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Systematic Review

Prognostic relevance of the revised R status definition in pancreatic cancer: meta-analysis

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Abstract

Background: The prognostic impact of margin status is reported with conflicting results after pancreatic cancer resection. While some studies validated an uninvolved resection margin (R0) 1 mm or more of tumour clearance, others have failed to show benefit. This systematic review and meta-analysis aimed to investigate the effects of margin definitions on median overall survival (OS).

Methods: MEDLINE, Web of Science, and the Cochrane Central Register of Controlled Trials were searched for studies reporting associations between resection margins and OS between 2010 and 2021. Data regarding margin status (R0 circumferential resection margin (CRM) negative (CRM–), R0 CRM positive (CRM+), R0 direct, and R1 and OS were extracted. Hazard ratios (HRs) were pooled with a random-effects model. The risk of bias was evaluated with the Quality in Prognosis Studies (QUIPS) tool.

Results: The full texts of 774 studies were screened. In total, 21 studies compromising 6056 patients were included in the final synthesis. In total, 188 (24 per cent) studies were excluded due to missing margin definitions. The R0 (CRM+) rate was 50 per cent (95 per cent confidence interval (c.i.) 0.40 to 0.61) and the R0 (CRM–) rate was 38 per cent (95 per cent c.i. 0.29 to 0.47). R0 (CRM–) resection was independently associated with improved OS compared to combined R1 and R0 (CRM+; HR 1.36, 95 per cent c.i. 1.23 to 1.56).

Conclusion: The revised R status was confirmed as an independent prognosticator compared to combined R0 (CRM+) and R1. The limited number of studies, non-standardized pathology protocols, and the varying number of margins assessed hamper comparability.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is expected to become the second most common cause of cancer-related mortality in the USA by 2030[1], but approximately 20 per cent of patients are candidates for surgical resection (currently the only potential cure) at the time of diagnosis. Resection margins in PDAC have been traditionally considered an indicator of surgical quality for adequate oncological resections. However, the frequency of local recurrences seems to be at odds with the reported rates of R0 resections, which vary widely between 10 to 80 per cent, due to differences in definitions of what is included in the term R0[2,3]. New protocols for pathological assessment of resection specimens and a revised definition for resection margins have been introduced. Initially introduced in 2002 by the UK Royal College of Pathologists, a wide resection margin with R0 of 1 mm or more from tumour cells to the margin was endorsed as a revised definition of R status by the International Study Group of Pancreatic Surgery, as well as the 8th edition of the AJCC Cancer Staging Manual[4–9].

Although the importance of assessing circumferential resection margins (CRM) is now widely accepted, margins definition remains controversial[3]. The prognostic relevance of the revised R status[10] has been confirmed in some studies, while others have failed to demonstrate such an association[11]. Similarly, recent meta-analyses have reported conflicting results, given the lack of strict criteria for margin definitions or the inclusion of patients treated with neoadjuvant therapy[12,13]. Owing to this heterogeneity, widespread adoption of the revised R0 definition is lacking, hampering comparability between studies and outcomes[10,14].

This systematic review aimed to assess the prognostic role of the revised R status in patients with PDAC submitted to primary pancreatic resections undertaken with curative intent.

Methods

This study is reported according to the PRISMA guidelines[15].

Systematic literature search

A systematic literature search was performed in the MEDLINE, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) databases on 14 January 2021[16]. The following

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search strategy was used for MEDLINE with the search strategies for the other databases available upon request:

((('resection margin'[tiab] OR 'resection margins'[tiab] OR R1[tiab] OR R0[tiab] OR ((negative[tiab] OR positive[tiab]) AND margin*[tiab]) OR (prognostic[tiab] AND factor*[tiab]) OR prognosis[tiab] OR survival[tiab] OR (((lymph[tiab] AND node*[tiab]) OR nodal[tiab]) AND metastasis[tiab]) OR Prognosis [Mesh] OR 'Margins of Excision'[Mesh]))) AND ((((pancreas[tiab] OR pancreatic) AND (cancer*[tiab] OR neoplasm*[tiab] OR carcinoma[tiab] OR tumor*[tiab] OR tumour*[tiab] OR adenocarcinoma[tiab])) OR PDAC[tiab] OR 'ductal adenocarcinoma' [tiab] OR 'Pancreatic Neoplasms'[Mesh])) AND ((pancreaticoduodenectom*[tiab] OR pancreatoduodenectom* [tiab] OR pancreatectom*[tiab] OR duodenopancreatectom*[tiab] OR ((left[tiab] OR distal[tiab]) AND resection*[tiab]) OR Whipple[tiab] OR ppWhipple[tiab] OR dpphr[tiab] OR PPPD[tiab] OR Kausch-Whipple[tiab]) OR ('Pancreaticoduodenectomy'[Mesh] OR 'Pancreatectomy'[Mesh]) OR ((pancreas [tiab] OR pancreatic [tiab] OR pancreato*[tiab]) AND (resection* [tiab] OR removal [tiab] OR enucleation* [tiab])))) AND (2010:2021 [dp]).

Study selection

All randomized trials, observational studies with or without controls, and case series, providing hazard ratios (HRs) for the association of resection margin status and median overall survival (OS) in patients with PDAC who underwent primary resection intent, were included. To limit heterogeneity and associated differences in pathology protocols, the year 2010 as the publication date was chosen as a cutoff for the earliest inclusion date[12]. Exclusion criteria included pancreatic tumours other than PDAC, neoadjuvant chemotherapy, R2 resections, studies not reporting separate HRs, and those not providing detailed information on resection margin definitions. Reviews, meta-analyses, meeting abstracts, letters, comments, editorials, and publications without available full texts were excluded.

Titles and abstracts were independently reviewed by two investigators. Any disagreements were resolved by consensus.

Data extraction

The two reviewers independently extracted data using a standardized form, which included the following items: title; first author; country; year of publication; journal; study design and period; duration of follow-up; sample size; type of operation; adjuvant chemotherapy regimen; the applied definition of resection margin; examined margins; slicing technique; vascular resections; survival outcomes as median OS; and median time of follow-up.

To account for differences in terminology and to enable cross-comparison, data were extracted based on the distance of tumour cells to the margin. Subsequently, these data were grouped into four categories: R0 (CRM negative (CRM−)), corresponding to 1 mm or more tumour-free margin distance; R0 (CRM positive (CRM+)) with a tumour-free margin of less than 1 mm (classified as R1 in the revised definition)[10]; R1, with tumour cells directly at the resection margin; and R0 direct, with no tumour cells at the resection margin. Rates of margin status were pooled by meta-analysis of proportions.

Critical appraisal

The risk of bias and the quality of studies was assessed using the Quality in Prognosis Studies (QUIPS) tool[17]. The six respective domains, 'participation', 'attrition', 'prognostic factor measurement', 'confounding measurement and account', 'outcome measurement', and 'analysis and reporting' were graded as low risk, moderate risk, or high risk of bias for each study. Funnel plotting was performed to explore potential bias if more than 10 trials were available. Egger's test was performed in the case of funnel plot asymmetry[18].

Data handling and statistical analysis

The following comparisons between the four groups were performed:

- R1 *versus* R0 direct from on uni- (UV) and multivariable (MV) data
- R1 *versus* R0 (CRM+)
- R1 *versus* R0 (CRM−)
- R0 (CRM−) *versus* R0 (CRM+) from UV and MV data
- Given the small number of studies reporting HRs comparing R0 (CRM−) and R0 (CRM+) separately, and that R0 (CRM+) and R1 are frequently considered together or not fully diversified in some studies, these latter categories were combined: R0 (CRM+) with R1 *versus* R0 (CRM−) from UV and MV data.

Additionally, R0 (CRM+) with R1 was compared to R0 (CRM−) from studies reporting only UV data or MV data, respectively. A subgroup analysis, including all studies reporting HR for pancreatic head tumours, was performed. Data handling was the same as for the whole cohort.

Meta-analyses were carried out with R programming language[19]. Forest plots were generated. A random-effects model was used to account for study heterogeneity. Statistical heterogeneity among the estimated effect of the included studies was evaluated using the I^2 statistic. An I^2 of less than 25 per cent indicated low heterogeneity, while an I^2 of more than 75 per cent a high heterogeneity, with 25 to 75 per cent indicating moderate heterogeneity. HRs were pooled using a random-effects model according to DerSimonian and Laird[20].

Meta-regression was performed using a mixed-effects model with median follow-up time as a covariate to assess if follow-up time independently influenced results. Meta-regression was limited to group comparisons that included six or more studies.

Results

Study characteristics

A total of 10 459 articles were potentially eligible. After removing duplicates and screening titles and abstracts, the remaining 774 records were screened in full text. From these, 265 (34.2 per cent) studies were excluded because of other type of intervention or study design ($n = 195$; 25.2 per cent), no margin definitions ($n = 188$; 24.3 per cent), investigation of other tumours ($n = 29$; 3.7 per cent), and other reasons ($n = 76$; 9.8 per cent). A PRISMA flow chart is shown in *Fig. 1*. Finally, 21 studies were included in the qualitative and quantitative synthesis, including 6056 patients (*Table 1*). Of these, 14 were single-centre, while seven were multicentre studies. The majority ($n = 17$) were retrospective series, with four being prospective, two of which were randomized controlled trial. The multicentre trial by Delpero *et al.* prospectively enrolled patients to evaluate the prognostic implications of different resection margin definitions without any randomization procedure[14], while the study by Jamieson *et al.* mentions a prospective study design without further details[25].

On proportional meta-analysis, the R0 (CRM−) rate was 38 per cent (95 per cent confidence interval (c.i.) 29 to 47); the R0 (CRM+)

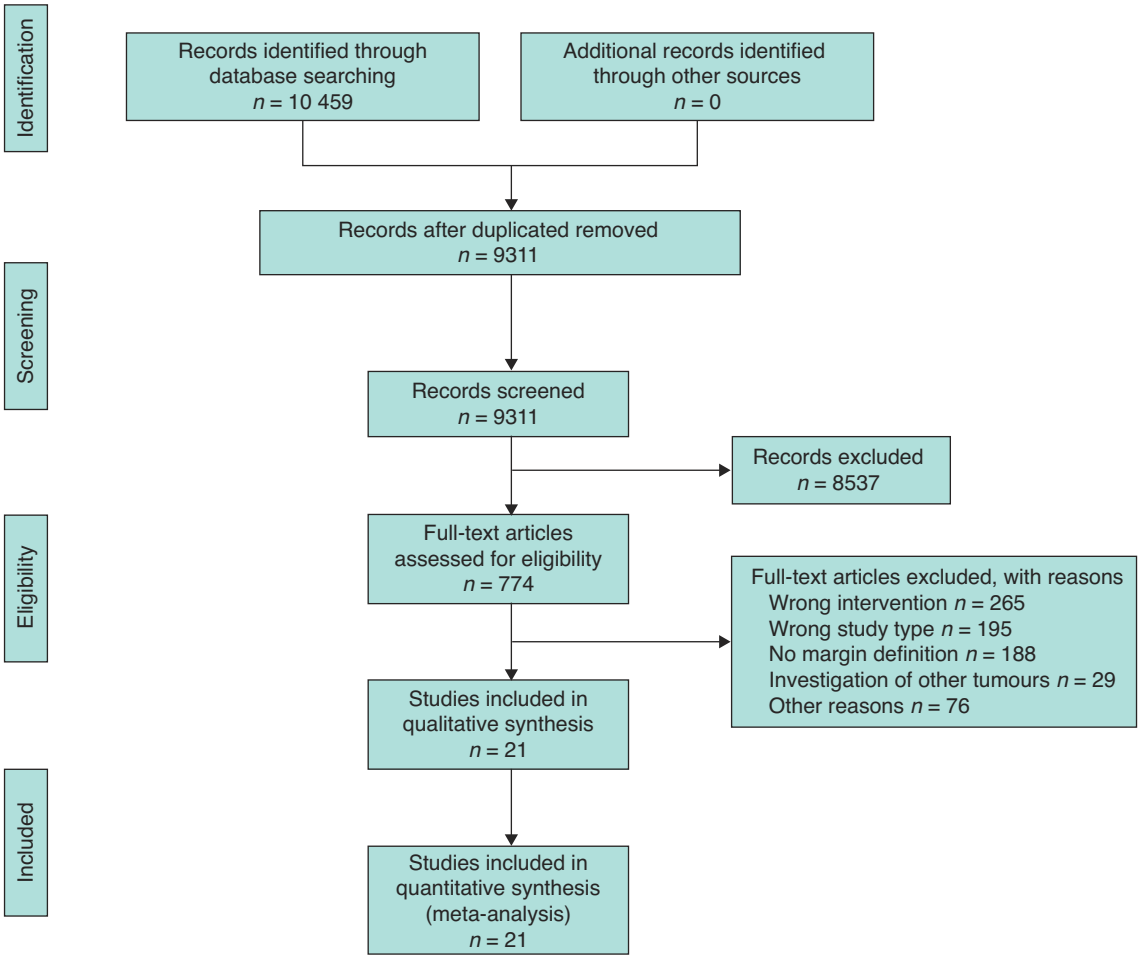


Fig. 1 PRISMA flow diagram for inclusion and exclusion of studies

rate was 50 per cent (95 per cent c.i. 40 to 61); the R1 rate was 30 per cent (95 per cent c.i. 20 to 43); and the R0 direct rate was 72 per cent (95 per cent c.i. 69 to 76) (*Fig. S1*).

In total, 4965 patients received either a Whipple pancreaticoduodenectomy (PD) or a pylorus-preserving PD. Of the remaining patients, 440 underwent a total pancreatectomy

Table 1 Studies included in the final qualitative and quantitative synthesis

First author	Publication year	Number of patients	Procedure	Margin definition*	Follow-up (months)
Gebauer[11]	2015	118	PD	Wide	17
Delpero[14]	2017	117	PD	Wide	83
Demir[12]	2018	254	PD, DP, TP	Wide	47
Neoptolemos[21]	2017	730	PD, DP, TP	Wide	43
Nitta[22]	2017	117	PD	Wide	47
Strobel[10]	2017	561	PD	Wide	29
van Roessel[23]	2018	531	PD	Wide	50
Hank[24]	2018	455	DP, TP	Wide	33
Jamieson[25]	2011	217	PD	Wide	20
Ghaneh[26]	2019	1151	PD, DP, TP	Wide	34
Serenari[27]	2019	99	n.s.	Wide	n.r.
Panaro[28]	2019	79	PD	Wide	30
Vuarnesson[29]	2013	188	PD	Wide	45
Kishi[30]	2019	500	PD	Narrow	n.r.
You[31]	2019	194	PD	Wide	17
Tummers[32]	2019	322†	PD, DP, TP	Wide	n.r.
Li[33]	2019	124	PD	Narrow	n.r.
Ocana[34]	2020	80	PD	Wide	n.r.
Di Martino[35]	2020	33	PD	Wide	n.r.
Pine[36]	2020	107	PD	Wide	30
Prochazka[37]	2020	79	PD, TP	Wide	n.r.

*Wide: 1 mm margin clearance; narrow: direct margin clearance. †Only PD used for association of overall survival and margin status. PD, pancreaticoduodenectomy; DP, distal pancreatic resection; TP, total pancreatectomy; n.s., not specified; n.r., not reported.

and 378 a distal pancreatic resection. One study of 99 patients did not specify the type of pancreatic resection performed[27]. The reported median OS in the entire cohort ranged from 12 months for patients with an R1 resection to 62.9 months for those with an R0 (CRM−) resection[22]. The median follow-up time varied between 17 and 83 months but was missing in seven studies (*Table 1*).

Risk of bias and study heterogeneity

The QUIPS tool showed a moderate risk of bias in most studies, as displayed in the funnel plots (*Fig. S2*). Egger's test did not reveal significant asymmetry of either funnel plot ($P = 0.22$ and $P = 0.11$, respectively).

Resection margin and overall survival

R1 *versus* R0 direct

Six studies were included in the analysis. Using UV data, the pooled HR for OS comparing R1 with R0 direct resections was 1.97 (95 per cent c.i. 1.52 to 2.56; $I^2 = 53$ per cent) (*Fig. 2a*). Five of the included studies showed that R0 direct resections were independently associated with an improved OS *versus* R1 resections (HR 1.77, 95 per cent c.i. 1.44 to 2.16; $I^2 = 24$ per cent) (*Fig. 2b*).

R1 *versus* R0 (CRM+) and R1 *versus* R0 (CRM−)

Seven studies reported HRs for survival differences between R1 and R0 (CRM+) resections (*Fig. 3a*). Tumour cells directly at the resection margin (R1) were associated with a worse OS than tumour cells less than 1 mm distance from the resection margin (R0 (CRM+); HR 1.50, 95 per cent c.i. 1.12 to 2.00 ($I^2 = 72$ per cent)). This association was even more pronounced comparing R1 *versus* R0 (CRM−) resections in five eligible studies (HR 1.77, 95 per cent c.i. 1.31 to 2.37; $I^2 = 67$ per cent) (*Fig. 3b*).

R0 (CRM−) *versus* R0 (CRM+)

Six studies reported separate HRs using UV data (*Fig. 4a*). The revised R0 definition with a margin clearance of 1 mm or more (R0 (CRM−) was associated with an improved OS *versus* R0 (CRM+) resections (HR 1.68, 95 per cent c.i. 1.10 to 2.56). Using MV data (reported in three eligible studies), no significant association was confirmed (HR 1.27, 95 per cent c.i. 0.82 to 1.96) (*Fig. 4b*). Pooled HR from UV and MV data had moderate study heterogeneity($I^2 = 71$ per cent and $I^2 = 65$ per cent, respectively).

R0 (CRM−) *versus* R0 (CRM+) and R1

R0 (CRM−) resections showed a statistically significant survival benefit compared with the combined category: R0 (CRM+) with R1 resections (HR 1.49, 95 per cent c.i. 1.32 to 1.69; $I^2 = 30$ per cent) (*Fig. 5a*). These results were confirmed when the UV (HR 1.68, 95 per cent c.i. 1.39 to 2.02; $I^2 = 14$ per cent) (*Fig. 5b*) and MV data (HR 1.40, 95 per cent c.i. 1.25 to 1.56; $I^2 = 14$ per cent) were considered separately (*Fig. 5c*). Studies reporting HR exclusively from MV analysis confirmed that R0 (CRM−) was significantly associated with an improved median OS (HR 1.36, 95 per cent c.i. 1.23 to 1.51; $I^2 = 0$ per cent) (*Fig. 5d*). A summary chart comparing the two resection margin status definitions is provided in *Fig. 6*.

Meta-regression analysis

Meta-regression analysis revealed that a median follow-up time of 83 months had an independent effect on results of R0 (CRM−) and R0 (CRM+) using MV data and between R0 direct and R1 using UV data ($P = 0.03$ and $P = 0.04$, respectively). In the meta-regression analyses of other subgroup analyses, follow-up time had no independent effect on median overall survival (*Table 1*).

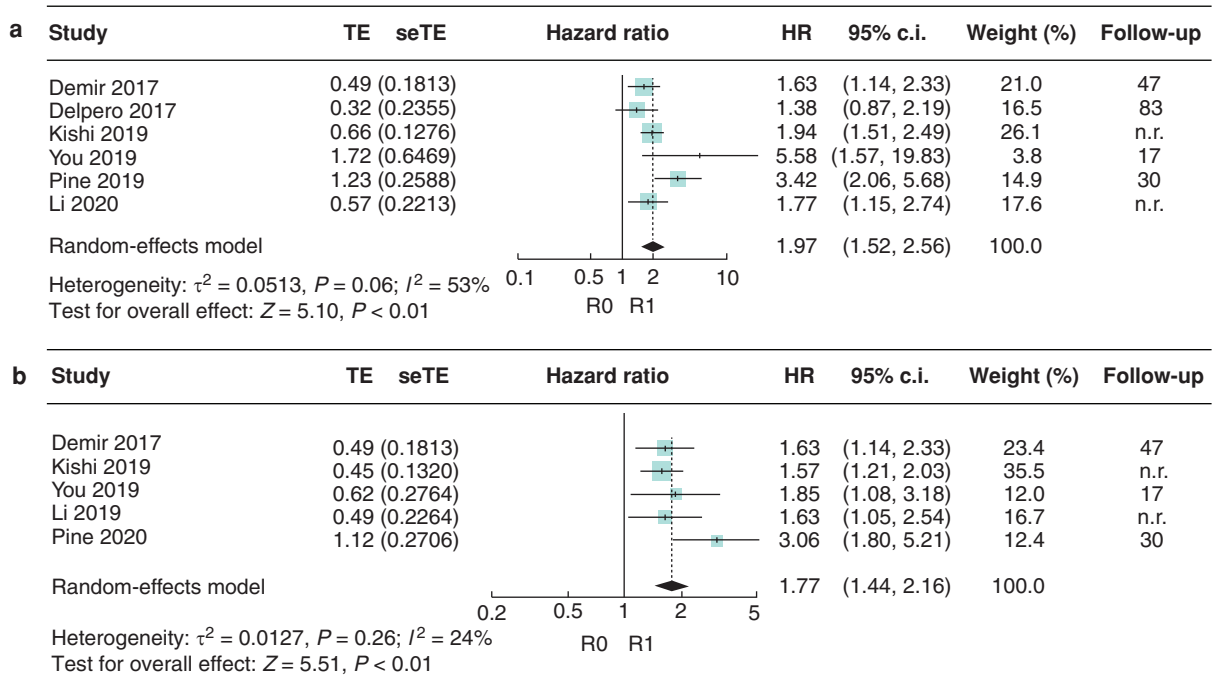


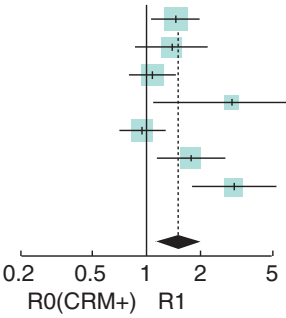
Fig. 2 Forest plot of the meta-analysis of median overall survival comparing R1 *versus* R0 direct margin status

a Univariable and **b** multivariable data. TE, estimated treatment effect; seTE, standard error of treatment estimate; n.r., not reported.

a

Study	TE	seTE	HR	95% c.i.	Weight (%)	Follow-up
Strobel 2017	0.37	(0.1568)	1.45	(1.07, 1.97)	17.4	29
Delpero 2017	0.32	(0.2355)	1.38	(0.87, 2.19)	14.0	83
van Roessel 2018	0.08	(0.1496)	1.08	(0.81, 1.45)	17.7	50
Panaro 2019	1.10	(0.5132)	3.00	(1.10, 8.19)	6.0	30
Ghaneh 2019	–0.05	(0.1483)	0.95	(0.71, 1.27)	17.8	34
Li 2019	0.57	(0.2213)	1.77	(1.15, 2.74)	14.6	n.r.
Pine 2020	0.12	(0.2706)	3.06	(1.80, 5.21)	12.5	29
Random-effects model			1.50	(1.12, 2.00)	100.0	

Heterogeneity: $\tau^2 = 0.0999$, $P < 0.01$, $I^2 = 72\%$
Test for overall effect: $Z = 2.74$, $P < 0.01$



b

Study	TE	seTE	HR	95% c.i.	Weight (%)	Follow-up
Delpero 2017	0.97	(0.2553)	2.65	(1.61, 4.37)	17.1	83
Strobel 2017	0.36	(0.1718)	1.43	(1.02, 2.00)	23.3	29
Hank 2018	0.80	(0.1931)	2.22	(1.52, 3.24)	21.6	33
Panaro 2019	0.81	(0.4544)	2.24	(0.92, 5.45)	8.3	30
Ghaneh 2019	0.27	(0.0917)	1.31	(1.09, 1.57)	29.7	34
Random-effects model			1.77	(1.31, 2.37)	100.0	

Heterogeneity: $\tau^2 = 0.0681$, $P = 0.02$; $I^2 = 67\%$
Test for overall effect: $Z = 3.77$, $P < 0.01$

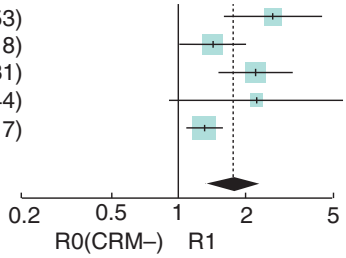


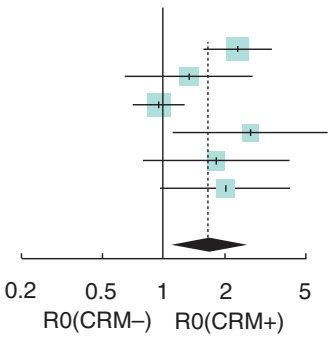
Fig. 3 Forest plot of the meta-analysis of median overall survival

a Comparing R0 (CRM+) resections *versus* R1 resections and **b** R0 (CRM–) resections *versus* R1 resections. TE, estimated treatment effect; seTE, standard error of treatment estimate; n.r., not reported.

a

Study	TE	seTE	HR	95% c.i.	Weight (%)	Follow-up
Hank 2018	0.84	(0.1916)	2.31	(1.59, 3.36)	21.7	33
Panaro 2019	0.29	(0.3672)	1.34	(0.65, 2.75)	14.9	30
Ghaneh 2019	–0.05	(0.1483)	0.95	(0.71, 1.27)	23.3	34
Prochazka 2020	0.99	(0.4480)	2.68	(1.11, 6.45)	12.3	n.r.
Ocana 2020	0.60	(0.4189)	1.82	(0.80, 4.13)	13.2	n.r.
Pine 2020	0.70	(0.3758)	2.02	(0.97, 4.22)	14.6	30
Random-effects model			1.68	(1.10, 2.56)	100.0	

Heterogeneity: $\tau^2 = 0.1782$, $P < 0.01$; $I^2 = 71\%$
Test for overall effect: $Z = 2.39$, $P < 0.02$



b

Study	TE	seTE	HR	95% c.i.	Weight (%)	Follow-up
Hank 2018	0.56	(0.2107)	1.75	(1.16, 2.65)	35.7	34
Panaro 2019	0.29	(0.3672)	1.34	(0.65, 2.75)	21.5	30
Ghaneh 2019	–0.05	(0.1483)	0.95	(0.71, 1.27)	42.7	34
Random-effects model			1.27	(0.82, 1.96)	100.0	

Heterogeneity: $\tau^2 = 0.0926$, $P = 0.06$; $I^2 = 65\%$
Test for overall effect: $Z = 1.09$, $P = 0.28$

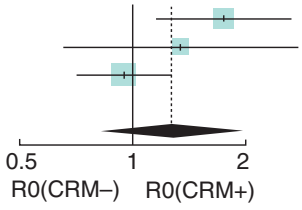


Fig. 4 Forest plot of the meta-analysis of median overall survival

Comparing R0 (CRM–) resections *versus* R0 (CRM+) resections using **a** univariable and **b** multivariable data. TE, estimated treatment effect; seTE, standard error of treatment estimate; n.r., not reported.

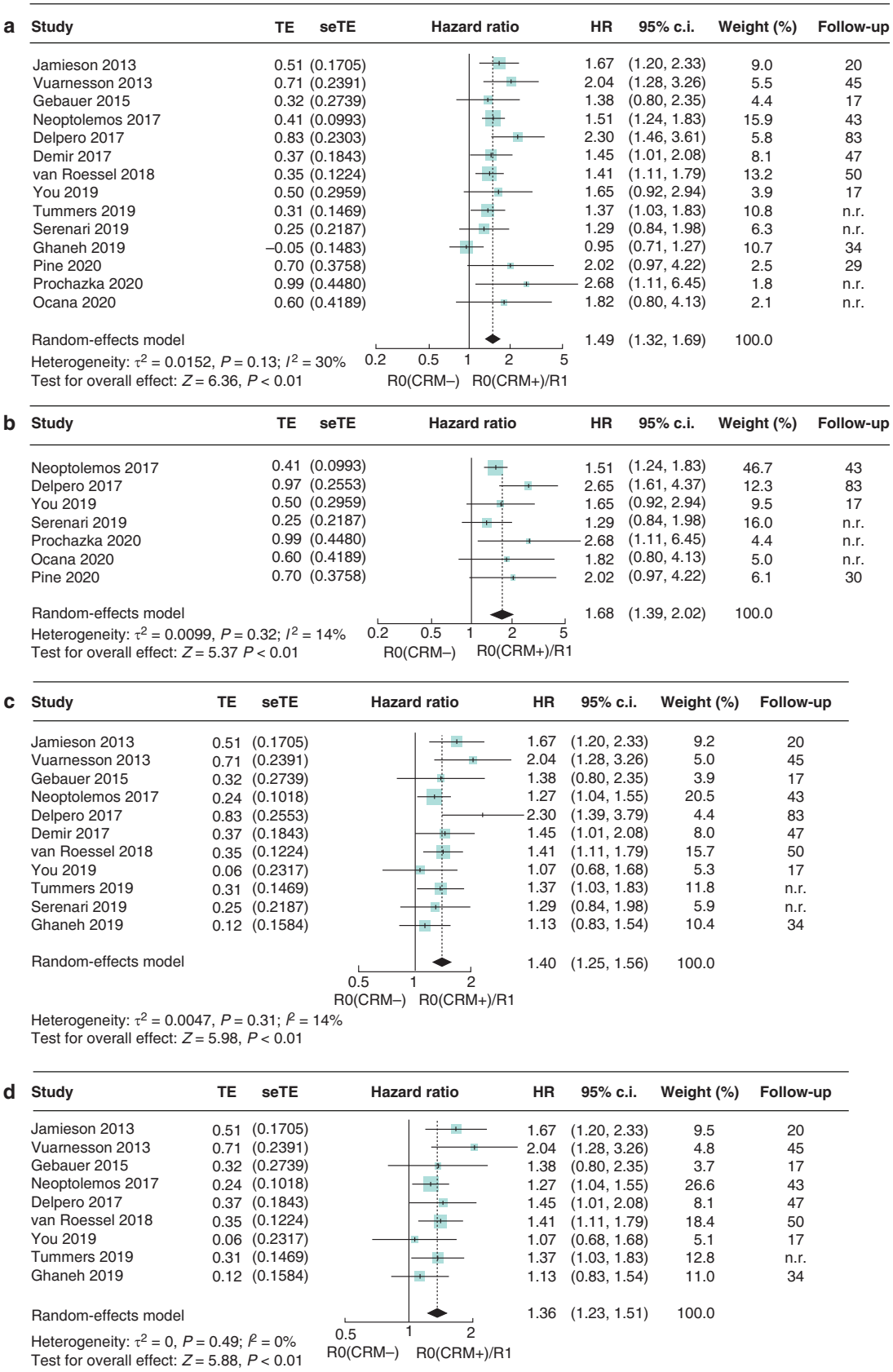


Fig. 5 Forest plot of the meta-analysis of median overall survival comparing R0 (CRM−) *versus* the combined category: R0 (CRM+) with R1 resections

a Studies reporting univariable hazard ratios and **b** studies reporting only univariable data. **c** Studies reporting hazard ratios from multivariable data and **d** studies reporting hazard ratios only from multivariable data. TE, estimated treatment effect; seTE, standard error of treatment estimate; n.r., not reported.

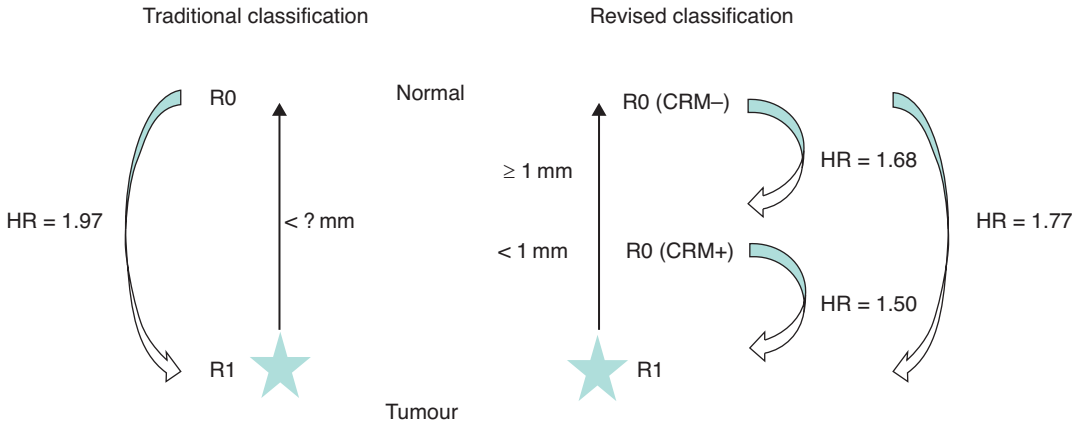


Fig. 6 Summary chart comparing resection margin status definitions and associated hazard ratios using univariable data

Subgroup analysis of pancreatic head tumours

A subgroup analysis of studies reporting separate HRs for PDAC of the pancreatic head was performed. The association between margin status and OS mimicked the results obtained by including all types of resections (*Figs S3 to S5*).

Discussion

This systematic review and meta-analysis provided evidence that a circumferential margin of resection of 1 mm or more (according to the revised R0 definition) was associated with improved survival compared to less than 1 mm in patients with PDAC after primary pancreatic resections. This survival benefit was evident from UV but not MV analysis, probably reflecting the limited number of studies available.

Because of the small number of eligible studies, the groups with positive margins, namely R0 (CRM+; margin clearance less than 1 mm) and R1 indicating direct margin involvement, were combined. A significant and independent survival benefit for R0 (CRM–) resections (1 mm tumour-free margin) was identified, irrespective of the R1 definition used.

Variations in specimen processing could also explain the lack of R0 (CRM–) confirmation as an independent predictor for longer OS than R0 (CRM+) using MV data. Similarly, the relatively low pooled R0 (CRM+) rate of approximately 58 per cent compared to large single-centre studies with standardized pathology protocols has probably been affected by such variability[2,10]. Pathology protocol differences across various centres are reflected in this meta-analysis. While axial slicing techniques are commonly used in Europe, pathologists in the USA frequently opt for bivalving protocols[5], and, in some studies, the pathology protocol was not reported[22,30]. Although it is accepted that standardized pathology protocols and resection margin definitions strongly influence positivity rates[38], the Dutch APOLLO randomized trial, which compared axial slicing and bivalving protocols, failed to detect a significant difference in R1 rates[39].

Microscopic tumour infiltration occurs mainly at the medial and posterior cut surface, and, in most cases, only one is involved[3,12,13,40–42]. A handful of studies have rigorously addressed which cut surface has the greatest implications for patient outcome, but the number of margins examined and the terminology has varied[5]. Data from the ESPAC-3 trial were analysed to assess the prognostic implications of each cut surface. Positivity of the posterior margin was associated with significantly shorter survival, while a positive anterior cut surface was not associated with reduced survival compared to an overall R0 of 1 mm or more on UV analysis[26].

Other studies have not detected an association between affected margin locations and survival[32]. The 8th edition of the AJCC Cancer Staging Manual explicitly refers to the uncinate margin for the circumferential assessment, but the others remain unspecified[5,9]. Tummers *et al.* found no significant difference in local recurrence between R1 of less than 1 mm *versus* R0 of 1 mm or more. Once a subgroup analysis was performed, stratifying for lymph node involvement, the R1 groups (R1N0 and R1N1) showed local recurrence significantly earlier[32].

A recent large institutional series showed that the revised R0 definition was also an independent prognostic determinant in these patients, and an R0 (CRM–) resection may identify a subset with a favourable prognosis and a median OS of 62.4 months[24].

Recently, novel adjuvant chemotherapy regimens have significantly improved median OS in PDAC patients undergoing upfront surgery[21,43]. Although a separate and stratified analysis is desirable, few studies strictly defined margin status to analyse their prognostic significance given the regimen of adjuvant chemotherapy used. The importance of resection margins after neoadjuvant chemotherapy has recently been addressed, but the results are controversial[44–47].

A wide R0 margin definition may also have a prognostic relevance as PDAC exhibits a diffuse infiltrative growth pattern[40]. Chang *et al.* identified a distance of 1.5 mm or more as a new cut-off for better outcomes in a cohort of 365 upfront resected patients with disease-specific survival as primary endpoint[42]. Delpero *et al.* showed that clearance of 1.0 mm or less and 1.5 mm or less for at least two positive margins were independent determinants of decreased survival[14]. Although with interesting implications, the limited number of studies addressing the prognostic implication of different tumour cell distances to resection margins prevented such an analysis in this study.

This systematic review has several strengths. The selection was limited to studies published after 2010 as earlier studies frequently did not apply standardized protocols for pathological assessment and adjuvant chemotherapy regimens varied significantly[12]. While this time frame reduced the number of

included studies, it strengthened the validity of conclusions. Only studies that provided detailed information on resection margins were included, and all studies that did not report separate HRs for OS in primary resections were excluded.

This study has several limitations. Most of the included studies had a retrospective design, associated with inherent flaws, including selection bias. Owing to the strict inclusion criteria, the number of appropriate studies identified was relatively small, preventing subgroup analysis.

In summary, the revised R status definition is valid and shows a favourable prognosis compared to R0 (CRM+) and R1. A key limitation of a systematic review is the quality of the original studies contained within. This study used the QUIPS tool to assess study quality and risk fo bias. While the risk of bias was rated as moderate and Egger's test did not reveal significant asymmetry, this systematic review highlights that most studies lack essential information on margin definitions and applied pathology protocols. Furthermore, most studies were of retrospective design and therefore of limited quality. This limits the conclusions of this systematic review and meta-analysis. Detailed information on pathological specimen processing and standardised reporting is necessary for further progress in PDAC treatments and facilitates comparisons between studies and institutions. The implications of the revised R status after neoadjuvant treatment and pancreatic resections other than PD require further investigation.

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This study was not preregistered in an independent registry. No review protocol was prepared for this study.

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Data availability

Data relating to the results of this study, including search strategy, are available upon request by contacting the corresponding author. Search strategies for Web of Science and CENTRAL are available upon request.

Supplementary material

Supplementary material is available at *BJS Open* online.

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