment and reporting needs to be agreed and, based on this analysis, it is recommended that a margin of 1 mm be adopted as the internationally accepted norm.

Collaborators

Collaborators in this study were: J. Fawcett (University of Queensland, Princess Alexandra Hospital, Brisbane, Queensland, Australia); P. S. Grimison (Department of Medical Oncology, Chris O'Brien Lifehouse and University of Sydney, New South Wales, Australia); C. Christophi

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Acknowledgements

The authors acknowledge grant support from Cancer Australia and Cancer Institute New South Wales for M.D.C. and the statistical analyses respectively.
Disclosure: The authors declare no conflict of interest.

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Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 Studies reporting R0 resection with a minimum 1-mm margin according to pathological slicing technique (Word document)

Table S2 Studies reporting R0 resection with a minimum margin of 0 mm (group 3) (Word document)

Table S3 Studies of neoadjuvant therapy in pancreatic cancer reporting R0 resection rates (Word document)

Snapshot quiz

Snapshot quiz 15/11

Question: What is this condition, and which procedure has the lowest recurrence rate after reduction and repair?

The answer to the above question is found on p. 1532 of this issue of *BJS*.

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